Exogenously-induced apparent hypermineralocorticoidism associated with ingestion of "asam boi"

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ABSTRACT

A 31-year-old woman presented with a one-week history of headache, generalised lethargy, weakness and poor appetite. Clinical examination showed that her blood pressure was 200/120 mmHg. On an earlier occasion, her blood pressure was found to be normal by a general practitioner whom she last visited three months earlier when she had an upper respiratory tract infection. Investigations showed hypokalaemia, suppressed serum renin and aldosterone. Further history was taken and revealed that she had been craving for guava fruits which she ate with flavoured "asam boi" (containing glycyrrhizic acid) at least three spoonfuls twice a day for the past six weeks. The hypertension and hypokalaemia resolved after two weeks of stopping the "asam boi". Her clinical picture was compatible with exogenously-induced hypermineralocorticoidism.

Keywords: asam boi, exogenously-induced hypermineralocorticoidism, glycyrrhizic acid, hypermineralocorticoidism

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INTRODUCTION

Chronic ingestion of compounds that contain glycyrrhizic acid induces a syndrome that mimics primary hyperaldosteronism. These include hypertension, hypokalaemia, metabolic alkalosis, and a low plasma renin activity. The only unique feature to this syndrome is that plasma aldosterone levels are reduced. "Asam boi" has been widely used and consumed by the Singapore and Malaysian population. It is usually taken with local fruits like guava, mango, and star fruit. "Asam boi" is richly flavoured with sweetener, preservatives and contains glycyrrhizic acid. Prolonged ingestion of substances containing glycyrrhizic acid is a well-known cause of exogenously-induced apparent hypermineralocorticoidism[3,4].

The major action of this compound is to inhibit the enzyme 11-beta-hydroxysteroid dehydrogenase (11-βHSD), thereby allowing cortisol to act as the major endogenous mineralocorticoid. 11-βHSD promotes the conversion of cortisol to cortisone, and one form of this enzyme (11-βHSD2) is largely restricted in the kidneys to the aldosterone-sensitive sites in the collecting tubules. This effect is physiologically important because cortisol binds as avidly as aldosterone to the mineralocorticoid receptor[3,5]. Therefore inhibition of 11-βHSD2 will cause an increase of cortisol restricted in the kidneys and invariably cause an apparent hypermineralocorticoidism.

CASE REPORT

A 31-year-old housewife first presented to our casualty department in March 2000 with a headache of one-week duration, which was associated with generalised weakness, lethargy and poor oral intake. She never had any similar problems before. She had just been checked by a general practitioner three months earlier for an upper respiratory tract infection, and was also told to be normotensive and normoglycaemic. Her previous visits to the same general practitioner were also uneventful. She is married with two children, with the youngest being two years old. Perinatal check-ups were also noted to be uneventful. She was on oral contraception since the last childbirth.

Physical examination revealed that she was hypertensive with blood pressure of 200/120 mmHg and pulse rate of 95/min. She was not cushingnoid. There was mild generalised weakness over all four limbs (power grade 4-5) with reduced reflexes. However, there were neither focal neurological deficits nor any long tract signs elicited. Examination of the fundus was normal. There was no radio-femoral delay and renal bruit was absent. The cardiovascular examination was also normal.

Investigations showed that she was hypokalaemic (serum potassium 2.8 mmol/L), with other blood levels being: serum sodium 148 mmol/L, urea

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Fig. 1 Asam boi, available as a preserved dried fruit or in powdered form, is easily obtainable in supermarkets.

7.6 mmol/L, random blood glucose 6.5 mmol/L and creatinine 109 umol/L. Blood gases showed pH 7.49, bicarbonate 30 mmol/L, pCO_2 25 mmHg, pO_2 98 mmHg, and oxygen saturation 98%. Liver function and thyroid function tests were normal. Chest radiographs and ultrasonography of the kidneys were also normal. Random serum cortisol was normal (420 nmol/L). Analysis of urinary catecholamines was normal; epinephrine, 28 µg/day (normal range 3-41 µg); norepinephrine, 124 µg/day (normal range 31-160 µg); and dopamine, 518 µg/day (normal range 280-1100 µg). However her plasma rennin activity and aldosterone (both done supine) were suppressed; with plasma renin activity of 0.096 ng/ml/hr (0.96-3.61 ng/ml/hr) and aldosterone of 160 pmol/L (320-2000 pmol/L).

She was then asked for further history and interestingly gave a history of taking and craving for powdered "asam boi" (Fig. 1), initially in smaller quantities but later up to at least three spoonfuls twice daily for the past six weeks (with guava fruit). She had stopped taking the "asam boi" since admission. She was started on a short course of irbesartan 150 mg mane (3 days). The blood pressure was easily controlled and even after stopping the drug, she remained normotensive. The hypokalaemia was also corrected and she was discharged well. She was seen in the clinic two weeks and three months later, and was found to be normotensive and normokalaemic.

DISCUSSION

The case reported showed that in an otherwise normal/normotensive person, glycyrrhizic acid could raise renal cortisol concentrations, resulting in hypokalaemia, hypertension, metabolic alkalosis and renin/aldosterone suppression. Based on these clinical and biochemical parameters, the diagnosis of exogenously-induced hypermineraloorticoidism can be made. If there is no significant history suggesting that exogenous substance containing glycyrrhizic acid is consumed, then the other possible differential diagnosis would be apparent mineralocorticoid excess (AME), Liddle's syndrome and deoxycorticosterone excess[4,6].

In Malaysia, liquorice is found in many traditional medications, as sweeteners and preservative agents in "asam boi", "jeruk buah" and other preserved fruits and in canned drinks[1,2]. "Asam boi" (in Malay) or "sng buay" (in Chinese) is popular among the Malaysian population and is directly consumed (packaged in small plastic packets) or made in powder form to be eaten with fruits. Some people developed cravings and will slowly increase the consumption of these products. "Asam boi" is the equivalent of liquorice in the European countries as it also contains glycyrrhizic acid. Mineralocorticoid activity after the consumption of the extract of Glycyrrhiza glabra root was first described more than 50 years ago in the Netherlands, where liquorice is popular. Even then, the diagnosis was almost overlooked. Today, liquorice-based products are widely used in confectioneries, health products, chewing tobacco, chewing gums, and in some alcoholic drinks.

Glycyrrhizic acid is hydrolysed into glycyrrhetenic acid, which is the active metabolite that inhibits renal 11-βHSD. This enzyme catalyses the inactivation of cortisol to cortisone[7]. Cortisol, unlike cortisone, has the same affinity as mineralocorticoids for the mineralocorticoid receptors of the cells in the cortical collecting ducts. Given this equal receptor affinity and the much higher circulating concentrations of cortisol compared with aldosterone, inhibition of 11-BHSD2 increases the kidney exposure to the mineralocorticoid effects of cortisol. A dose response study of glycyrrhizic acid in healthy volunteers showed that a significant fall in plasma potassium concentrations from 4.3 mmol/l to 3.5 mmol/l occurred at a dose of 800 mg or more a day. However, there were also a few reports of people using chewing gum, which only contains a small amount of glycyrrhizic acid developing hypermineralocorticoidism[8,9].

Why some people are susceptible to low doses of glycyrrhizic acid remains to be elucidated. Oestrogens may react with the mineralocorticoid receptor or inhibit 11-βHSD activity, which may explain why the female sex and the use of oral contraceptives can increase the susceptibility to glycyrrhizic acid. Interestingly, the patient reported

is a woman using oral contraceptive and this predisposed her to develop this condition[10]. In a few case reports, the effects of liquorice become visible after 3-10[11] days and are usually reversible after days to several weeks. In our case report, the effects were reversed rather early and easily within days.

In conclusion, exogenously-induced apparent hypermineralocorticoidism is under diagnosed and can be easily missed without careful consideration. However, the most important factor in the diagnosis is a good diet history on substances suspected to contain glycyrrhizic acid, especially in a previously-normotensive patient. This should be a routine aspect of investigating the causes of secondary hypertension.

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