CASE REPORT

All sorts of tests, only one question: an unexpected cause of hypertension

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SUMMARY

A 48-year-old woman presented to the Accident and Emergency department with a 4 month history of headaches, nausea and dizziness. She was found to have severe hypertension and hypokalaemia. Extensive investigations did not find any secondary cause for hypertension. The patient was discharged with oral doxazosin therapy which controlled the blood pressure. Before the follow-up appointment at the hypertension clinic, the patient and her husband identified that her headaches coincided with liquorice tea consumption of up to three cups per day. This information was not obtained in the clinical assessment. The patient is now headache and medication free after cessation of liquorice tea. Liquorice ingestion is often a forgotten reversible cause of hypertension. A good history is key to this diagnosis.

BACKGROUND

Hypertension is a common medical condition managed predominantly in primary care. In majority of cases, this is attributed to essential hypertension commonly associated with cardiometabolic conditions such as obesity or diabetes. On some occasions, patients are admitted to hospital for uncontrolled severe hypertension. In this clinical scenario, rarer causes are considered, particularly in younger patients. The diagnostic endeavour often focuses on endocrine aetiology. Liquorice, a common ingredient used in food products such as confectionary and beverages, is a recognised cause of hypertension, producing a clinical condition similar to primary hyperaldosteronism. With the increasing belief that herbal drinks, such as liquorice tea, is a healthy option, greater awareness of its impact on health is needed. This case illustrates the importance of exploring lifestyle factors to ascertain an unusual cause of a common condition.

Case presentation

A 48-year-old woman was referred to the Accident and Emergency department by her general practitioner after being found to have significantly elevated blood pressure with persistent headaches. She was diagnosed with hypertension 4 days prior to this admission and was treated with amlodipine 5 mg daily. Her blood pressure remained uncontrolled with systolic readings of 200–210 mm Hg despite this treatment. There was a concern that she might be developing malignant hypertension.

The patient described a bilateral dull continuous headache which had been present daily for 4 months apart from during a recent holiday when she was headache free. Although not increasing in severity, she described her reducing ability to cope with the headaches, compounded by nausea and dizziness. Over the counter analgesia with paracetamol and ibuprofen did not ameliorate the symptoms. Prior to this presentation, the patient led a healthy and independent life with no significant medical or family history. She was a non-smoker and did not take any regular medication.

Physical examination revealed an anxious woman with a slender built who was clinically well. Her body mass index was 20.1 kg/m². There was no peripheral stigmata of cortisol excess. Cardiovascular and neurological examinations were normal and funduscopy did not show hypertensive retinopathy or papilloedema. Her clinical observations were unremarkable apart from persistently elevated blood pressure with systolic readings between 160 and 200 mm Hg. ECG did not show any evidence of left ventricular hypertrophy or ischaemia.

Investigations

The urea and electrolyte showed hypokalaemia of 3.0 mmol/L which resolved with oral potassium replacement. The CT scan of the head did not demonstrate any intracranial pathology such as a space-occupying lesion. The urine dipstick was normal, and the pregnancy test was negative. Further investigations with CT scan of the abdomen and pelvis did not show any adrenal mass. There was no evidence of left ventricular hypertrophy on the echocardiogram. The kidney function and endocrine investigations such as glucose, cortisol, thyroid function and 24 hours urine catecholamines and metadrenalines were normal. The plasma renin activity and aldosterone level were low. The results of the biochemical investigations are shown in table 1.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses were poorly controlled essential hypertension due to inadequate treatment, hypertension due to raised intracranial pressure or secondary hypertension due to Conn's syndrome or pheochromocytoma. Raised intracranial pressure and secondary endocrine causes were excluded by relevant investigations. Adrenal cause was unlikely with absence of mass lesion. It was thought that

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Table 1 Results of the biochemical investigations

Blood tests	
Sodium	139 mmol/L (133–146)
Potassium	3.0 mmol/L (3.5–5.3)
Urea	2.5 mmol/L (2.5–7.8)
Creatinine	62 µmol/L (44–80)
Bicarbonate	25 mmol/L (22–29)
Glucose	4.7 mmol/L
Plasma renin activity	0.2 nmol/L/hour (0.3–2.2)
Plasma aldosterone	<100 pmol/L (up to 630)
Urine tests	
Norepinephrine	319 nmol/24 hours (0–490)
Epinephrine	44 nmol/24 hours (0–93)
Dopamine	1712 nmol/24 hours (0–3400)
Metanephrine	0.8 µmol/24 hours (0–1.7)
Normetanephrine	1.5 µmol/24 hours (0–3.0)

the patient had poorly controlled essential hypertension. Given the young age, she was referred to the hypertension clinic for follow-up after discharge.

TREATMENT

During the hospital stay, the patient was treated with amlodipine 5 mg daily which was subsequently changed to doxazosin 8 mg daily. This controlled the blood pressure with systolic readings of 120–130 mm Hg when she was discharged.

OUTCOME AND FOLLOW-UP

Prior to the appointment at the hypertension clinic, the patient and her husband discovered that liquorice could cause hypertension. By omitting liquorice tea, the blood pressure normalised and headache resolved, although this cause was identified 2 months after her initial presentation. The patient stopped drinking liquorice tea altogether which allowed successful withdrawal of the antihypertensive therapy and complete resolution of the headache. Since the blood pressure normalised, she was discharged from the hypertension clinic. The patient will be followed-up by her general practitioner to ensure that the electrolytes and blood pressure remain normal.

DISCUSSION

Liquorice is an exogenous cause of hypertension through the mechanism of pseudohyperaldosteronism which results in the syndrome of apparent mineralocorticoid excess, with sodium and water retention, hypokalaemia and hypertension.¹

It was originally thought that glycyrrhetic acid, the active component of liquorice, bound to the mineralocorticoid receptors to cause the apparent mineralocorticoid excess.¹ However, in laboratory studies, glycyrrhetic acid had a very low receptor affinity in comparison to endogenous aldosterone² and did not lead to the clinical sequelae of mineralocorticoid excess when administered to patients with Addison's disease or hypoadrenalism unless given alongside exogenous steroids.³

It is now understood that liquorice interferes with the cortisol metabolism to cause pseudohyperaldosteronism. Glycyrrhetic acid inhibits the enzyme 11-β hydroxysteroid dehydrogenase (11β-OHSD), which functions to physiologically convert cortisol to the inactive cortisone. Because the kidneys contain high concentration of 11β-OHSD, this enzymatic inhibition produces high levels of cortisol in the kidneys. Although typically involved with stress response, cortisol also possesses intrinsic

mineralocorticoid properties. Through the binding of cortisol to the renal mineralocorticoid receptors, liquorice indirectly causes increased sodium and water reabsorption, with resultant hypertension, and increased potassium excretion leading to hypokalaemia, along with suppression of the renin–aldosterone system. Stewart *et al*⁴ demonstrated that although the pituitary axis and plasma cortisol levels were normal, the half-life of cortisol (and therefore its activity) was prolonged, indicative of 11β-OHSD inhibition.⁴

Older literature described similar cases to our patient with pseudohyperaldosteronism where patients presented with either hypertension or hypokalaemic myopathy. Heikens *et al* reported a 40-year-old woman with severe hypertension and hypokalaemic metabolic alkalosis following chronic ingestion of liquorice.⁵ Achar *et al*⁶ and Omar *et al*⁷ separately described male patients who presented with flaccid paralysis after consuming 1 L of the liquorice drink 'erk soos' daily during observation of the holy month of Ramadan. Their symptoms and biochemical abnormalities rapidly resolved through intravenous potassium replacement and both patients made a full recovery after cessation of liquorice ingestion.

The importance of a good dietary history is highlighted by a recent Canadian case report by Foster *et al*.⁸ The authors described a case of pseudohyperaldosteronism through heavy consumption of jelly beans in a 70-year-old man where the

Patient's perspective

'I had always suffered from headaches but recently they had changed and become more frequent. I also noticed that when I was away from home for long periods i.e. 3–4 weeks the headaches stopped. After a few days back home they started again. By May 2016 they were getting really bad, I started to drink more water and cut down on my caffeine intake and replaced my lunch time coffee with an extra liquorice tea. I was now drinking 3 cups a day, I liked it and considered it a healthy option. My headaches were now constant and I was miserable and taking painkillers around the clock. I went to see my GP who after putting me on medication for high blood pressure (something I had never suffered from in the past) advised me after 4 days to go to A&E as my BP was so high. I was admitted to the Northern General and kept in for 1 week. My BP regulated (I was on medication). Once back home (still on meds) my BP started to creep back up again. My husband began to research my condition and we realised liquorice tea was to blame. In the past whenever I was away I would not drink the tea so my headaches stopped. Once back on the tea, they resumed. I stopped drinking the tea and have never had a headache since'.

Learning points

- ▶ Given its popularity as a healthy herbal drink, liquorice should be considered as a cause of hypertension, particularly when it is associated with hypokalaemia.
- ▶ It is important to diagnose this condition as hypertension is reversible on cessation of liquorice ingestion, thus, avoiding unnecessary treatment and expensive investigations.
- ▶ A good dietary history is crucial to the diagnosis.
- ▶ Greater awareness of its medical complications and clarity on safe consumption limit are needed among the healthy normotensive population.

history was key to diagnosis. Sontia *et al*⁹ reported a 55-year-old woman with uncontrolled hypertension from consuming up to 250g of liquorice daily and this diagnosis was clinched by dietary history.⁹ Our case report underpins the importance of this fundamental clinical skill and practice. Had the liquorice history been ascertained, the unnecessary treatment and expensive investigations could have been avoided.

The UK Food Standard Agency stipulates food products that contain liquorice must carry a warning against excessive consumption in people with hypertension.¹⁰ Our case study shows that liquorice can also cause hypertension in normotensive subjects, implying that this warning should also apply to this population of consumers. The definition of 'excessive consumption' is vague. The European Scientific Committee on Food advises a safe daily intake of up to 10mg/person/day of glycyrrhizin in liquorice-containing food products.¹¹ Since a cup of liquorice tea with 250mL volume contains approximately 31.5 mg of glycyrrhizin,¹² this equates to one-third of a cup daily. Our patient drank three cups of liquorice tea daily, an amount deemed not excessive by lay person standard, but this equated to at least nine times above the safe limit for glycyrrhizin ingestion. This case report highlights the need to define 'excessive consumption' in a language understood by a lay person.

In conclusion, liquorice is often a forgotten cause of hypertension given its perception as a historical phenomena. This case report highlights the need to resurrect its awareness among clinicians and healthy lay people given the increasing popularity as a healthy beverage.

Contributors SF wrote the main body of the text as the junior doctor. RF, PJ and SS were supervising consultants involved with the patient's care from an acute medicine and medical physician perspective as well as being involved with follow-up. RF and SS reviewed and edited the case report.

Competing interests None declared.

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REFERENCES

- 1 Card WJ, Mitchell W, Strong JA, *et al*. Effects of liquorice and its derivatives on salt and water metabolism. *Lancet* 1953;1:663–8.
- 2 Armanini D, Karbowiak I, Funder JW. Affinity of liquorice derivatives for mineralocorticoid and glucocorticoid receptors. *Clin Endocrinol* 1983;19:609–12.
- 3 Borst JG, ten Holt SP, deVries LA, *et al*. Synergistic action of liquorice and cortisone in Addison's and Simmonds's disease. *Lancet* 1953;1:657–63.
- 4 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.
- 5 Heikens J, Fliers E, Endert E, *et al*. Liquorice-induced hypertension--a new understanding of an old disease: case report and brief review. *Neth J Med* 1995;47:230–4.
- 6 Achar KN, Abduo TJ, Menon NK. Severe hypokalemic rhabdomyolysis due to ingestion of liquorice during Ramadan. *Aust N Z J Med* 1989;19:365–7.
- 7 Omar HR, Komarova I, El-Ghonemi M, *et al*. Licorice abuse: time to send a warning message. *Ther Adv Endocrinol Metab* 2012;3:125–38.
- 8 Foster CA, Church KS, Poddar M, *et al*. Licorice-induced hypertension: a case of pseudohyperaldosteronism due to jelly bean ingestion. *Postgrad Med* 2017;129:329–31.
- 9 Sontia B, Mooney J, Gaudet L, *et al*. Pseudohyperaldosteronism, liquorice, and hypertension. *J Clin Hypertens* 2008;10:153–7.
- 10 Food Standards Agency. Food Labelling; giving food information to consumers. 2016 <https://www.gov.uk/guidance/food-labelling-giving-food-information-to-consumers> (accessed 18 Jul 2017).
- 11 Scientific Committee on Food, European Commission, Health and Consumer Protection Directorate General. Opinion of the Scientific Committee on Food on glycyrrhizinic acid and its ammonium salt. 10 Apr 2003 https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out186_en.pdf (accessed 18 Jul 2017).
- 12 Maas P. Liquorice root in food stuffs: survey of the glycyrrhizin content of tea, herbal mixtures, alcoholic drinks and liquorice. *De Ware (n) Chemicus* 2000;30:65–74.

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