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Teaching Point

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Low-dose liquorice ingestion resulting in severe hypokalaemic paraparesis, rhabdomyolysis and nephrogenic diabetes insipidus

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Background

In daily practice hypokalaemia is frequently observed. It can be accompanied by various adverse events and can even be life threatening. Frequent causes are intestinal and urinary loss, i.e. diarrhoea or use of diuretics.

Glycyrrhizin-containing substances, such as liquorice, are a well-known but rare cause of hypokalaemia. They can induce an apparent mineralocorticoid excess-like syndrome, often accompanied by hypertension, metabolic alkalosis, sodium retention and renal potassium wasting [1].

We will discuss a case of liquorice-induced hypokalaemia causing serious electrolyte disorders and severe clinical symptoms.

Case report

Presentation

A 52-year-old Caucasian man presented to our emergency department with severe asthenia and muscle cramps. Several days before admission he noticed muscle weakness in his limbs. This gradually progressed, resulting in a fall and inability to stand. He denied nausea, vomiting, diarrhoea or use of laxatives. There were no respiratory or cardiac complaints. His daily nutritional intake predominantly consisted of soup and bread and he had abstained from consuming alcohol a few months previously.

Relevant medical history included hypercholesterolaemia and hypertension, treated with lisinopril 20 mg per day, hydrochlorothiazide 12.5 mg per day and amlodipine 5 mg per day, but with questionable therapeutic adherence. He ceased the statin therapy 1 year before admission.

Clinical examination revealed severe paraparesis with preserved sensory input and low reflexes: he was unable to lift his limbs against gravitational force. He was cachectic, with a total body weight of 44 kg at admission, a length of 166 cm and a body mass index of 16.0 kg/m^2. He had mild hypertension with a blood pressure of 156/103 mmHg. All other physical findings were normal.

Investigations

Laboratory investigations at admission revealed metabolic alkalosis (pH: 7.54; pCO_2: 46.4 mm Hg; HCO_3^-: 39 mmol/L) and severe hypokalaemia (1.6 mmol/L). Nine hours later, a control sample showed further decrease of the kalaemia to 1.5 mmol/L, despite intravenous potassium and magnesium substitution. Urine collection revealed a high urinary potassium: 188.6 mmol/24 h (reference range (RR): 26.0–123.0). The transtubular potassium gradient (TTKG) was 10.2, indicating marked renal potassium wasting.

In addition there were arguments for rhabdomyolysis: CK levels were 118.87 μkat/L (RR: 0.83–2.84) [7118 U/L (RR: 50–170)] at admission and increased to 925.48 μkat/L (55 418 U/L) few days after admission; urinary myoglobin was 930.37 nmol/L (RR: <0) [16 300 μg/L (RR: <0)]. The kidney function remained normal during his stay.

In the endocrine investigations the suppression of renin and aldosterone and the elevated urinary free cortisol are most noticeable (Table 1). We also noted a marked polyuria (up to 5 L/24 h in the first few days) inconsistent with the amount of intravenous fluid administration.

Differential diagnosis

The key abnormalities of our case were an extreme hypokalaemia, accompanied by metabolic alkalosis, moderate hypertension, rhabdomyolysis and polyuria. Diuretic abuse was excluded through urinary sampling and our patient denied laxative abuse. Bartter and Gitelman syndrome, Liddle syndrome, congenital adrenal hyperplasia and other congenital or genetic disorders were highly unlikely in view of his age and since previous potassium levels were normal. The suppressed renin and aldosterone and normal morning cortisol suggested an apparent mineralocortoid excess-like disorder. Other endocrinopathies, such as Cushing syndrome and ectopic corticotrophin syndrome, could be excluded through laboratory findings (Table 1). Through a careful medication and dietary history our patient disclosed the consumption of two centimetres of liquorice root a day for the last 2 months, an equivalent of 1.5 g liquorice daily.

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Table 1. Endocrine findings and urinary potassium

Variable	At admission	After 1 month liquorice cessation	Reference range
Aldosterone (pmol/L) [pg/mL]	<28 [<10]	42 [15]	28–4440 [10–160] (supine)
Renin (pmol/L) [pg/mL]	0.05 [1.9]	0.48 [20.2]	0.06–0.52 [2.4–21.9] (supine)
TSH (mU/L)	1.724		0.465–4.68
Morning ACTH (pmol/L) [pg/mL]	1.4 [6.2]		1.0–10.7 [4.7–48.8]
Morning cortisol (nmol/L) [μg/dL]	535 [19.4]	265 [9.6]	185–623 [6.7–22.6]
24-h urine free cortisol (nmol/d) [μg/d]	762.8 [276.0]		<248.4 [<90]

Treatment

All oral medication and liquorice ingestion was ceased. Up to 15 mmol potassium chloride per hour was needed to correct the hypokalaemia, which took about 3 days. Due to persistent hypertension an ACE-inhibitor was started.

At discharge alkalosis was still present, but the kalaemia remained within the normal range without further need for substitution. One month after permanent cessation of the liquorice ingestion, all ion, metabolic and endocrine disorders returned to normal. This confirmed our diagnosis of liquorice-induced apparent mineralocorticoid excess syndrome with hypokalaemic paraparesis, rhabdomyolysis and nephrogenic diabetes insipidus.

Discussion

Liquorice is made from the root of Glycyrrhiza glabra, commonly known for its sweet flavour. Throughout history it has been used in herbal medicine and there are even reports of anti-inflammatory, antiviral, antimicrobial, antioxidative, hepatoprotective and cardioprotective properties [2]. Nevertheless liquorice is also well known for inducing hypertension and other health hazards.

The active component is glycyrrhizin, which inhibits renal 11-betahydroxysteroid dehydrogenase type 2 (11-beta-HDS2). This enzyme converts active cortisol to the inactive cortisone. Hence cortisol escapes inactivation and this leads to the characteristics of the syndrome of apparent mineralocorticoid excess [1, 3].

Despite worldwide use, glycyrrhizin toxicity is a rare condition which typically manifests itself with muscle weakness, fatigue, hypertension, renal potassium loss, sodium and fluid retention, metabolic alkalosis and pseudohyperaldosteronism. Dose–response correlations for cortisol-cortisone ratio, systolic blood pressure, fall in plasma potassium and fluid retention have been reported [4–7]. The onset and severity of the symptoms depend on the dose and duration of liquorice intake, as well as individual susceptibility [8].

The European Union states that an upper limit for regular ingestion of 100 mg of glycyrrhizin a day is safe for the majority of the population [9]. However our patient developed severe hypokalaemic paraparesis, rhabdomyolysis and nephrogenic diabetes insipidus on ingesting an estimated 1.5 g of liquorice a day, which contains 27.0–48.5 mg of glycyrrhizin (assuming a glycyrrhizin concentration of 18.0–32.3 mg/g) [9, 10]. This is far below the suggested upper limit for ingestion.

The reasons why some individuals are more susceptible than others remain unclear, but possible risk factors have been reported. In our case use of diuretics (though not detectable in urine sample) and anorexia may have contributed to the severity of the symptoms [11, 12].

Other known risk factors for increased sensitivity to liquorice ingestion are essential hypertension, old age and salt sensitivity [13–15]. The increased susceptibility in chronic inflammatory conditions can be explained by suppression of 11-beta-HDS2 and stimulation of ACTH secretion by inflammatory cytokines [16]. Mutations in the 11-beta-HDS2 enzyme can also contribute to increased liquorice sensitivity [17]. It is unclear whether male or female sex imposes a higher susceptibility. Some authors suggest increased sensitivity for liquorice in females and use of contraceptives, which may be explained by inhibition of 11-beta-HDS2 by oestrogens or through interaction with the mineralocorticoid receptor [18]. In contrast, other authors report the renin-angiotensin-aldosterone system is more responsive to liquorice in men [19].

Teaching points

1. Liquorice toxicity must be considered in unexplained metabolic alkalosis or hypokalaemia and in treatment-resistant hypertension.
2. This case demonstrates that serious adverse events are possible even in consumption of low doses of liquorice.
3. Susceptibility is variable between individuals depending on endo- and exogenous risk factors, such as essential hypertension, salt sensitivity, old age, malnutrition, use of diuretics, chronic inflammatory conditions and mutations in the 11-beta-HDS2 gene. The influence of male or female sex is unclear.
4. The effects of liquorice are reversible upon cessation. Potassium suppletion is often necessary in hypokalaemic states. Addition of spironolactone or dexamethasone may be considered.

Conflict of interest statement. None declared.

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