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Acute Renal Failure After Licorice Ingestion: A Case Report

Research Article

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Abstract: A 39-year-old female presented to the nephrology clinic emergency department with a complaint of muscle weakness and stomach pain. A detailed personal history revealed ingestion of 50-100 g herbal products which contained licorice, every day for 8 weeks to treat sterility. The herbal product was studied and determined to contain 'licorice' containing glycyrrhizic acid. Licorice (a plant which contains glycyrrhizic acid) induced hypokalemia which usually has a mild progression. However, it may cause critical failure in physical action by means of weakness followed by paralysis and may cause rhabdomyolysis, acute renal failure and hyperaldosteronism. This report presents the first case with acute renal failure due to licorice consumption from Serbia. In addition, the report aims to emphasize the importance of obtaining the detailed personal history of a patient for precise diagnosis.

Keywords: *Licorice • Hypokalemic myopathy • Renal damage • Hyperaldosteronism*

1. Introduction

Weakness is encountered in a number of medical and psychiatric disorders but is highly a non-specific symptom. Therefore, evaluation and differential diagnosis of weakness in emergency room is often difficult and time consuming. Hypokalemia is one of the electrolyte problems that can lead to weakness. When hypokalemia is determined, underlying causes should be investigated. Many herbal medications are used to treat diseases but while they are often efficacious, their safety is rarely considered by physicians or users [1,2]. Ingestion of Glycyrrhizic acid, which is the active component in licorice, causes a metabolic syndrome mimicking primary hyperaldosteronism. Chronic intoxication with glycyrrhizic acid may cause hypertension, metabolic alkalosis and hypokalemia. Licorice-induced hypokalemia usually has a mild progression. However, it may cause a critical failure in physical action by means of weakness followed by paralysis and may cause rhabdomyolysis, acute renal failure and hyperaldosteronism [3,4]. Generally, the onset and severity of the symptoms depend on the dose and duration of licorice intake, as well as individual susceptibility [5].

2. Case Presentation

A 39-year-old Serbian female presented to the nephrology clinic the emergency department with the complaint of weakness and stomach pain. The patient complained of difficulty moving her extremities. During previous weeks she felt pain and cramping in the legs. Two days before the hospitalization she started to have headaches, nausea and stomach pains, with persistent general weakness.

Upon physical examination, her blood pressure was 140/80 mmHg, heart rate 86 beat/min, respiratory rate 18/min, and body temperature 37.6°C. The patient was cooperative, and oriented. There was generalized weakness, without paralysis in over all four limbs (in

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all limbs or in more areas including all four limbs). There was no sensory and motor deficit. Systemic and neurologic examinations were normal.

The results of the laboratory evaluation were as follows: potassium (K^+) 1.6 mEq/L and sodium (Na^+) 142 mEq/L, urea 12.7 mmol/l, creatinine 349 mmol/l, blood glucose 6.11mmol/l and total creatine kinase concentration of 4,500 U/L, plasma aldosterone activity of 1.11 ng/dL (0.08 nmol/L), and a mean plasma renin activity of 0.15 ng/mL/h (0.11 $L^{-1}h^{-1}$). Blood gases showed pH 7.4, bicarbonate 24 mmol/L, pCO_2 31.3 mmHg, pO_2 95 mmHg and oxygen saturation 98%. Biochemical analyses of urine and thyroid function tests were normal, as was hemogram. There was specific finding typical of hypokalemia at electrocardiogram. Adrenal magnetic resonance imaging (MRI) did not confirm the diagnosis adenoma. MRI and MRI angiography were normal.

While taking medical history the patient stated that she had been trying to treat sterility and that during the previous year she had three unsuccessful attempts of in vitro fertilization. She was then asked for further history, it was recorded that about 4 months ago, the patient started using an over-the-counter herbal extract product to treat sterility. The patient was asked to bring a sample of the product and refrain from using it. The herbal product was studied and determined to contain 'licorice' containing glycyrrhizic acid. Apart from licorice geranium, Melissa and Salvia officinalis (is this a last name or does it mean officials) were also found.

During hospitalization period, initial therapy included 10 mmol of potassium chloride (7.4% KCL) per hour given by the intravenous route and potassium sparing diuretic, spironolactone 100mg per day. Within four days, serum levels of potassium normalized and all clinical symptoms improved. The values of urea and creatinine were normalized after 10 days. The patient was discharged with recommendations of taking 1 tablet of oral potassium and spironolactone 100mg per day. The serum K^+ level was normal after one week when she applied to the endocrinology outpatient clinic and she was asymptomatic. In the follow-up visit after 2 months, the serum potassium level, BUN and creatinine of the patient were completely normalized and the patient was asymptomatic.

3. Discussion

Licorice as a dry extract and tincture is often used in conjunction with other plants in order to achieve synergic effects and/or to mask bitter taste due to its pronounced sweetness. Licorice-induced hypokalemia is a rare condition; the most common symptom is generalized muscle weakness. The mechanism of this effect relates to glycyrrhizic acid in licorice roots being hydrolyzed to glycyrrhetenic acid which is an inhibitor of renal 11-hydroxysteroid dehydrogenase. This enzyme catalyzes the inactivation of cortisol to cortisone. Cortisol accumulates in the kidney and stimulates the aldosterone receptors in cells of the cortical collecting duct thus increasing Na^+ reabsorption [3,4,6]. Licorice-induced pseudoaldosteronism also has been reported [7]. Therefore, concentrations of cortisol may increase. The mineralocorticoid stimulation by licorice is reversible, usually recovering within days, but may be sustained for several weeks according to amount taken and individual susceptibility [8,9]. Metabolic studies revealed that licorice caused the suppression of two enzyme systems, but at different rates: 11-beta-hydroxysteroid dehydrogenase (which normally converts cortisol to cortisone in the glucocorticoid pathway), and the renin-aldosterone system.

In our patient, when obtaining the initial history, no history of licorice was recorded. The patient did not have vomiting, diarrhea, sweating and denied using drugs, including diuretics, alcohol, herbal medication, and laxatives. She had generalized muscle weakness. In laboratory evaluations, hypokalemia was determined. There was no other pathology. When the patient was asked about any drug and substance use for the second time, she said that he had been using a over-the-counter herbal product which he bought in order to sterility. This is the first case of hypokalemia related to licorice consumption from Serbia. Thus, we could not expect or guess the content of the product. Still, she was asked to bring a sample of the product and quit using it. We determined that the active compound causing hypokalemia was Glycyrrhizic acid but were not able to determine its amount by analysis due to lack of technical support. In Serbia, the herbal products or supplementary food are not licensed by Ministry of Health, and the amounts of active ingredients in those products are not under control. This product has not been licensed by the Ministry of Health; its content is defined, but the amount of active ingredients is not listed nor is standardized. The product, as written on its directions and instructions, can be bought and used by anyone, up to 3 times a day, and no precautions or limitations are noted and neither the name of plants nor their quantities. So we were not able to identify or tell the quantity of licorice or Glycyrrhizic acid in the product.

It is already known that licorice consumption may cause undesirable mineralocorticoid-like side effects including hypokalemia. Similar symptoms and findings are also seen in Cushing's syndrome including ectopic ACTH syndrome and genetic diseases such

as congenital adrenal hyperplasia, mineralocorticoid receptor abnormalities, Liddle syndrome, and the syndrome of apparent mineralocorticoid excess [10,11], although the possibility of these conditions could also be excluded because the patient was too old for congenital and genetic causes and had not experienced a similar disorder previously, in addition, her condition improved rapidly after the withdrawal of licorice containing tea and replacement of K^+. Adrenal magnetic resonance imaging (MRI) did not confirm the diagnosis adenoma. MRI and MRI angiography were normal.

A patient with a history of anorexia nervosa developed licorice-induced hypokalemic myopathy. With potassium replacement, high CPK blood level and myopathic signs returned to normal. However, the patient manifested persistent hypokalemia and impaired renal function to concentrate and acidify the urine. Renal biopsy demonstrated intense degeneration and vacuolation of tubules with a normal glomerulus which was consistent with hypokalemic nephropathy. Prolonged hypokalemia in anorexia nervosa is sometimes attributed to surreptitious purging or taking diuretics, but it is necessary to check the urine pH, the urine-specific gravity, and the urine potassium level in order to find underlying renal damage even after hypokalemic myopathy is treated successfully [12].

Yamamoto T et al showed clinical characteristics of five elderly patients with severe hypokalemia induced by glycyrrhizin derivatives. All patients developed progressive muscle weakness with elevated creatinine phosphokinase. Three of the patients had received Chinese medicine which contained licorice, one received glycyrrhizin and the other one had received both. They diagnosed these cases as pseudoaldosteronism induced by glycyrrhizin [13].

It is interesting to note that hypokalemic effect of licorice can prevent hyperkalemia in pre-dialysis and dialysis patients. In patients on hemodialysis, Farese *et al.* report that inhibition of the enzyme 11β-hydroxysteroid dehydrogenase type 2 by glycyrrhetinic acid, the active compound of licorice, reduces serum potassium concentration and the frequency of hyperkalemia, possibly by enhancing intestinal potassium loss. This finding could be an important tool to maintain predialysis $[K^+]$ within safe limits in dialysis patients at risk for hyperkalemic arrhythmias [14].

A large number of in vivo and in vitro experiments and clinical studies have cast light on the possible effects of botanical products and phytochemicals on the many enzymes and transporters involved in gastrointestinal drug absorption. The most widely sold herbal medicinal products; include liquorice, garlic, ginger, ginkgo, green tea, St. John's wort, saw palmetto, turmeric, valerian, milk thistle and echinacea. Sound knowledge of the mechanisms of herb-drug interactions is essential for clinical risk assessment, in turn vital to healthcare practitioners in their efforts to reduce risk and ensure that taking herbal medicines is as safe as possible [15-19].

4. Conclusion

In this case, we want to draw attention to uncontrolled use of herbal drugs, especially of non-licensed products, as well as the significance of adequate taking of pharmacological history. In patients admitted with muscle weakness, hypokalemia and acute renal failure, particularly when there is a clinical picture mimicking primary hyperaldosteronism, the use of such substances should be kept in mind.

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