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CASE REPORT

Pseudo Hyperaldosteronism Secondary to Herbal Medicine Use

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Abstract

Glycyrrhizic acid, better known as licorice, is commonly found in various food and cosmetic products. Excessive consumption is known to cause a syndrome of apparent mineralocorticoid excess or pseudo hyperaldosteronism. Patients typically present with resistant hypertension and hypokalemia mimicking symptoms of primary hyperaldosteronism however laboratory workup will reveal low or normal levels of plasma renin and aldosterone in the serum. While diagnosis of licorice toxicity is relatively straight forward, the challenge lies in determining the culpable agent. We report the case of a Chinese man who initially presented with resistant hypertension and hypokalemia refractory to therapy and was later diagnosed with pseudo hyperaldosteronism secondary to licorice toxicity.

Keywords: Pseudohyperaldosteronism, Licorice, Apparent mineralocorticoid excess, Herbal medicine

1. Introduction

Licorice is a commonly used flavoring agent in food and health products, including herbal medicines. Glycyrrhizic acid is the principle active ingredient in licorice extract and was approved by the United States Food and Drug Administration for widespread use in 1985.[1] Studies, including those performed by the World Health Organization, have shown a wide range of therapeutic usage by virtue of its anti-cancer, anti-inflammatory, anti-oxidation, anti-viral, and anti-bacterial properties.[2] It is not without consequence. Excessive consumption can lead to hyper mineralocorticoidism via the inhibition of 11 beta-hydroxysteroid dehydrogenase (11 beta- HSD) by glycyrrhetic acid, a metabolite of glycyrrhizic acid. 11 beta-HSD converts cortisol to cortisone, inactivating its mineralocorticoid properties since cortisone cannot bind to the mineralocorticoid receptors within the renal tubules. The inhibition of 11 beta-HSD prevents cortisol conversion, leading to cortisol binding to the aldosterone receptors and producing the aldosterone-like effect. While the inhibitory effect of 11 beta-HSD is reversible, the body's compensatory mechanisms may last several months before resolving. We report the case of a Chinese man who initially presented with resistant hypertension and hypokalemia refractory to therapy and was later diagnosed with pseudo hyperaldosteronism secondary to licorice toxicity.

2. Case presentation

A 56-year-old Chinese man with a known history of hypertension was sent to the emergency department by his primary care physician due to profound hypokalemia of 2.6 mEq/L (ref. 3.5 to 5.2 mEq/L) during outpatient workup. The patient endorsed 10 days of dizziness and weakness to the point where he had difficulty standing up, which prompted him

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to go to the doctor. Review of systems were negative for chest pain, palpitations, muscle aches, shortness of breath, cough, vomiting, diarrhea, or weight change. The patient had no allergies and denied both tobacco and alcohol use. His family history was unremarkable. The patient was diagnosed with hypertension 10 years ago however over the last year, his PCP changed his anti-hypertensives multiple times due to poor control despite complete medication compliance. His current medication regimen included hydrochlorothiazide (HCTZ), losartan, labetalol and nifedipine.

In the ED, the patient's vital signs revealed blood pressure of 170/100, heart rate of 90, and respiratory rate of 22. The patient was afebrile. On examination, he was resting comfortably in bed in no acute distress. Heart and lung examination was unremarkable. The abdomen was soft, non-tender, and non-distended. No organomegaly was appreciated. Significant laboratory results were as follows: potassium of 2.3 mEq/L (ref. 3.5 to 5.2 mEq/L), bicarbonate of 32 mEq/L (ref. 22–29 mEq/L) and creatinine of 1.4 mg/dl (ref. 0.7–1.2 mg/dL). EKG showed sinus rhythm. On admission, the patient's diuretic, and anti-hypertensive medications (hydrochlorothiazide and losartan) were held as they were a potential contributor to the witnessed hypokalemia and acute kidney injury. The spot urinary potassium level was 45 mmol/L (ref. 20 mMol/L), and the calculated trans-tubular potassium gradient was reflective of renal potassium wasting. Primary hyperaldosteronism was suspected due to the triad of hypertension, hypokalemia, and alkalosis, and hence plasma renin and aldosterone investigations were ordered. Plasma renin was 2.1 ng/dl (ref. 0.7–3.3 ng/dL), whereas plasma aldosterone level was 15 ng/dl (ref. < 15 ng/dl). The aldosterone to renin ratio was less than 20:1, ruling out primary hyperaldosteronism. The 8 am cortisol level was also normal. Normal levels of creatine phosphokinase, thyroid stimulating hormone and plasma metanephrine, along with a normal renal artery doppler study ruled out secondary causes of hypertension.

Upon further investigation, the patient's wife revealed he had been taking Niu Huang Jie Du Pian, a Chinese herbal medicine, for many years but over the past year had increased usage due to throat aches. One of the main ingredients of this herbal medicine was licorice root, a notorious cause of pseudo hyperaldosteronism. Over the following days, the patient's blood pressure was managed with medication and potassium levels were repleted. On days 4 and 5 of hospitalization, the patient's creatinine and potassium levels normalized, and his blood pressure stabilized at 140/90. Upon discharge, both the patient and his wife were counseled extensively on discontinuing the herbal medicine due to its interference with mineralocorticoid levels in the body. Spironolactone was added to his current list of medications due to its antihypertensive and potassium sparing effect.

3. Discussion

Despite its ubiquity, licorice remains an uncommon cause of apparent mineralocorticoid excess or pseudo hyperaldosteronism. Chronic ingestion of licorice or licorice-like compounds induces a syndrome with similar findings to that seen in primary hyperaldosteronism, presenting with hypertension, hypokalemia, and metabolic alkalosis. These metabolic abnormalities, in turn, lead to low plasma renin activity via a negative feedback mechanism. However, a low plasma aldosterone concentration makes licorice toxicity unique.[3] Symptoms of licorice-induced mineralocorticoid excess may also mimic genetic conditions like Liddle's syndrome, which is characterized by a defect in the epithelial sodium channel resulting in increased sodium absorption and potassium wasting.[4] Risk factors for pseudo hyperaldosteronism include female gender, old age, hypertension, hypokalemia due to diarrhea or diuretic therapy, and chronic inflammatory conditions.

These clinical manifestations are attributable to glycyrrhizic acid and its inhibition 11 beta-HSD, thus preventing the conversion of cortisol to its inactive form, cortisone. This leads to the binding of cortisol in the renal tubules and the activation of its hypermineralocorticoid effect.

When patients present with symptoms of mineralocorticoid excess, differential diagnoses should include licorice-induced apparent mineralocorticoid excess (AME), primary hyperaldosteronism, adrenal adenoma, and renal artery stenosis. Emphasis should be placed on careful history of patients' diet and use of supplements. Physicians should inquire about licorice consumption when coming across patients with unexplained hypertension, peripheral edema, or hypokalemia. Excess of mineralocorticoid activity must initially be determined by the plasma renin activity and aldosterone levels. Measuring cortisol levels and performing a dexamethasone suppression test may also help in ruling out other conditions causing corticosteroid excess. Measuring the spot urinary potassium levels may also be of clinical significance in confirming diagnosis.

The signs and symptoms of licorice induced pseudo hyperaldosteronism can be categorized into: (A) Symptoms linked to salt and water retention i.e.,

edema and hypertension or (B) Symptoms linked with serum potassium depletion i.e., asthenia, paralysis, and myopathy.[5]

It is not possible to determine the minimum amount of glycyzzrhizic acid to induce these symptoms just based on the nature of individual variations in susceptibility. In most countries, a daily intake of no more than 1–10 mg glycyrrhizic acid/person is recommended.[6] With that in mind, it is difficult to regulate the intake of glycyzzrhizic acid, especially in herbal medicines that have been brought from overseas or have not been FDA approved, such as was the case in our patient. As a provider, especially if working with diverse and multicultural patient populations, it is important to educate patients on the risks of non-FDA approved medications or over-the-counter supplements in order to avoid adverse side effects. Licorice-induced mineralocorticoid excess is usually reversible following cessation of intake. The expected recovery time is often a few days (typically less than a week). Physicians should consider admitting patients with any of the following findings: severe electrolyte abnormalities, symptomatic hypokalemia with ECG changes, severe or symptomatic hypertension, progressive weakness or paralysis, rhabdomyolysis, and pulmonary edema. Endocrine and toxicology consultations have also proven to be helpful in the management of the condition. The urgency of potassium replacement therapy depends on the severity of hypokalemia, associated comorbidities, and the rate of decline of serum potassium. Oral potassium supplements are recommended to treat hypokalemia.[3] Spironolactone and eplerenone therapy may also play a role in treatment due to their aldosterone antagonist effects.[7]

4. Conclusion

The use of licorice as a part of different food and herbal products is very common. Pseudo hyperaldosteronism is a rare side effect of licorice intake in which patients can present with refractory hypertension, hypokalemia, and metabolic alkalosis. Biochemical workup will reveal a low or low-normal renin and aldosterone level with a normal plasma cortisol level. Careful history taking and strong cultural competency can be essential when investigating if licorice is a constituent of the patient's dietary intake. Removal of the offending agent from their diet will usually help in controlling blood pressure and bringing the potassium level to normal range. Anti-hypertensive medication and potassium-sparing diuretics can also be used as part of treatment.

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Conflcits of interest

The authors declare no conflict of interest.

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