Case Report

The Royal Society of Medicine

Journal of the Royal Society of Medicine Open;
8(2) 1–3
DOI: 10.1177/2054270416685208

Liquorice: a root cause of secondary hypertension

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Lesson

We describe a patient presenting with hypertension and hypokalaemia who was ultimately diagnosed with liquorice-induced pseudohyperaldosteronism. This rare cause of secondary hypertension illustrates the importance of a methodical approach to the assessment of hypertension.

Keywords

Liquorice, secondary hypertension, pseudohyperaldosteronism, AME excess

Case history

A 70-year-old woman was admitted to the Acute Medical Unit with newly diagnosed hypertension. A systolic blood pressure of 200 mmHg was measured during a routine medical assessment and a serum K^+ of 2.4 mmol/L (3.5–5.0) prompted this admission.

The patient had no specific complaints and there were no symptoms of catecholamine excess. There was no family history of hypertension: her mother had a stroke at age 70 and her father had a myocardial infarction at age 69. Medications included felodipine 2.5 mg (for two weeks), simvastatin 40 mg nocte, aspirin 75 mg daily and lansoprazole 15 mg daily. The patient was taking no over-the-counter preparations.

On examination, the patient was not Cushingoid. Her blood pressure was 190/89 mmHg and no radio-radial or radio-femoral delay was evident. There was no abdominal bruit. The heart rate was 64/min and regular and heart sounds were normal. She was euvolaemic.

Initial investigations included: serum K^+ – 2.8 mmol/L; serum Na^+ – 142 mmol/L; HCO_3^- venous – 33 mmol/L (22–30), eGFR 90 ml min^{-1}; urine dipstick – negative for blood and protein; ECG – no evidence of left ventricular hypertrophy; ultrasound urinary tract – symmetrical and normal sized kidneys. Investigations for secondary hypertension were requested and – with the exception of renin and aldosterone which are discussed sequentially in the text – were non-contributory. The blood test for renin and aldosterone was collected before any inpatient change to treatment.

The patient was given intravenous and then oral potassium supplements. She was commenced on spironolactone 25 mg daily – in place of felodipine – for a presumptive diagnosis of hyperaldosteronism and was discharged to outpatient follow-up.

At the initial outpatient assessment, two weeks later, the patient's blood pressure remained was increased at 178/102 and the spironolactone dose increased to 50 mg with recommendations for monitoring in primary care. By the second outpatient assessment, six months later, the blood pressure had improved to 130/64. However, the renin and aldosterone results from the initial admission were now available and both hormone concentrations were suppressed. A subsequent random renin and aldosterone assay – on spironolactone – showed a functional renin:aldosterone axis (see Table 1).

A decision was made to discontinue spironolactone and to reassess blood pressure, electrolytes and the renin–aldosterone axis. At a subsequent review, on no treatment, the blood pressure was 154/70. The serum K^+, plasma renin and aldosterone remained normal.

At this point, the patient volunteered that in the year preceding her first referral and hospital admission she had been consuming, on average, six tea bags of '*Twinings Comforting*' liquorice tea daily. She had self-discontinued the tea several weeks prior to her initial admission to hospital. The patient was advised to avoid further liquorice consumption.

Discussion

This case describes an uncommon though well-recognised cause of secondary hypertension and underlines the importance of a methodical approach to the assessment of hypertension.[1–3]

The patient had no evidence of end-organ damage at presentation indicating new hypertension. Hypertension with suppressed renin and aldosterone

Table 1. Blood pressure, serum potassium and plasma renin–aldosterone measurements.

	Blood pressure (mm Hg)	Serum potassium (3.5–5.0 mmol/L)	Plasma renin (5.4–60 mU/L)	Plasma aldosterone (90–720 pmol/L)	Treatment
Presentation	190/89	**2.8**	**3**	**<70**	Felodipine 2.5 mg daily
2 weeks	178/102	4.8	–	–	Spironolactone 25 mg daily
6 months	130/64	**5.2**	34	–	Spironolactone 50 mg daily
9 months	130/72	4.8	26	584	Spironolactone 25 mg daily
11 months	–	4.5	19	168	No treatment
14 months	154/70	–	–	–	No treatment

Note: Out of range results in bold.

Table 2. Causes of pseudohyperaldosteronism.

Disorder	Mechanism of hypertension
Syndrome of apparent mineralocorticoid excess	(1) Autosomal recessive inactivating mutation of 11β-HSD2 gene (2) Inhibition of 11β-HSD2 by Liquorice or Carbenoxolone
Cushing's syndrome and ectopic ACTH syndrome	Substrate cortisol excess and relative deficiency of 11β-HSD2 enzyme
Liddle's syndrome	Autosomal dominant activating mutation of gene for ENaC

11β-HSD2: 11 beta hydroxysteroid dehydrogenase type 2; ENaC: epithelial sodium channel; ACTH: adrenocorticotropic hormone.

concentrations has specific differential diagnoses. The patient's age excluded Liddle's syndrome. Urine cortisol measurements excluded Cushing's syndrome. An apparent mineralocorticoid excess (AME) syndrome was ultimately diagnosed, albeit after stopping liquorice intake and months after the initial presentation.

Liquorice is the root of *Glycyrrhiza glabra* and has been traditionally used for both its culinary and medicinal properties. Its active ingredient is glycyrrhizin which is hydrolysed *in vivo* to glycyrrhetinic acid. Glycerrhetinic acid inhibits 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), an enzyme located in renal tissue that converts active cortisol to inactive cortisone. Inhibition of 11β-HSD2 results in a significant increase in cortisol concentration at the renal mineralocorticoid receptors. The consequent uncontrolled mineralocorticoid activation leads to unrestricted sodium reabsorption and potassium excretion.[4,5] This results in hypertension, hypokalaemia and suppression of the renin–aldosterone axis. This pattern of an elevated blood pressure and hypokalaemia in the context of a suppressed plasma renin and aldosterone is referred to as pseudohyperaldosteronism and constitutes one of the variants of the AME syndromes: Table 2 outlines the causes. The inhibition of 11β-HSD 2 decreases the urinary ratio of cortisone metabolites to cortisol metabolites which is a diagnostic clue for this mechanism of secondary hypertension.[4,5]

The European Union's scientific committee on food recommends a daily upper limit of 100 mg for glycyrrhizin[6] which is present in approximately 50 g liquorice (assuming a content of 0.2% glycyrrhizin). Based on an analysis of the liquorice content of food items, a daily glycyrrhizin consumption of 1–10 mg/person has been estimated for several countries and 1 mg/person in the UK.[7,8] Our patient had been consuming six liquorice tea bags daily. Each tea bag contained 100 mg of glycyrrhizin and therefore her total daily intake approximated 600 mg which significantly exceeded the recommended limit.

Chronic liquorice consumption may cause ongoing, though ultimately transient, suppression of the renin–aldosterone axis following discontinuation of ingestion: this may continue for up to four months.[9,10] In contrast, the activity of 11β-HSD2 recovers earlier. The enzyme is suppressed for two weeks after liquorice is withdrawn and its activity increases as the urinary glycyrrhetinic acid levels decrease.[9,10] We were unable to find published data on the duration of hypertension following liquorice

withdrawal. Our patient presented to hospital having self-discontinued liquorice a few weeks earlier. The reduced plasma renin and aldosterone on admission represented a true suppression of the hormone axis due to recent liquorice intake. Her hypertension suggested persistent inhibition of 11β-HSD2.

In conclusion, liquorice consumption should be considered in the evaluation of hypertension and hypokalaemia. A methodical approach is required to avoid diagnostic delay and inappropriate intervention.

Declarations

Competing interests: None declared.

Funding: None declared.

Ethics approval: Written informed consent for publication was obtained from the patient.

Guarantor: CR.

Contributorship: RV wrote the case report, obtained patient consent and was involved in the patient's care. CR is the patient's consultant and edited the report before submission.

Provenance: Not commissioned; peer-reviewed by Mark Pucci.

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