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### Liquorice-induced severe hypokalemic rhabdomyolysis with Gitelman syndrome and diabetes: A case report

Yang LY *et al.*Liquorice-induced hypokalemia with Gitelman syndrome

Lu-Yang Yang, Jin-Hua Yin, Jing Yang, Yi Ren, Chen-Yu Xiang, Chun-Yan Wang

**Lu-Yang Yang, Jing Yang, Chen-Yu Xiang, Chun-Yan Wang,** Department of Endocrinology, First Hospital of Shanxi Medical University, Taiyuan 030001, Shanxi Province, China

**Jin-Hua Yin, Yi Ren,** Department of Endocrinology, First Hospital of Shanxi Medical University, Shanxi Medical University, Taiyuan 030001, Shanxi Province, China

**ORCID number:** Lu-Yang Yang (0000-0002-1637-4002); Jin-Hua Yin (0000-0002-5495-995X); Jing Yang (0000-0001-8855-6254); Yi Ren (0000-0002-1163-3642); Chen-Yu Xiang (0000-0002-4555-3501); Chun-Yan Wang ([0000-0003-2101-7461](http://orcid.org/0000-0003-2101-7461)).

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**Corresponding author:** **Jin-Hua Yin, MD, Assistant Professor,** Department of Endocrinology, First Hospital of Shanxi Medical University, Shanxi Medical University, No. 85, South Jiefang Road, Taiyuan 030001, Shanxi Province, China. yinjjhh@163.com

**Telephone:** +86-351-4639756

**Fax:** +86-351-4639758

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### Abstract

***BACKGROUND***

Licorice-induced severe hypokalemic rhabdomyolysis is clinically rare. Gitelman syndrome (GS) is the most common inherited renal tubular disease, while diabetes is one of the most prevalent diseases in the world. Recently, some studies have found that GS patients had higher diabetic morbidity. However, the coexistence of these three diseases has yet to be reported.

***CASE SUMMARY***

We report the case of a 62-year-old Chinese man who was admitted with weakness in the extremities, muscle pain, and dark-colored urine. He had consumed liquorice water daily for seven days prior to admission. The laboratory tests revealed a serum potassium level of 1.84 mmol/L, magnesium 0.68 mmol/L, creatinine phosphokinase (CK) 10117 IU/L, and marked hemoglobinuria. Fractional chloride excretion and fractional magnesium excretion were increased. Plasma renin activity and aldosterone concentration were within the normal ranges. Sequence analysis of the *SLC12A3* gene revealed that he had compound heterozygous mutations. The diagnosis of liquorice-induced severe hypokalemic rhabdomyolysis with GS and diabetes was thus genetically confirmed. Serum potassium and CK quickly improved with potassium replacement therapy, hydration, and discontinuation of liquorice ingestion. Upon follow-up at 3 mo, the levels of CK, myoglobin, and potassium remained normal, and magnesium was above 0.6 mmol/L.

***CONCLUSION***

This case emphasizes that liquorice consumption and GS should be considered causes of hypokalemia and that the diabetic status of GS patients should be noted in the clinic.

### Key words: Hypokalemia; Rhabdomyolysis; Liquorice; Gitelman syndrome; Diabetes; Case report

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### Core tip: This is the first reported case of liquorice-induced severe hypokalemic rhabdomyolysis with Gitelman syndrome and diabetes.

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### INTRODUCTION

Rhabdomyolysis is a relatively rare but potentially lethal condition. Hypokalemia is a common electrolyte disorder and an established cause of rhabdomyolysis[[1](#references1)]. Frequent causes of hypokalemia are intestinal and urinary potassium loss through diarrhea or the use of diuretics. Liquorice-induced pseudo-hyperaldosteronism and Gitelman syndrome (GS) are well known but rare causes of hypokalemia. GS is an autosomal recessive disorder, which was first described by Gitelman, Graham, and Welt[[2]](#reference2) in 1966.Symptoms of liquorice-induced hypokalemia and GS are usually mild. However, GS combined with liquorice-induced pseudo-hyperaldosteronism may cause weakness followed by paralysis, and even rhabdomyolysis or ventricular fibrillation, which can be deadly if left untreated. Furthermore, hypokalemia and hypomagnesemia in GS patients may cause abnormal glucose metabolism[[3]](#reference3). Here, we report the first case of liquorice-induced severe hypokalemic rhabdomyolysis with GS and diabetes.

### CASE PRESENTATION

***Chief complaints***

A 62-year-old Chinese man complained of intermittent weakness in the extremities (particularly the calves), muscle pain, and walking difficulty.

***History of present illness***

The patient’s weakness in the extremities started 30 years ago, but spontaneously recovered in one week after each instance. Twenty years ago, he was admitted to the hospital because of difficulty walking upstairs and a diagnosis of hypokalemia was made. The patient’s symptoms quickly improved with potassium replacement therapy. Despite any medicine treatment, his serum potassium levels ranged from 2.8 to 3.1 mmol/L in the past 10 years. The patient presented with muscle pain and walking difficulty 15 d ago. He took potassium chloride sustained-release tablets 1.5 g per day for 5 d. Furthermore, he described dark-colored urine for 3 days. Thus, the patient was sent to the hospital for further evaluation. There was no history of diarrhea or vomiting, signs of infection or alcohol intoxication. He denied ever taking any statins. Upon further questioning, a detailed history revealed that he had consumed liquorice water daily for 7 days preceding admission.

***History of past illness***

The past medical history revealed only type 2 diabetes mellitus since the age of 52. For that reason, he was treated with 10 mg of dapagliflozin and 25 mg of alogliptin daily.

***Personal and family history***

The patient denied tobacco, alcohol, and illicit drug use. His family history was unremarkable, and there were no similar cases in his family.

***Physical examination upon admission***

On admission, the patient’s body weight was 60.0 kg, and his height was 168.2 cm. His blood pressure was 128/92 mmHg and his pulse rate was 86 beats/min. There was generalized paralysis in all four limbs (power grade 3/5). There was no sensory deficit. The examination of the thyroid and other systems was unremarkable.

***Laboratory examinations***

[Table 1](#table) shows laboratory data of the patient. Serum potassium level was 1.84 mmol/L. Serum magnesium was 0.68 mmol/L. Creatinine phosphokinase (CK) was 10117 IU/L, and he had marked hemoglobinuria. Fractional chloride excretion and fractional magnesium excretion were calculated as 1.9% and 4.4%, respectively. Urinary calcium/creatinine ratio was calculated as 0.24. Plasma renin activity and aldosterone concentration were within the normal ranges. Serum alkaline phosphatase and parathormone levels were normal. According to the laboratory tests, the level of CK at presentation was 30 times more than the upper limit of the normal range. Furthermore, the level of serum myoglobin (MYO) was significantly increased. Consequently, rhabdomyolysis was diagnosed.

Rhabdomyolysis can have various causes, such as metabolic disease, direct trauma to muscle, muscle necrosis due to ischemia, muscle inflammation, or exposure to drugs and toxins[[2]](#reference2). Recent studies suggest that liquorice can induce hypokalemia and muscle weakness and can even lead to life-threatening rhabdomyolysis[[4]](#reference4). However, considering the medical history, the patient had a history of hypokalemia for 30 years. Moreover, considering the results of the laboratory tests including hypomagnesemia, normal plasma renin activity, and aldosterone concentration, the etiology of pre-existing hypokalemia should be considered. With informed consent, we investigated the *SLC12A3* gene of the patient. Sequence analysis of the *SLC12A3* gene of the patient revealed that he had compound heterozygous mutations. One missense mutation was a heterozygous G to A base pair substitution at position 1567 in exon 12, which caused an Ala to Thr substitution at position 523. A second missense mutation, a heterozygous G to A base pair substitution at position 2542 in exon 21, causing an Asp to Asn substitution at position 848, was also present ([Figure 1](#figure)).

***Imaging examinations***

The 12-lead electrocardiogram (ECG) demonstrated a sinus rhythm with inverted T-waves on leads V1-V6 and ST-depression on leads V4-V6, but no prolongation of the QTc interval and U waves. Abdominal sonography did not reveal renal stones or nephrocalcinosis. Peripheral neuropathy in both lower limbs was found by examining the electromyogram. Muscle biopsy was rejected by the patient.

### FINAL DIAGNOSIS

Liquorice-induced severe hypokalemic rhabdomyolysis with GS syndrome and diabetes.

### TREATMENT

The patient’s signs and symptoms improved with potassium replacement therapy (10 g of potassium chloride injection daily), hydration, and discontinuation of liquorice ingestion. His serum potassium was increased to normal within 5 days. Correspondingly, CK decreased to normal within 8 days. Moreover, the ECG returned to normal on the third hospital day. Five weeks later, the patient was started on antisterone (20 mg, po, bid) and potassium magnesium aspartate tablets (2 tablets, po, tid), following the *SLC12A3* gene results.

### OUTCOME AND FOLLOW-UP

Upon follow-up at 3 mo, the levels of CK, MYO, and potassium remained normal and magnesium was above 0.6 mmol/L.

### DISCUSSION

Liquorice is the root of *Glycyrrhiza glabra* and is mostly recognized as a flavoring agent. It has also been used in herbal medicine and even in anti-inflammatory, antiviral, antimicrobial, antioxidative, hepatoprotective, and cardioprotective properties[[5]](#reference5). Glycyrrhizic acid or its hydrolytic product, glycyrrhetinic acid, is found in liquorice extracts and has a well-known mineralcorticoid activity, inhibiting 11 beta-hydroxysteroid dehydrogenase type 2, the enzyme that converts cortisol to cortisone[[4]](#reference4). Glycyrrhizic acid can also directly bind to the mineralocorticoid receptor or suppress 5-β-reductase activity and can therefore slow down the hepatic metabolism of aldosterone, resulting in pseudo-hyperaldosteronism and suppression of plasma renin activity, which manifests as hypokalemia, hypertension, and metabolic alkalosis[[6]](#reference6). The onset and severity of the symptoms depend on the dose and duration of liquorice intake, as well as individual susceptibility[[7]](#reference7). GS is characterized by hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria, with secondary renin-angiotensin-aldosterone system (RAAS) activation and normal blood pressure[[8]](#reference8). With an incidence of 1 in 40000, GS is one of the prevalent autosomal recessive diseases[[9]](#reference9). The *SLC12A3* gene is located on chromosome 16 and comprises 26 exons. Liu *et al*[[10]](#reference10) analyzed the characteristics of the genotype and phenotype in 67 patients with GS. They found that compound heterozygous mutations were detected in 42 (62.7%) patients, 10 (14.9%) patients carried homozygous mutations, and 11 patients had only one heterozygous mutation. Of note, there were four patients who had three different mutations, while three unrelated (5.7%) families were found to have triple *SLC12A3* mutant alleles[[10]](#reference10). Mutations in the *SLC12A3* gene encoding the thiazide sensitive Na+Cl– cotransporter (NCCT) on the apical membrane of distal convoluted tubule cells are usually responsible for GS. Until now, more than 180 mutations in the *SLC12A3* gene have been identified in patients with GS[[11]](#reference11). Impaired NCCT function leads to decreased Na+ and Cl– reabsorption in the distal convoluted tubule. Secondary hyperaldosteronism results in renal potassium wasting[[12]](#reference12). Both mutations in this case have been previously reported[[13](#reference13)[,14](#reference14)]. Unfortunately, the patient’s father was not currently alive. Only his asymptomatic mother was alive; thus, his carrier status could not be ascertained. There were no other family members who underwent genetic testing. This is a deficiency of our case.

Based on the above metabolic pathways, the hypokalemia, rhabdomyolysis, increased cortisol, and normal RAAS level in our case can be explained. In the past 5 years, abnormal glucose metabolism and insulin secretion have been reported in GS patients[[11]](#reference11). Liu’s study indicated that compared with normal Chinese adults, GS patients had a higher diabetic morbidity[[10]](#reference15). Hypokalemia and hypomagnesemia were thought to be the main reasons for diabetes in GS patients. However, the exact mechanism has not been well understood until recently. The pancreatic release of insulin is controlled by ATP-sensitive potassium channels and L-type calcium channels on the β cell surface. Hypokalemia may prevent the closure of these channels and consequently prevent glucose-stimulated insulin secretion[[4]](#reference4). It is thought that chronic hypomagnesemia may induce altered cellular glucose transport, reduce pancreatic insulin secretion, increase defective post receptor insulin signaling, and alter insulin-insulin receptor interactions[[15]](#reference16). Furthermore, secondary RAAS activation may lead to insulin resistance[[16]](#reference17). However, a study[[3]](#reference3) in 2017 showed that glucose metabolism and insulin secretion were impaired in GS patients, but insulin sensitivity was comparable between GS patients and patients with type 2 diabetes mellitus. Therefore, further studies are required to address this question.

### CONCLUSION

In conclusion, hypokalemic rhabdomyolysis is often under-recognized and can be associated with life-threatening sequelae. Vigilance and prompt treatment are crucial to improve clinical outcomes. From this case, we would like to stress the importance for physicians to keep liquorice consumption and GS in mind as a cause for hypokalemia. We suggest that genetic analysis is advisable to determine whether the suspicion of GS is warranted. At the same time, the diabetic status of GS patients should be considered.

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Grade E (Poor): 0

**Table** **1 Laboratory investigations of the patient**

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Test value before treatments | Test value after treatments | Reference range |
| Potassium (mmol/L) | 1.841 | 4.05 | 3.5-5.5 |
| Sodium (mmol/L) | 144 | 138 | 137-147 |
| Chlorine (mmol/L) | 981 | 99 | 99-110 |
| Calcium (mmol/L) | 2.31  | 2.14 | 2.11-2.52 |
| Magnesium (mmol/L) | 0.681 | 0.78 | 0.75-1.02 |
| CK (U/L) | 101171 | 275 | 50-310 |
| Myoglobin (μg/L) | >41501 | 98.4 | 17.4-105.7 |
| HbA1c (%) | 7.03%1 | - | 4.8-5.9 % |
| 8 am cortisol (nmol/L) | 423.5 | - | 171-536 |
| 4 pm cortisol (nmol/L) | 183.7 | - | 64-327 |
| 0 am cortisol (nmol/L) | 279.1 | - | - |
| ACTH (pmol/L) | 4.76 | - | 1.6-13.9 |
| pH | 7.471 | 7.40 | 7.35-7.45 |
| HCO3- (mmol/L) | 321 | 24 | 21-26 |
| BE (mmol/L) | 7.11 | 2.4 | -3-3 |
| Urinary pH | 8.01 | 6.0 | 5-6 |
| Urinary sodium (mmol/24 h) | 2401 | - | 40-220 |
| Urinary potassium (mmol/24 h) | 1091 | - | 25-125 |
| Urinary chloride (mmol/24 h) | 2601 | - | 110-250 |
| Urinary calcium (mmol/24 h) | 2.01 | - | 2.5-7.5 |
| Urinary magnesium (mmol/24 h) | 4 | - | 3.0-4.5 |
| Urinary free cortisol (mmol/24 h) | 379.681 | - | 100-379 |
| FECl | 1.9%1 | - | - |
| FEMg | 4.4%1 | - | - |
| Urinary calcium/creatinine | 0.24 | - | - |

### 1Abnormal values. FECl: Fractional chloride excretion; FEMg: Fractional magnesium excretion; ACTH: Adrenocorticotropic hormone; CK: Creatinine phosphokinase; HbA1c: [Haemoglobin A1c](http://xueshu.baidu.com/s?wd=paperuri%3A%284bce0221e9c9c9ea9d845e81a788adf2%29&filter=sc_long_sign&sc_ks_para=q%3DUse%20of%20haemoglobin%20A1c%20%28HbA1c%29%20in%20the%20diagnosis%20of%20diabetes%20mellitus.%20The%20implementation%20of%20World%20Health%20Organisation%20%28WHO%29%20guidance%202011&sc_us=6521559194077252039&tn=SE_baiduxueshu_c1gjeupa&ie=utf-8).

A c.1567G>A, p.Ala523Thr



B c.2542G>A, p.Asp848Asn



**Figure 1 Partial electropherograms from exon 10 and exon 21 of the *SLC12A3* gene showing two heterozygous missense mutations in the patient.** A and B:One is from G to A at nucleotide position 1567 [NM\_000339, c.1567G>A; p.Ala523Thr] (A), and the other is from G to A at nucleotide position 2542 [NM\_000339, c.2542G>A; p.Asp523Asn] (B).