Severe hypokalemia with miopathy in a young woman with a liquorice abuse hystory

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ABSTRACT

A 29-year-old caucasian female presented to general practitioner with muscular pain, weakness and fatigability. Laboratory tests showed severe hypokalemia (1.5 mmol/L), metabolic alkalosis (pH 7.61), and marked enzyme abnormalities (creatine kinase, 22235 U/L, lactate dehydrogenase, 8456 U/L). Severe hypokalemia with paralysis and rhabdomyolysis is a potentially life-threatening medical emergency; besides potassium chloride supplementation, a search for the underlying cause is necessary to avoid missing treatable causes: in our case, chronic liquorice consumption.

INTRODUCTION

Usually glycyrrhizin is considered safe as flavoring agent, although not as sweeter, but in Europe there is a recommendation suggesting that people should not consume more than 100 mg of glycyrrhizin acid a day, equivalent to approximately 50g/day of liquorice candy (1). Chronic hyperingestion of liquorice or liquorice-like compounds induces a syndrome with clinical aspects similar to those of primary hyperaldosteronism. This syndrome is characterized by sodium retention, hypertension, hypokalemia, metabolic alkalosis, and low plasma renin activity. The hypokalemia is usually mild, but it could become severe and even life threatening (2). A frequently undiagnosed serious complication of hypokalemia is rhabdomyolysis (3). Here, we describe a patient who showed a plasma potassium (K) concentration of 1.53 mmol/L, muscular paralysis and severe rhabdomyolysis after habitual consumption of natural liquorice.

CASE REPORT

A 29-year-old Caucasian female presented to general practitioner with muscular pain, weakness and fatigability that progressed to paresis involving all extremities. She was unable to stand up from the sitting position (Gower's phenomenon). She denied nausea, vomiting, diarrhea or use of drugs, including diuretics. She did not abuse alcohol. However, she had been eating liquorice during the last three weeks after quitting smoking. Her family and past medical histories were unremarkable. On physical examination, performed on day 07/10/2009, her blood pressure was 180/100 mm Hg, heart rate 90 beats/min, respiratory rate 15/min, and body temperature 37.1 °C. The thyroid gland was not enlarged. Cardiopulmonary examination was unremarkable. There was a symmetric muscular weakness with hyporeflexia more evident in the lower extremities. Fasciculations, myoclonus and muscular atrophy were not observed. The remainder of the physical examination was normal.

The general practioner required some laboratory tests, performed on 08/10/2009 as outpatients, showing hypokalemia (1.7 mmol/L), microcytic anemia [hemoglobin (Hb) 94 g/L, mean cells volume (MCV) 66 fL], and glucose, sodium (Na), chloride (Cl), magnesium (Mg), phosphorus (P), calcium (Ca), and creatinine concentrations in serum within references intervals. The general practitioner was advised by phone of the critical K result and the patient was sent to the emergence department of our hospital. At first observation (19:45 of the same day) laboratory tests showed severe hypokalemia (1.5 mmol/L), metabolic alkalosis (pH 7.61), and marked enzyme abnormalities, compatible with rhabdomyolysis (Table 1). Urinary K excretion was 17 mmol/L, plasma renin 5 mU/L (reference interval, 12-79 mU/L), and serum aldosterone was 0.04 nmol/L (reference interval, 0.08-0.28 nmol/L), Values observed for these analytes were far below the concentrations of healthy subjects. Urinary catecholamines were within reference limits, cortisol was 341 nmol/L (reference interval, 276-731 nmol/L), and adrenocorticotropic hormone (ACTH) was 17 ng/L (reference interval, 10-50 ng/L). The following imaging studies were performed: computed axial tomography (TC) scan for thorax and abdomen, ultrasound scan for kidneys and suprarenal glands, ultrasound scan for heart, with no evident abnormalities. An electromiographic study showed alterations suggestive of muscular damage. The electrocardiogram (ECG) showed flattened T waves and increased U-wave prominence, resulting in a long QT(U) syndrome; moreover, the ECG showed signs of antero-septal subendocardic lesion. These ECG alterations vanished after therapy and restoration of physiologic K concentrations in blood.

The patient was admitted to the cardiologic intensive care unit to perform a monitoring for insurgence of cardiac arrhythmias. Initial therapeutic approach included K supplementation: 10 mmol of potassium chloride (KCl) per hour given by the intravenous route and a K-sparing diuretic (spironolactone, 100 mg/day). After 48 h, the

Table 1
Time course variation of laboratory data in the studied patient

Test	08/10/09	09/10/09	10/10/09	11/10/2009	12/12/09	Reference limits
Serum K, mmol/L	1.5	1.6	2.0	2.8	3.1	3.5–5.1
Serum Na, mmol/L	141	143	144	142	144	137–145
Serum Cl, mmol/L	102	101	100	104	103	98–107
Serum Ca, mmol/L	1.88	1.88	2.02	2.11	2.3	2.10–2.55
Serum Mg, mmol/L	0.81	0.84	0.87	0.91	0.95	0.7–1.0
Serum P, mmol/L	0.92	0.95	0.99	1.10	1.20	0.81–1.61
Serum CK, U/L	22,235	24,274	14,634	12,361	2,570	30–135
Serum LDH, U/L	8,456	7,635	2,789	1,847	937	313–618
Serum aldolase, U/L	1,180	NA	530	NA	134	0.1–7.6
Serum AST, U/L	680	692	568	509	163	14–36
Serum ALT, U/L	310	318	258	260	105	9–52
Blood pH	7.61	7.54	7.52	7.49	7.42	7.35–7.45
Base excess, mmol/L	19.7	20.1	15.5	10.4	5.8	-2.3–2.3
HCO_3^-, mEq/L	43.7	43.6	39.2	34.0	32.1	26–28
Serum myoglobin, μg/L	3,105	2,918	2,396	1,819	214	12–76
Serum creatinine, μmol/L	47	53	66	55	62	46–92
Urine K, mmol/24h	NA	NA	171	152	127	25–125
Urine Na, mmol/24h	NA	NA	250	274	155	40–220
Urine Cl, mmol/24h	NA	NA	418	321	267	110–250
Urine Ca, mmol/24h	NA	NA	5.21	3.43	3.12	2.5–7.5
Urine P, mmol/24h	NA	NA	22	18	21	13–42
Blood pressure, mm Hg	180/100	210/120	170/100	170/90	150/90	–

CK, creatinkinase; LDH, lactate dehydrogenase; AST, aspartate transaminase; ALT, alanine transaminase; NA, not available.

patient was transferred to the nephrology unit to prosecute with therapy. KCL supplementation was needed for several days. The markers of metabolic alkalosis reverted in few days, but biochemical signs of muscular necrosis needed a longer period for normalization.

DISCUSSION

Liquorice is used as an additive in foods and drinks (flavored tea, white beer, grapefruit juices, candy, etc.) because of a very sweet constituent called glycyrrhizic acid, which is the substance that causes hypertension and hypokalemia. Furthermore, liquorice is used in herbal drugs and traditional Chinese medicine (4). The potential dangers of ingesting liquorice, even in small amounts such as 50 g daily for only two weeks, are reported in literature (5). Liquorice induced hypokalemia is a rare disorder, first described by Revers in 1946 (6); since that time the potential neuromuscular complications of severe hypokalemia have been demonstrated in a number of case reports (5, 7-9). Hypokalemic muscular weakness and rhabdomyolysis due to liquorice consumption are, however, rare.

Our patient had an extreme degree of hypokalemia and rhabdomyolysis in combination with metabolic alkalosis. Together with the mild hypertension found on physical examination, this suggested that she had a condition with high mineralocorticoid activity. Differential diagnosis for hypokalemia with metabolic alkalosis presents a broad different conditions that should be systematically approached (10). Skin or gastrointestinal losses was ruled out by measuring urine K concentrations. The patient's random urine K concentration of 17 mmol/L, in the setting of hypokalemia, suggested renal K loss. Hypomagnesemia-induced hypokalemia was ruled out because Mg concentrations were within the reference interval and the increased HCO_3^- excluded the possibility of diabetic ketoacidosis (blood glucose concentrations were normal) or renal tubular acidosis as causes.

Urinary K wasting can be caused by loop diuretics. These diuretics lower blood pressure, but may not be enough to normalize it in refractory hypertension. Our patient denied diuretic use. Some genetic conditions can mimic diuretic use. Bartter syndrome is a rare autosomal recessive disease. Patients with this condition present in childhood with metabolic alkalosis and increased urinary K, Na, and Cl concentrations (serum concentrations of Na are low). Gitelman syndrome is an autosomal recessive channelopathy of the Na/Cl transporter in the distal collecting tubule that can mimic hyperaldosteronism and may be present later in life. Patients with these genetic defects usually have low to normal blood

pressure and low Mg concentrations in serum.

Among hypertensive patients with hypokalemia and metabolic alkalosis, Cushing syndrome or excess mineralocorticoids from primary or secondary hyperaldosteronism may cause hypokalemia. Our patient, however, had low serum aldosterone and did not have findings consistent with Cushing syndrome: cortisol and ACTH were both within reference intervals. Pseudohyperaldosteronism presents with low plasma aldosterone and renin and may result from genetic or acquired etiologies. Liddle syndrome (autosomal dominant channelopathy of the Na/K transporter in the renal collecting duct) would manifest at an earlier age. Genetic deficiency of 11-β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) leading to apparent mineralocorticoid excess is very uncommon and usually this condition present in childhood. Congenital adrenal hyperplasia presents with low serum aldosterone, but the late-onset form usually does not produce significant renal electrolyte losses. Ectopic ACTH syndrome or a deoxycorticosterone-secreting adrenocortical adenoma could also present with low plasma aldosterone and renin, but our patient showed a normal TC scan of thorax and abdomen, ultrasound scan for kidneys and suprarenal glands; moreover, ACTH was within the reference interval.

Measurements of renin and aldosterone plasma concentrations were helpful. Low plasma renin and aldosterone concentrations suggested an apparent mineralocortoid excess-like disorder. Diagnosis depends on elicitation of a thorough history and laboratory evidence of hypokalemia. During our investigation and interviews with the patient, she revealed that was taking several liquorice candy 75-100 g/day, equivalent to about 100-130 mg/day, of glycyrrhinic acid. It quickly became evident that this syndrome was caused by an excess in liquorice consumption. The mechanism behind liquorice-induced hypokalaemic hypertension is well described (11). Liquorice causes hypokalemia through its active metabolite, glycyrrhizic acid, which inhibits the renal enzyme 11 hydroxysteroid dehydrogenase. This enzyme is responsible for renal conversion of cortisol to cortisone, which is inactive and does not bind to the mineralocorticoid receptor (12). The acquired dehydrogenase inhibition due to liquorice thus leads to activation of renal mineralocorticoid receptors by cortisol, resulting in a state of apparent mineralocorticoid excess. Hypokalemia is caused by renal and extrarenal loss of K or by an acute shift of K into the cells. Hypokalemia is associated with typical ECG changes and marked acid-base disturbance. Incidentally, paralysis and even rhabdomyolysis have been reported (13). The most frequent symptoms of rhabdomyolysis are fatigue, weakness, muscular pain and swelling, although it is possible that some patients are completely asymptomatic (14-17). The severity of neuromuscular disorders tends to be proportionate to the rate at which hypokalemia develops. Muscle destruction due to rhabdomyolysis causes the release of large amounts of K into the circulation. Consequently, when the clinical syndrome of hypokalemia and rhabdomyolysis develops, the absolute concentration of K is far below the reference limit. Large amounts of KCl supplementation are necessary.

In conclusion, as severe hypokalemia with paralysis and rhabdomyolysis is a potentially life-threatening medical emergency, besides KCl supplementation, a search for the underlying cause is necessary. Liquorice has become widely available as a flavouring agent in foods and drugs. So that, it is important for physicians to keep liquorice consumption in mind as a cause for hypokalaemic rhabdomyolysis.

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