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Turkish pepper (extra hot)

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Abstract
A 38 year old female office worker was admitted with a newly discovered blood pressure of 250/110 mm Hg. Evaluation for secondary forms of hypertension was negative and treatment was begun. Sodium excretion was markedly reduced, plasma aldosterone was normal, and plasma renin activity was low. Therefore, presence of an aldosterone-like activity was suspected. Eventually, the patient confessed to abusing "Turkish Pepper", a brand of Scandinavian liquorice candies and "Fisherman's Friend", another brand of liquorice candies, concurrently. After eliminating liquorice from her diet, the hypertension disappeared thus allowing her antihypertensive treatment to be stopped.
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Keywords: liquorice; hypertension

Hypertension is among the most frequently encountered medical problems. Having excluded secondary forms of hypertension such as renal artery stenosis, hyperthyroidism, phaeochromocytoma, mineralocorticoid and cortisol excess, clinicians commonly assign their patients the label of "essential" hypertension. Dietary causes of hypertension such as excessive liquorice consumption are often overlooked. Clinicians often fail to ask about liquorice ingestion and patients are unaware of liquorice as a potential health hazard. We present a case of liquorice "abuse", a common form of hypertension in industrialised countries, and provide a brief review of the disorder.

Case report

A 38 year old office worker presented with worsening headache and decreased appetite. She had suffered from migraine for years. The remainder of her previous medical history was unremarkable. She received no regular medication except for an oral contraceptive preparation. On admission, she appeared distressed but not acutely ill. Her blood pressure was 230/130 mm Hg and a trace of pitting pedal oedema was present. Grade 1 hypertensive retinopathy was noted. The remainder of the physical examination was unremarkable.

Serum creatinine, urine analysis, arterial blood gas values, and thyroid hormones were normal. Her serum potassium concentration was 3.9 mmol/l. Urinary catecholamines and plasma cortisol were normal. Electrocardiography, chest radiography, and a duplex scan of the renal arteries were normal. Urine sodium excretion was reduced to 17 mmol/day. Urinary cortisol was 196 nmol/24 hour (high normal), urinary aldosterone was 1.3 nmol/24 hour (low), and plasma renin activity was 0.15 ng/l (very low) suggesting presence of an aldosterone-like substance.

Further inquiries revealed daily consumption of large amounts of "Turkish Pepper" (Karl Fazer Ltd, Helsinki, Finland, fig 1), a brand of liquorice candies containing 200 mg glycyrrhicinic acid and 1.5 g of sodium/100 g. Moreover, to our astonishment, the patient was incidentally seen ingesting "Fisherman's Friend" (Lofthouse Ltd, Fleetwood, UK, fig 2) liquorice lozenges containing 200 mg glycyrrhicinic acid and 60 mg sodium chloride/100 g.

Figure 1 "Turkish Pepper": a strong brand of liquorice candies manufactured in Finland.

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Figure 2 "Fisherman's Friend": a popular brand of strong liquorice candies manufactured in the UK.

Box 1: Inhibitors of 11β-HSD capable of inducing hypertension
- Confectionery: liquorice sticks, bricks, cakes, toffee, bars, balls, tubes, Catherine wheels, pastilles
- Chewing gum (Stimorol)
- Liquorice flavoured cough mixtures and teas
- Herbal cough mixtures
- Liquorice tea
- Liquorice root
- Chewing tobacco
- Belgian beers
- Alcoholic beverages: pastis, raki, ouzo, Pernod

She also reported ingestion of increasing amounts of the lozenges before admission.

Blood pressure control was first achieved with intravenous urapidil; subsequently, metoprolol was begun. Later, ramipril and hydrochlorothiazide were added. However, while receiving a strictly liquorice-free diet, the patient became hypotensive. Ramipril and hydrochlorothiazide were discontinued and she was discharged with metoprolol as a maintenance treatment for migraine.

Discussion

Liquorice is manufactured from the root of *Glycyrrhiza glabra*, a Mediterranean shrub from the family papilionaceae. Its medicinal use has been advocated since antiquity. The Greek physician Dioskorides reported its use in wound treatment and a liquorice root was reportedly found in the vicinity of Tutankhamun's grave in Egypt. In the 14th century, Conrad of Meganberg in Germany mentioned liquorice called "bear's droppings". Even the French emperor Napoleon was reportedly a notorious liquorice addict.

Hypertension due to liquorice was first recognised in the 1950s in the Netherlands where liquorice is extremely popular. Initially, a direct mineralocorticoid effect was proposed.[1] Forty years later, research into steroid metabolism led to an understanding of the disorder. For years, specificity of mineralocorticoid action had been believed to be receptor mediated. However, more recent research showed that both cortisol and mineralocorticoid hormones are capable of binding the mineralocorticoid receptor. These findings led to the discovery of 11β-hydroxysteroid dehydrogenase (11β-HSD),[2] an enzyme that oxidises cortisol into cortisone, the 11-keto form that is incapable of binding to the mineralocorticoid receptor. Therefore, specificity of mineralocorticoid action is enzyme, not receptor, mediated.[3] In mineralocorticoid sensitive tissues, such as the distal tubule, 11β-HSD prevents excess cortisol from binding to the mineralocorticoid receptor thus allowing for aldosterone action.[4] Subsequently, a genetic defect in 11β-HSD was found to be the cause of the syndrome of apparent mineralocorticoid excess (AME), a rare form of hypertension in children clinically resembling hyperaldosteronism except for the fact that plasma aldosterone is undetectable. Endogenous cortisol, which binds to the renal mineralocorticoid receptor because of absent 11β-HSD is the salient feature of AME.[5] Subsequently, remarkable similarities between AME and liquorice induced hypertension were appreciated, leading to the discovery that glycyrrhetenic acid, a metabolite of glycyrrhicinic acid in liquorice, is a potent inhibitor of 11β-HSD.[6] The time course of liquorice ingestion, suppression of the renin-aldosterone axis, and increased urinary excretion of cortisol metabolites has been demonstrated in healthy volunteers.[7]

A broad variety of confectionery and beverages contain glycyrrhicinic acid (box 1). However, severe hypertension is almost exclusively due to heavy consumption of strong liquorice candies whereas ingestion of moderate amounts is quite safe. A study in Iceland demonstrated that regular consumption of small amounts of liquorice suffices to induce hypertension in volunteers.[8] Our patient concomitantly ingested two brands of liquorice candies containing large amounts of glycyrrhicinic acid

Learning points
- Both cortisol and aldosterone bind the mineralocorticoid receptor. In target tissues for mineralocorticoid action, specificity of aldosterone action in the presence of cortisol is mediated by 11β-HSD which converts cortisol into cortisone. The latter is incapable of binding the mineralocorticoid receptor.
- Inherited defects of 11β-HSD are responsible for endogenous renal cortisol excess associated with the syndrome of AME, a rare form of hypertension in children. Glycyrrhetenic acid, the metabolite of glycyrrhicinic acid in liquorice, is a potent inhibitor of 11β-HSD and liquorice induced hypertension closely resembles AME from a pathogenetic point of view.
- In hypertensive patients, particularly in young women employed in office jobs and in patients who have recently stopped smoking, inquiring into dietary habits is mandatory in order to identify ingestion of 11β-hydroxysteroid dehydrogenase inhibitors such as liquorice.

and sodium chloride. Her urinary sodium excretion was markedly reduced suggesting that (provided that urine collection was adequate) she was not in equilibrium which would eventually have led to normal urinary sodium excretion. Therefore, although we cannot strictly prove a cause-and-effect relationship, we assume that her hypertension was caused by recent large amounts of liquorice.

Women receiving oral contraceptives are predominantly affected and a large proportion of patients is employed in office jobs. Individual susceptibility may play a part as many normotensive women report abuse of liquorice. An occasional patient may be a smoker who recently stopped only to "abuse" liquorice as a substitute. Near fatal cases have been reported[9] and severe neurological rhabdomyolysis may occur when profound hypokalaemia is present.[10]

Hypertension in among the most frequently encountered problems in general internal medicine. Inquiring into liquorice habits must be part of the initial assessment to allow for a timely diagnosis of this common and easily treatable form of hypertension.

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