CASE REPORT

Bitter experience with liquorice sweetening agent resulting in apparent mineralocorticoid excess with periodic paralysis

Roshna Ramchandran, Shivendra Verma, Riddhi Dasgupta, Nihal Thomas

Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore, Tamil Nadu, India

Correspondence to
Dr Riddhi Dasgupta,
riddhi_dg@rediffmail.com

Accepted 26 July 2018

SUMMARY

Chronic liquorice ingestion is a rare cause of secondary hypertension and hypokalaemia with periodic paralysis. We report the case of a middle-aged Indian man who presented with hypertension and hypokalaemic alkalosis with recurrent bouts of periodic paralysis. Biochemical investigations revealed suppressed plasma renin and aldosterone concentrations with normal cortisol concentration. A detailed history revealed that he was addicted for the last 5 years to a form of chewing tobacco mixed with herbal preparations as a sweetening agent which on analysis revealed active principles of glycyrrhizin using the thin liquid chromatography method. The hypokalaemia resolved and hypertension control improved significantly after discontinuing liquorice consumption, and the patient was asymptomatic at 1-year follow-up. Long-term liquorice ingestion should be kept in mind as a reversible cause of hypokalaemic periodic paralysis, with a meticulous history and biochemical evaluation helping in identifying this recognisable and curable medical disorder.

BACKGROUND

Hypokalaemia is one of the most common medical emergencies encountered in up to 20% of hospitalised patients,[1] with increasing frequencies among those on diuretics.[2] While the milder forms present with weakness, fatiguability and polyuria, severe disease can have significant complications, including cardiac arrhythmias and quadriparesis. While gastrointestinal loss and diuretic use contribute to the majority of causes,[3] transcellular shifts and renal wasting are occasionally important. Excessive dietary intake of liquorice is a rare cause of refractory hypokalaemia as it can lead to a syndrome mimicking hyperaldosteronism characterised by hypertension, hypokalaemia, alkalosis, low renin activity and hypoaldosteronism. The active ingredient in liquorice, glycyrrhizin (glycyrrhizic acid, glycyrrhizinate, glycyrrhetinic acid), induces pseudohyperaldosteronism by inhibiting the 11 beta□hydroxysteroid dehydrogenase type 2 (11β□HSD2) which converts active glucocorticoid cortisol to locally inactive cortisone.[4] This inhibition results in activation of renal mineralocorticoid receptors by cortisol. The net effect of renal mineralocorticoid receptor activation is sodium (Na^+) reabsorption and potassium (K^+) excretion with transient hyponatraemia, persistent hypokalaemia and metabolic alkalosis, leading to a phenotype similar to that of the syndrome of apparent mineralocorticoid excess.[5] We report the case of a patient with resistant hypertension and hypokalaemia who had been consuming excessive quantities of liquorice daily for 5 years in the form of herbal preparations mixed with chewing tobacco. The significance of this case relates to the elaborate and meticulous approach to refractory hypokalaemia. Though rarely reported, liquorice is used commonly in herbal preparations and teas and as a flavouring agent in sweets, chewing gums, breath fresheners and food products; therefore, physicians are encouraged to obtain detailed dietary and drug histories when patients present with hypokalaemia and hypertension.

CASE PRESENTATION

A 45-year-old man, farmer from West Bengal, presented with history of progressive difficulty in getting up from squatting position and difficulty in climbing stairs for the last 9 months. He also reported polyuria with nocturia for the same duration. There was no history of polyphagia, loss of appetite or loss of weight. Over the last 6 months, he had two episodes of acute flaccid quadriparesis for which he was taken to the local hospital and was treated with intravenous fluids after which his condition improved. Historically, his admission documents revealed presence of hypokalaemia (lowest serum potassium 2.8 mEq/L). There was no history of diarrhoea, vomiting or abdominal pain. There were no history of palpitations, weight loss, heat intolerance or diaphoresis with biochemical investigations revealing normal thyroid function tests. He was diagnosed to have hypertension since past 2 years, with initial blood pressure recordings of 150/100 mm Hg. His blood pressure recordings persisted to be uncontrolled despite being on maximal doses of angiotensin receptor blocker (telmisartan tablet 80 mg/day), calcium channel blocker (amlodipine tablet 20 mg/day) and beta blocker atenolol tablet 50 mg/day). He was also using syrup potassium chloride (10 mL three times daily) intermittently for the past 6 months. There was no history of diabetes mellitus or any other chronic illness. On examination, he was of normal build with no pallor, cyanosis or other abnormalities on general survey. His pulse rate was 80 per min and blood pressure in the right arm was

To cite: Ramchandran R, Verma S, Dasgupta R, *et al*. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2018-225686

146/84 mm Hg in the supine position and 144/80 mm Hg in the erect position, with no discrepancies in blood pressures documented between the right and left upper and lower limbs. His systemic examination was essentially normal. He was found to have normal higher mental functions, no cranial neuropathies with essentially normal motor and sensory system examination. He did not have a history of use of alternative medications.

INVESTIGATIONS

In order to avoid discrepancies in biochemical reports while testing the plasma renin and aldosterone levels, the patient's antihypertensive medications were modified after admission, and the patient was initiated on prazosin-XL tablet (20 mg/day) and verapamil tablet (120 mg/day). Arterial blood gas analysis revealed metabolic alkalosis (arterial pH 7.55, normal: 7.35–7.45; bicarbonate 32 mmol/L, normal: 22–28 mmol/L) and hypokalaemia (K^+ 2.9 mmol/L, normal: 3.3–5.1 mmol/L) with normal chloride (98 mmol/L, normal: 101–111 mmol/L) and mildly elevated sodium (146 mmol/L, normal: 135–145 mmol/L) levels. Serum magnesium level (1.93 mmol/L, normal: 1.5–2.5 mmol/L) was normal. Direct renin (3.2uIU/mL; normal range in upright position: 4.4–46.1uIU/mL) and serum aldosterone (34.1; normal: 40–310) levels sent after correction of hypokalaemia (corresponding serum K^+ 3.7 mmol/L) were both found to be suppressed. Cortisol and adrenocorticotropic hormone (ACTH) levels at 08:00 hours were within normal limits (cortisol 16 mcg/dL, ACTH 29 pg/mL), 24-hour urinary free cortisol was 145 mcg/dL (normal <100 mcg/dL) which was repeated and found to be 92 mcg/dL (normal <100 mcg/dL) while overnight 1 mg dexamethasone suppression test was 0.8 mcg/dL (normal <1.8 mcg/dL). The transtubular potassium gradient in the presence of hypokalaemia was 9, thus suggestive of a renal loss of potassium. He underwent a contrast-enhanced CT scan of the abdomen which failed to show any adrenal lesions. ECG, done at admission, did not reveal any U-wave or ST-T changes.

DIFFERENTIAL DIAGNOSIS

Our patient thus had features of hypokalaemia with metabolic alkalosis along with hypertension in the background of chronic liquorice ingestion. Hence, he was provisionally diagnosed to have an apparent mineralocorticoid excess (AME) syndrome with suppressed renin and aldosterone levels. The differentials considered included genetic (11β□HSD2 mutation), acquired (overconsumption of liquorice, carbenoxolone or grapefruit juice), ectopic ACTH-secreting tumours and rarer aetiologies like Liddle's syndrome, deoxycorticosterone-secreting tumours and some variants of congenital adrenal hyperplasia.[6] Congenital AME with very little 11β□HSD2 activity usually presents in children with low birth weight, failure to thrive, short stature and severe, often fatal, hypertension with hypokalaemic metabolic alkalosis and muscle weakness (type I).[7] There is a milder form that presents in adolescents or young adults, often with some residual activity of 11β□HSD2 (type II).[8] Among the acquired causes of AME, liquorice is an important aetiology that contributes to hypertension and hypokalaemia through its active metabolites glycyrrhizic and glycyrrhetinic acid.[9] Liquorice is used in commercial preparations as herboristic and cosmetic, along with use in cough remedy, tea, Arabic gum, sugar, alcohol and tobacco.[10] Ectopic ACTH-dependent Cushing's syndrome is another significant aetiology associated with the development of an AME-like clinical picture. Though ACTH has no direct effect on 11β□HSD2, the enzyme is saturated in ectopic ACTH syndrome by very high concentrations of cortisol and corticosterone. The cortisol overproduced has a 'spillover' effect on the mineralocorticoid receptor, leading to hypertension and hypokalaemia.[11] In addition, impaired 11β□HSD2 activity is seen in patients with renal or hepatic disease and occasionally in patients with pre-eclampsia.[12] Biochemically, suppressed plasma renin activity, undetectable serum aldosterone levels and hypokalaemia with high tetrahydrocortisol+allo-tetrahydrocortisol/tetrahydrocortisone ratio have been used in the diagnosis of AME. Similarly, a very high urinary free cortisol/urinary free cortisone ratio is specific for AME.[13]

Liddle's syndrome also needs to be considered in cases of suspected secondary hypertension in the setting of hypokalaemia, low renin and low plasma aldosterone levels. As opposed to elevated levels of cortisol causing activation of the mineralocorticoid receptors, Liddle's syndrome[14] is characterised by an overactivating defect in the epithelial sodium channel resulting in increased sodium absorption and potassium wasting. Differentiation of Liddle's syndrome from AME is most easily accomplished based on the urinary cortisol levels[15] (elevated in AME and normal in Liddle's syndrome), but can also be distinguished based on the therapeutic response to spironolactone (hypertension is responsive to spironolactone in AME, but is not altered in Liddle syndrome).

On detailed review of the history, he was addicted to a concoction of chewing tobacco powder with different indigenous herbs, the latter being added as a sweetening agent. He had been consuming this mixture at least 8–10 times in a day for the last 5 years. In the background of his clinical presentation, the possibility of addition of liquorice as a sweetener was considered, and the mixture was sent for toxicology analysis. It was reported to be positive for active principles of glycyrrhizin using the high-performance thin layer chromatography (HPTLC) method. Though liquid chromatography-mass spectrometry techniques are the gold standard for detection of liquorice derivatives, the HPTLC method has shown good sensitivity and specificity in resource-limited settings.[16] Thus, the diagnosis of liquorice-induced syndrome of AME was confirmed.

TREATMENT

At discharge, his potassium levels were normal, and he was asked to strictly abstain from using the tobacco mix and advised to continue the potassium-rich diet and potassium supplementation.

OUTCOME AND FOLLOW-UP

Three months later, serum K+ was 3.8 mmol/L, and potassium supplements were stopped. Twelve months after his initial presentation to the endocrine clinic and after stopping liquorice consumption, his blood biochemical profile was normal, blood pressures were controlled at 123/77 mm Hg (supine) and 128/75 mm Hg (sitting) on low doses of telmisartan (40 mg/day) and amlodipine (10 mg/day), and he was clinically stable.

DISCUSSION

A syndrome of mineralocorticoid excess (characterised by hypertension, sodium and water retention, and hypokalaemia) resulting from the ingestion of liquorice has been well-described.[17] Among the acquired causes of AME, the other important aetiologies include overconsumption of carbenoxolone and grapefruit juice. Carbenoxolone, developed as an anti-ulcer drug, is a hemisuccinate derivative of 18-alpha-glycyrrhetinic acid that has been associated with development of AME.[18] The flavonoids naringin and its aglycone naringenin present in grapefruit[19] seem to have an inhibitory effect on 11β□HSD2 similar to liquorice leading to

AME. Liquorice or licorice (Greek) refers to the root of a plant called *Glycyrrhiza glabra*. It is native to Europe and Asia. The liquorice extracts have several medicinal benefits. Glycyrrhizin is the main sweet flavour and is metabolised to glycyrrhetinic acid after ingestion. It is 30–50 times as sweet as sucrose. Liquorice is a US Food and Drug Administration-approved food supplement used in many products without precise regulations to prevent toxicity. Liquorice extract consumption by an individual should not exceed 30 mg/mL of glycyrrhizic acid to avoid unwanted side effects while WHO guidelines for food additives quote intake of 100 mg per day would be unlikely to cause adverse effects in the majority of adults.[20] Liquid form of liquorice extract is used as a commercial sweetener in sweets and beverages. It is also used as a flavouring agent for tobacco. The active metabolites in liquorice extract are glycyrrhizic acid and glycyrrhetinic acid that can lead to a syndrome known as AME.[20] After oral ingestion, glycyrrhizic acid is hydrolysed to glycyrrhetinic acid by intestinal bacteria.[21] Glycyrrhetinic acid is 200–1000 times more potent as an inhibitor of 11β□HSD2 than glycyrrhizic acid; therefore, its pharmacokinetics is more relevant after oral administration. The major dose-limiting mineralocorticoid effects include oedema, hypokalaemia, weight gain or loss, and hypertension. Liquorice causes suppression of 11β□HSD2 type 2 enzyme which converts cortisol to cortisone, in the kidneys at the aldosterone-sensitive sites in the collecting tubules.[22] It also acts by directly binding to the mineralocorticoid receptors. Excess cortisol acts on the mineralocorticoid receptors leading to hypertension and hypokalaemia producing a state of pseudohyperaldosteronism. Pseudohyperaldosteronism from chronic liquorice ingestion is characterised by low serum and urinary aldosterone levels and decreased serum renin activity. This differs from true primary hyperaldosteronism caused by aldosterone-producing adenomas or primary adrenal hyperplasia which is characterised by elevated urine and serum aldosterone levels.

Patients generally fully recover with discontinuation of exposure to liquorice and spontaneous correction of hypertension and hypokalaemia occurring within several weeks; however, months may pass before the renin-aldosterone system becomes active again.[5] Muscle weakness resolves within days of potassium replacement. The hypokalaemia precipitated by liquorice can be further compounded by the use of drugs like terbutaline[23] while rarer manifestations like thrombocytopenia have occasionally been reported with liquorice.[24]

Our case thus highlights a unique reversible aetiology of hypertension with hypokalaemic periodic paralysis. It is important to have an exhaustive history, as failure to identify the aetiology can lead to unnecessary investigations and delay in treatment initiation.

Learning points

- Hypertension with hypokalaemic periodic paralysis should raise the strong suspicion of a mineralocorticoid excess state.
- Liquorice, used as a sweetener agent in food materials, herbal medications and chocolates can mimic hyperaldosteronism.
- An exhaustive history is needed to identify potential liquorice ingestion along with presence of low levels of renin and aldosterone on biochemical evaluation.
- Avoidance of exposure to liquorice can reverse the metabolic abnormalities within few weeks to months of discontinuation.

Contributors RR and SV: planning, drafting, conception and design of the manuscript. RD and NT: acquisition of the data and contributed to the development and design. All authors contributed to the manuscript and declare no conflict of interest.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Kjeldsen K. Hypokalemia and sudden cardiac death. *Exp Clin Cardiol* 2010;15:96–9.
2 Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis. *Adv Physiol Educ* 2016;40:480–90.
3 Weir MR, Espaillat R. Clinical perspectives on the rationale for potassium supplementation. *Postgrad Med* 2015;127:539–48.
4 Card WI, Mitchell W, Strong JA, *et al*. Effects of liquorice and its derivatives on salt and water metabolism. *Lancet* 1953;1:663–8.
5 BORST JG, Ten Holt SP, De Vries LA, *et al*. Synergistic action of liquorice and cortisone in Addison's and Simmonds's disease. *Lancet* 1953;1:657–63.
6 White PC, Mune T, Agarwal AK. 11 beta-Hydroxysteroid dehydrogenase and the syndrome of apparent mineralocorticoid excess. *Endocr Rev* 1997;18:135–56.
7 Palermo M, Delitala G, Mantero F, *et al*. Congenital deficiency of 11beta-hydroxysteroid dehydrogenase (apparent mineralocorticoid excess syndrome): diagnostic value of urinary free cortisol and cortisone. *J Endocrinol Invest* 2001;24:17–23.
8 Ulick S, Tedde R, Mantero F. Pathogenesis of the type 2 variant of the syndrome of apparent mineralocorticoid excess. *J Clin Endocrinol Metab* 1990;70:200–6.
9 Whorwood CB, Sheppard MC, Stewart PM. Licorice inhibits 11 beta-hydroxysteroid dehydrogenase messenger ribonucleic acid levels and potentiates glucocorticoid hormone action. *Endocrinology* 1993;132:2287–92.
10 Bernardi M, D'Intino PE, Trevisani F, *et al*. Effects of prolonged ingestion of graded doses of licorice by healthy volunteers. *Life Sci* 1994;55:863–72.
11 Palermo M, Shackleton CH, Mantero F, *et al*. Urinary free cortisone and the assessment of 11 beta-hydroxysteroid dehydrogenase activity in man. *Clin Endocrinol* 1996;45:605–11.
12 Quinkler M, Johanssen S, Grossmann C, *et al*. Progesterone metabolism in the human kidney and inhibition of 11beta-hydroxysteroid dehydrogenase type 2 by progesterone and its metabolites. *J Clin Endocrinol Metab* 1999;84:4165–71.
13 Monder C, Shackleton CH, Bradlow HL, *et al*. The syndrome of apparent mineralocorticoid excess: its association with 11 beta-dehydrogenase and 5 beta-reductase deficiency and some consequences for corticosteroid metabolism. *J Clin Endocrinol Metab* 1986;63:550–7.
14 Liddle GW, Bledsoe T, Coppage WS Jr. A familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion. *Trans Assoc Am Physicians* 1963;76:199–213.
15 Nakada T, Koike H, Akiya T, *et al*. Liddle's syndrome, an uncommon form of hyporeninemic hypoaldosteronism: functional and histopathological studies. *J Urol* 1987;137:636–40.
16 Xiang Y, Song X, Qiao J, *et al*. An ultrahigh-performance liquid chromatography method with electrospray ionization tandem mass spectrometry for simultaneous quantification of five phytohormones in medicinal plant Glycyrrhiza uralensis under abscisic acid stress. *J Nat Med* 2015;69:278–86.
17 Armanini D, Fiore C, Mattarello MJ, *et al*. History of the endocrine effects of licorice. *Exp Clin Endocrinol Diabetes* 2002;110:257–61.
18 Lee YS, Lorenzo BJ, Koufis T, *et al*. Grapefruit juice and its flavonoids inhibit 11β-hydroxysteroid dehydrogenase*. *Clinical Pharmacology & Therapeutics* 1996;59:62–71.
19 Epstein MT, Espiner EA, Donald RA, *et al*. Liquorice toxicity and the renin-angiotensin-aldosterone axis in man. *Br Med J* 1977;1:209–10.
20 Stewart PM, Wallace AM, Valentino R, *et al*. Mineralocorticoid activity of liquorice: 11-beta-hydroxysteroid dehydrogenase deficiency comes of age. *Lancet* 1987;2:821–4.
21 Hattori M, Sakamoto T, Yamagishi T, *et al*. Metabolism of glycyrrhizin by human intestinal flora. II. Isolation and characterization of human intestinal bacteria capable of metabolizing glycyrrhizin and related compounds. *Chem Pharm Bull* 1985;33:210–7.
22 Armanini D, Karbowiak I, Funder JW. Affinity of liquorice derivatives for mineralocorticoid and glucocorticoid receptors. *Clin Endocrinol* 1983;19:609–12.
23 Buhl LF, Pedersen FN, Andersen MS, *et al*. Licorice-induced apparent mineralocorticoid excess compounded by excessive use of terbutaline and high water intake. *BMJ Case Rep* 2018;2018:bcr-2017-223918–60.
24 Celik MM, Karakus A, Zeren C, *et al*. Licorice induced hypokalemia, edema, and thrombocytopenia. *Hum Exp Toxicol* 2012;31:1295–8.