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Hypokalemic paralysis with rhabdomyolysis and arterial hypertension caused by liquorice ingestion

Sirs: We report about a 47-year-old male who acutely developed muscle weakness of the lower extremities accompanied by a tingling paraesthesia. By the next day the weakness had progressed and involved the thoracolumbar spine, the posterior neck, left shoulder and the finger flexors of the left hand. The patient had been feeling well until 5 days prior to admission, when he began having difficulty walking and climbing stairs. The patient denied strenuous exertion or alcohol or drug use. He had no family history of neuromuscular disorders and there were no similar cases in his family. The patient consulted an orthopaedist, who observed a marked hyporeflexia of the lower extremities and left arm. To exclude an acute spinal cord compression the patient underwent CT-scan and MR imaging, which revealed no pathologic findings. To determine the cause of the acute paraesthesia the patient was referred to a neurologist, who was unable to identify the aetiology of the patient's symptoms. Thus the patient was sent to hospital for further evaluation.

Upon admission he complained of progressive muscle weakness, muscle pain and discomfort in his legs while sitting. In addition he complained of dark-coloured urine for two days. The patient also reported malaise and lethargy over the last 3 months. The past medical history revealed only high blood pressure since the age of 25. For that reason he was treated with 10 mg of ramipril daily. On physical examination the patient was afebrile, his blood pressure was 165/100 mmHg and his pulse rate was 92 beats/min. He was alert with no confusion or disorientation. There were no signs of heart failure. Physical examination of the heart, lung and abdomen were unremarkable. His extremities showed a marked stiffness and pressure pain with hypotonia. Furthermore he was not able to raise his legs from the bed; however there were no signs of focal muscle wasting, atrophy or joint swelling. The deep tendon reflexes were absent. He denied ever taking any statins.

The laboratory tests revealed a potassium of 1.4 mmol/l, sodium 142 mmol/l, calcium 1.93 mm/l, AST 308 U/L, CRP 40 mg/l, glucose 6.6 mmol/l, LDH 1039 U/l, proteins 45 g/l, CHE 4.79 kU/l, BUN 1.8 mmol/l, creatinine 68 μmol/l, CK 26,794 U/l, myoglobin 9,807 μg/l. The blood gases showed a pH 7.58, pCO_2 46 Torr, pO_2 80 Torr, bicarbonate 43 mmol/l and BE 19.4 mmol/l. Complete blood counts showed a WBC of 11.9×10^9/l, Haemoglobin 12.5 g/dl and a hematocrit of 37.1%.

Urine analysis was performed and demonstrated a pH value of 6.0, osmolarity 489 mmol/kg. The urinary potassium excretion was normal whereas urinary sodium excretion was 8 mmol/l. Urine testing also

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showed a mild proteinuria, bilirubinuria, urobilinogenuria, and a marked hemoglobinuria. On light microscopy examination pigmented granular casts and erythrocytes were detected.

The 12-lead electrocardiogram (ECG) demonstrated a sinus rhythm with left axis deviation, prominent U-waves and ST-depression in leads V2 through V5. In addition, the QT-interval was significantly prolonged and the QTc (corrected for the R–R interval) was 0.50 s (Fig. 1a).

Electrophysical examination included electroneurography. The most prominent findings showed axonal damage in both peroneal nerves with a normal distal motor nerve latency, a reduced nerve conduction velocity and amplitude.

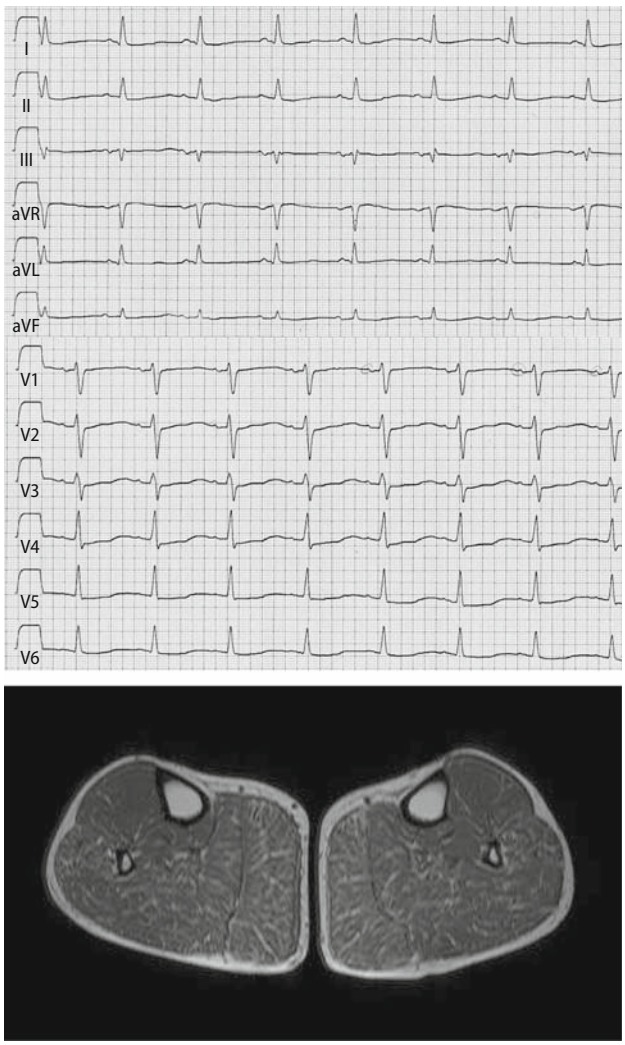

Fig. 1 **a** The 12-lead electrocardiogram demonstrates a sinus rhythm with left axis deviation, prominent U-waves and ST-depression in leads V2 through V5. In addition, the QT-interval is significantly prolonged. **b** The T1-weighted MR image reveals high signal intensity lesions, which are consistent with fatty degeneration in the musculus gastrocnemius

The patient was admitted to the intensive care unit because of the profound hypokalemia of unclear aetiology, metabolic alkalosis and the persistent tetraparesis.

Endocrinological work-up revealed a slightly low plasma aldosterone concentration, with a normal aldosterone excretion and an unremarkable plasma cortisol with an elevated cortisol excretion. The plasma renin activity was normal. To exclude Cushing's syndrome, a dexamethasone-test was performed, which appeared normal.

Muscle biopsy specimens obtained from the gastrocnemius muscle revealed necrotic changes and fatty degeneration without any sign of an inflammatory process. These findings were consistent with a necrotizing myopathy. The T1-weighted MR images revealed high signal intensity lesions, which were consistent with fatty degeneration in the affected muscle groups, especially in the musculus gastrocnemius (Fig. 1b). The lesions seen on MR correlated precisely with the symptoms and neurological deficits of the patient.

Upon further questioning, a detailed history revealed that the patient had a great fondness for liquorice candies. For the last 27 years, he had consumed excessive amounts of these candies, ingesting up to 600 g of liquorice weekly. During the days preceding admission, he had consumed 600 g of liquorice daily.

A diagnosis of apparent mineralocorticoid excess with significant hypokalemia, hypertension and metabolic alkalosis, attributable to liquorice ingestion, was made [2]. Liquorice is the root of *Glycyrrhiza glabra* and is mostly recognized as a flavouring agent. It has a long history as a medicinal herb and has been used to relieve symptoms in individuals with adrenal insufficiency, chronic hepatitis and for upper respiratory symptoms [1]. Glycyrrhizic acid or its hydrolytic product, glycyrrhetinic acid, is found in liquorice extracts and has a well-known mineralocorticoid activity, inhibiting 11 beta-hydroxysteroid dehydrogenase type 2, the enzyme that converts cortisol to cortisone [3].

The patient's signs and symptoms quickly improved with potassium replacement therapy and discontinuation of liquorice ingestion. On the fourth hospital day, the patient recovered from the painful myopathy and the ECG returned to normal. His rhabdomyolysis responded well to hydration and the metabolic alkalosis resolved. Three weeks later he was discharged. A follow up visit with a repeated MR study still showed high signal intensity lesions in the affected muscle groups.

Hypokalemic paralysis with rhabdomyolysis is a relatively uncommon clinical syndrome but can produce potentially life-threatening conditions like

arrhythmia. If recognised and treated appropriately, patients recover without any clinical sequelae. Initial management includes potassium replacement and a search for the underlying aetiology.

This case raised questions about the actual aetiology of the patient's long-standing hypertension. Was the 22 year history of hypertension a direct result of the chronic liquorice ingestion or was the high blood pressure from an essential hypertension? Another question was if the chronic use of an ACE-inhibitor allowed the hypokalemic manifestations to go undetected for a long period of time. We can only hypothesize, because we cannot retrospectively answer these questions. Nevertheless, it is likely that the hypertension enduring over years has affected the cardiovascular system negatively and seems to be a risk factor for atherosclerotic vascular diseases.

By this case we would like to stress the diagnostic importance of a careful history taking. It is important for physicians to keep liquorice consumption in mind as a cause for treatment resistant hypertension, hypokalemic paralysis and rhabdomyolysis.

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