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Glycyrrhizin (licorice)-induced hypokalemic myopathy with acute motor paralysis of bilateral upper extremities: A case report

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Abstract

Hypokalemic myopathy is a rare condition associated with progressive fixed muscle weakness due to a persistent low level of potassium. The accurate diagnosis of hypokalemia is critical since it affects the automaticity of pacemaker cells, consequently leading to multiple arrhythmias and occasionally atrioventricular heart block. We report a rare case of glycyrrhizin-induced hypokalemic myopathy with acute motor paralysis of the bilateral upper extremities. A 76-year-old woman with a 1-week history of rapidly progressing muscle weakness in the upper extremities and neck, numbness in the palms bilaterally, gait disturbance, and no history of trauma presented to our hospital. She had a history of persistent oral ingestion of a Chinese medicine containing licorice for a cramp in her calf. On initial examination, she was unable to lift her hands, bend her elbows on either side, or ambulate independently. Deep tendon reflexes in both upper and lower extremities were normal or hypoactive, and no sensory deterioration was apparent. Magnetic resonance imaging demonstrated no abnormality of the cervical spinal cord. Laboratory examination results were as follows: creatine phosphokinase, 3770 IU/L; K^+, 1.9 mEq/L; plasma renin activity, 0.2 ng/mL/h; and blood aldosterone concentration, 3.8 ng/dL. Consequently, we diagnosed pseudo-hyperaldosteronism caused by chronic licorice ingestion resulting in acute hypokalemic myopathy. We discontinued the licorice ingestion, administered an intravenous infusion of KCl for 6 days, and achieved complete cure. When treating a patient with neurologically unexplained paralysis in a clinical setting, metabolic paralysis, such as hypokalemic paralysis, must be considered in the differential diagnosis.

Keywords

pseudo-hyperaldosteronism; licorice; glycyrrhizin; hypokalemic myopathy; creatine phosphokinase; paralysis

Introduction

Acute progressive muscular weakness of the bilateral upper extremities with no history of trauma in elderly patients can be caused by various neurological or muscular diseases such as cervical spondylotic myelopathy; spinal infarction; central spinal cord injury following an unconscious minor traumatic episode; spinal cord tumor; syringomyelia; multiple sclerosis; and several types of myelitis,

neuropathy, and myopathy. Among them, hypokalemic paralysis is one of the most important diseases since it can potentially lead to serious cardiovascular events. Hypokalemic myopathy is a rare condition associated with progressive fixed muscle weakness due to a persistent low level of potassium, which is different from reversible flaccid paralysis where there is a matched decrease in the serum concentration of potassium during hypokalemic periodic paralysis [1]. Hyperaldosteronism, which is typically caused by a tumor in the adrenal glands, leads to a high level of aldosterone and low level of potassium [2]. In contrast, pseudo-hyperaldosteronism, which can potentially have a genetic basis and be caused by dietary intake, including chronic licorice ingestion, leads to low levels of both aldosterone and potassium [3,4]. Indeed, it has been reported that chronic licorice ingestion leads to acute hypokalemic myopathy [5]. Herein, we present a rare case of glycyrrhizin-induced hypokalemic myopathy with acute motor paralysis of bilateral upper extremities.

Case Presentation

A 76-year-old woman (height: 141cm, weight: 51kg) with a 1-week history of rapidly progressing muscle weakness in the upper extremities and neck, numbness in the palms bilaterally, gait disturbance, frequent urination, and no previous history of trauma, presented to the orthopedic department of our hospital. The past medical history of the patient included diabetes, hypertension, and hyperlipidemia, which were all treated with daily oral medicines, and uterine and ovarian cancers, which were previously treated with surgical resection followed by chemotherapy. In addition, the patient had a 3 year-history of ingestion of a Chinese medicine containing licorice, which she had persistently taken orally for a cramp in her calf. She had increased the dose from 5 g/day to 10 g/day for the past 5 months. On the initial neurological examination, she was unable to lift her hands (Fig.1A), bend her elbows bilaterally, or ambulate independently. Specifically, she was unable to make and release a fist with stiffness of her thumbs on both sides (Fig.1B, C). Manual muscle testing (grading scale range: 0 to 5) evaluated muscle weakness of both upper extremities, with low scores from 1 to 3. Deep tendon reflexes in both upper and lower extremities were normal or hypoactive; test findings for Hoffmann's reflex, ankle clonus, and Babinski's reflex were all negative. Sensory deterioration of thermal nociception, or tactile and vibratory sensation was not found.

Radiological examination showed no abnormality of the cervical spine. Both T1- and T2-weighted magnetic resonance imaging (MRI) demonstrated no spinal cord compression with normal intramedullary intensity. Furthermore, no abnormal signal change was detected on fluid-attenuated inversion recovery MRI.

Laboratory findings on admission were as follows: red blood cell count, 515 × 10^4/mm^3; hemoglobin, 15.5 g/dL; hematocrit, 45.8%, white blood cell count, 16,970/mm^3 (eosinophils, 3.0%; segmented neutrophils, 73.5%; monocytes, 6.0%; lymphocytes, 17.5%); platelets, 21.1 × 10^4/mm^3; C-reactive protein, 0.41 mg/dL; total bilirubin, 1.2 mg/dL; aspartate aminotransferase, 110 (normal: 10–40)IU/L; alanine aminotransferase, 72 (normal: 5–40)IU/L; lactate dehydrogenase, 476 (normal: 180–370)IU/L; gamma-guanosine triphosphate, 221 (normal: 0–50)IU/L; creatine phosphokinase (CPK), 3770(normal: 30–120)IU/L; total protein, 7.4 g/dL; albumin, 4.0 g/dL; blood urea nitrogen, 15.5 mg/dL; creatinine, 0.6 mg/dL;Na^+, 147 (normal: 135–145)mEq/L; K^+, 1.9 (normal: 3.5–5.0)mEq/L; Cl^-, 94 (normal: 98–108)mEq/L; Ca^{2+}, 8.1 (normal: 8.6–10.2)mEq/L;P^{3-}, 2.7 (normal: 2.9-4.3)mEq/L; and

Blood thyroid stimulating hormone, free triiodothyronine, and thyroxine were 2.64 (normal: 0.34–4.04)μIU/mL, 2.31 (normal: 2.36–5.00)pg/mL, and 1.6 (normal: 0.88–1.67)ng/mL, respectively. In addition, plasmarenin activity and blood aldosterone concentration were 0.2(normal: 0.3–2.9)ng/mL/h and 3.8(normal: 30–159)ng/dL, respectively. Arterial blood gas analysis showed the following: pH, 7.557 (normal: 7.34-7.45); pCO_2, 46.4 (normal: 35.0-45.0)mmHg; pO_2, 57.8 (normal: >80)mmHg; pCO_3; 40.3 (normal: 20-26)mmHg; and base excess, 16.0 (normal: -2-2) mEq/L, which was suggestive of metabolic alkalosis. No associated electrocardiogram changes, including a decrease in T-wave amplitude, were seen.

From these findings, we diagnosed the patient's condition as pseudo-hyperaldosteronism caused by chronic licorice ingestion resulting in acute hypokalemic myopathy. First, we advised the patient to stop the licorice intake, and commenced oral treatment with potassium L-aspartate. The next day after oral treatment, serum potassium concentration was 1.5 mEq/L, which was lower than that on admission. Therefore, we added an intravenous infusion of KCl at a daily dose of 20mEq for 6 days (Fig. 2). On the sixth day of the infusion, serum K^+ was standardized to 1.9–4.2 mEq/L. We then discontinued both the infusion of KCl and oral administration of potassium L-aspartate, and recommended ingestion of a potassium-rich diet, e.g., including fruit regularly. During the same period, the muscular strength of the upper and lower extremities was restored gradually. By the sixth day, serum CPK increased from 3,770IU/L to 8,475IU/L in a time-dependent manner. It then spontaneously decreased to 646 IU/L by the 11^{th} day. Furthermore, the arterial blood gas analysis on the 11^{th} day demonstrated the following: pH, 7.455; pCO_2, 42,2 mmHg; pO_2, 85.6 mmHg; pCO_3, 29.3 mmHg; and base excess, 4.9 mEq/L. After 3 weeks, she could ambulate independently again for more than 20 min with full motor recovery of the bilateral upper extremities. The frequency of urination, however, remained unchanged after the treatment, implicating a symptom of age-related changes.

Discussion

In Japan, Chinese medicines containing licorice have been widely used among elderly patients for a long period. The main ingredient of licorice is glycyrrhizin which is not only used as a strong sweetener in the confectionery industry, but also as a medicine for liver disease, gastrointestinal mucosal disorders, inflammation of the throat, allergic disorders, and clumping of the smooth muscle. However, it also has aldosterone-like effects [6]. Since aldosterone causes reabsorption of Na^+ into the blood and eliminates K^+ into the urine via the nephron, the over-ingestion of licorice containing glycyrrhizin can cause same condition as an excess of aldosterone. This is known as pseudo-aldosteronism, which has the major symptoms of hypokalemia, metabolic alkalosis, edema, and/or hypertension [7]. This subsequently suppresses therenin-angiotensin-aldosterone axis, lowering the plasma level of renin and aldosterone. Further, the loss of potassium can cause flaccid paralysis or myopathy due to the interruption of intracellular depolarization and repolarization in muscle cells by alterations in the intra- and extracellular Na^+ and K^+ concentrations [6]. The potassium loss in the blood also leads to metabolic alkalosis, which occurred in the present case, resulting in a secondary intracellular shift of hydrogen ions into the muscle cells, subsequently causing hypocalcemia. This is seen clinically as Trousseau's sign of latent tetany.

In the current case, the patient presented with neurologically unexplained progressive flaccid

paralysis, mainly of the bilateral upper extremities. She had apparent gait disturbance during the initial examination. Further, she also presented minor paralysis of the bilateral lower extremities. She had no sensory disturbance, however, which is atypical of cervical myelopathy. The fluid-attenuated inversion recovery MRI showed no abnormal signals of the spinal cord, suggesting there was no associated spinal infarction. It was noted that she had stiff palms and was unable to make and release a fist on both sides, which was similar to Trousseau's sign due to hypocalcemia. From these results, we suggested a diagnosis of metabolic paralysis, particularly hypokalemic paralysis, and a serological examination was performed. The serum CPK level had increased to above 3,000IU/L, indicative of the persistent type of hypokalemic paralysis. Thus, given her history of oral treatment with a Chinese medicine containing licorice, we diagnosed the patient with glycyrrhizin-induced hypokalemic myopathy, rather than periodic hypokalemic paralysis. In the current case, we suspected that the patient may have potentially been in a hypokalemic state since she restricted her fruit intake to control her diabetes. Moreover, she was elderly, and older people usually tend to have an unbalanced diet. Shintani et al. reviewed 59 cases of glycyrrhizin-induced hypokalemic myopathy in 1992 and reported that the mean serum K^+ level, CPK level, plasma renin activity, and blood aldosterone concentration were 1.98 mEq/L, 5,385.7 IU/L, 0.17 (range: 0.8–4.4)ng/mL/h, and 2.92 (range: 2.0–13.0)ng/dL, respectively, which were obviously in line with those reported in the current case [6]. They also described that a complete cure was achieved in 57 of the 59 cases by discontinuing the ingestion of licorice and potassium supplementation, as in our case. In the current case, the patient also complained of muscle weakness of the neck. Yoshida and Takayama [8] previously reported a case of licorice-induced hypokalemia with dropped head syndrome, resembling our case. The accurate diagnosis of hypokalemia is critical since it affects the automaticity of pacemaker cells, leading to multiple arrhythmias and occasionally atrioventricular heart block. Fortunately, there were no ECG changes that were associated with hypokalemia in this patient.

Figures

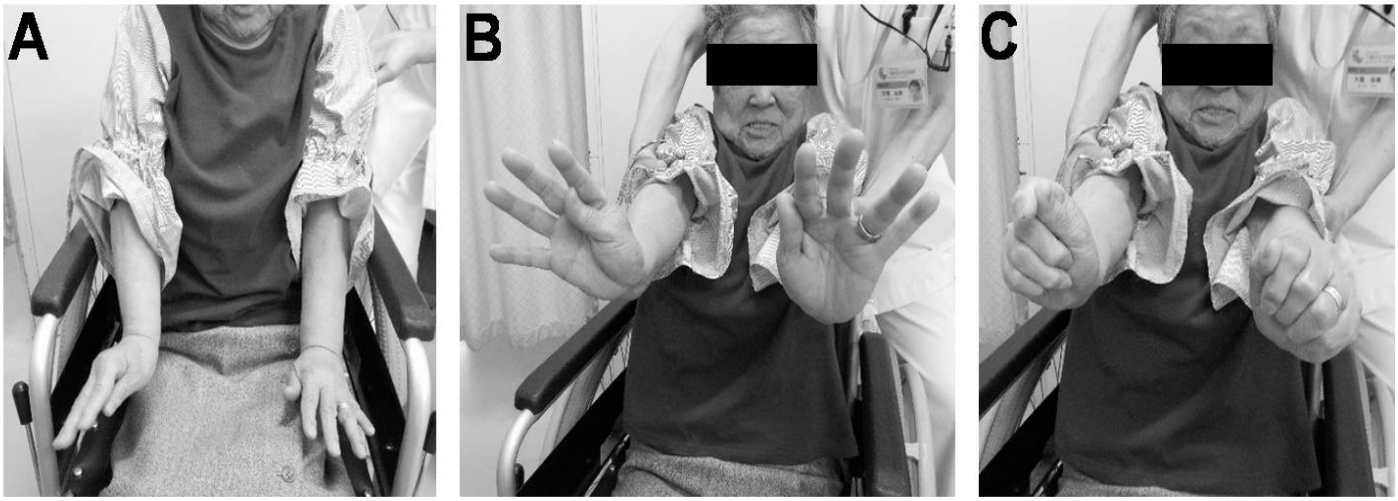

Figure 1: On initial admission, the patient was unable to lift her hands (A), and unable to make and release a fist with stiffness of her thumbs on both sides (B, C).

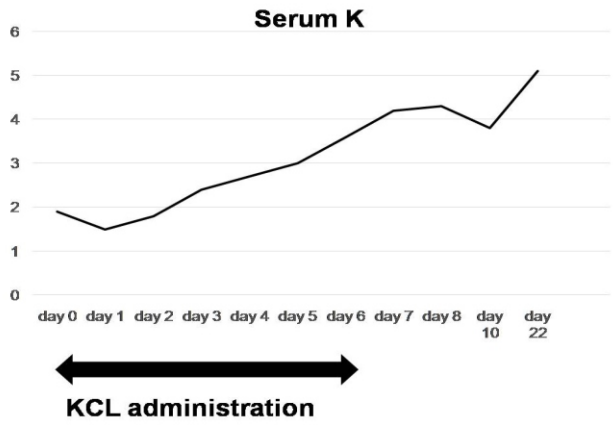

Figure 2: A graph of daily changes in the level of serum K^+ following the administration of intravenous KCl.

Conclusion

Here, we describe a patient with glycyrrhizin-induced hypokalemic myopathy with acute motor paralysis of bilateral upper extremities. When physicians encounter a patient with a neurologically unexplained paralysis in a clinical setting, metabolic paralysis such as hypokalemic paralysis, must be considered in the differential diagnosis.

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