Dear Madam(s) or Sir(s),

Thank you for your refereeing of my manuscript (NO. 45842) "Liquorice-induced severe hypokalemia rhabdomyolysis with Gitelman syndrome and diabetes: A case report". The relevant regulations had been made in the original manuscript according to the comments of reviewers, and the major revised portions were highlighted in the updated version of the manuscript. We also responded point by point to each reviewer comments as listed below, along with a clear indication of the location of the revision.

To Review 1:

Good case presentation of hypokalemia rhabdomyolysis and referring details.

RE:

Thank you for your refereeing of my manuscript.

To Review 2:

1. Some language editing is needed. For example, in line 61, it should be "well known", not "wellknown".

I have revised the language "well known" in line 71.

Liquorice-induced pseudo-hyperaldosteronism and GS are **well known** but rare causes of hypokalemia.

2. Please include references in the Introduction section.

References 2 and 3 are added in the Introduction section just as follows.

GS is an autosomal recessive disorder, which was first described by Gitelman, Graham, and Welt in 1966[2].

Furthermore, hypokalemia and hypomagnesemia in GS patients may cause abnormal glucose metabolism[3].

3. Please also include some introduction knowledge of SLC12A3 and its mutations.

I have added some introduction knowledge of SLC12A3 and its mutations in line 181-188 as follows.

SLC12A3 gene is located in chromosome 16 and comprises 26 exons. Liu et al analyzed the characteristics of the genotype and phenotype in 67 patients with GS. They found compound heterozygous mutations were detected in 42 (62.7%) patients, 10 (14.9%) patients carried homozygous mutations, whereas 11 patients had only one heterozygous mutation. Of note, there were 4 patients who had 3 different mutations while 3 unrelated (5.7%) families were found with triple SLC12A3 mutant alleles.

4 The description of lab examinations contained too many parameters. Please use tables to indicate the values of those parameter so that others are easy to check. Please also indicate the parameters that are out of the normal ranges.

I have used a table to indicate the values of those parameters.

Parameters signed with "*" are about the abnormal values.

Parameters	Test value before treatments	Test value after treatments	Reference range
Potassium (mmol/L)	1.84*	4.05	3.5-5.5
Sodium (mmol/L)	144	138	137-147
Chlorine (mmol/L)	98*	99	99-110
Calcium (mmol/L)	2.31	2.14	2.11-2.52
Magnesium (mmol/L)	0.68*	0.78	0.75-1.02
CK (U/L)	10,117*	275	50-310
Myoglobin (μg/L)	＞4150*	98.4	17.4-105.7
HbA1c (%)	7.03%*	-	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	7.47*	7.40	7.35-7.45
HCO_3^- (mmol/L)	32*	24	21-26
BE (mmol/L)	7.1*	2.4	-3-3
Urinary pH	8.0*	6.0	5-6
Urinary sodium (mmol/24 h)	240*	-	40-220

Urinary potassium (mmol/24 h)	109*	-	25-125
Urinary chloride (mmol/24 h)	260*	-	110-250
Urinary calcium (mmol/24 h)	2.0*	-	2.5-7.5
Urinary magnesium (mmol/24 h)	4	-	3.0-4.5
Urinary free cortisol (mmol/24 h)	379.68*	-	100-379
FE_{Cl}	1.9%*	-	-
FE_{Mg}	4.4%*	-	-
Urinary calcium / creatinine	0.24	-	-

Table 1 Laboratory investigations of the patient. ACTH = Adrenocorticotropic Hormone.*abnormal values.

5.In addition to data shown in Figures 1 and 2, it would be very helpful to show the full panel of plasma parameters after the treatments.

I have used a table instead of Figures 1 and 2 to show the full panel of plasma parameters before and after the treatments. At the same time, I have revised the laboratory examinations as follows.

Laboratory examinations

Table 1 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 10,117 IU/L and a marked hemoglobinuria. FECl

and FEMg were calculated as 1.9% and 4.4%, respectively. Urinary calcium/creatinine ratio was calculated as 0.24.

6.The history of GS discovery should be moved to the introduction section.

I haved moved GS discovery to the introduction section in line 72-73.

Introduction

Rhabdomyolysis is a relatively rare but potentially lethal condition. Hypokalemia is a common electrolyte disorder and an established cause of rhabdomyolysis[1]. Frequent causes of hypokalemia are intestinal and urinary potassium loss through diarrhea or the use of diuretics. Liquorice-induced pseudo-hyperaldosteronism and GS are well known but rare causes of hypokalemia. **GS is an autosomal recessive disorder, which was first described by Gitelman, Graham, and Welt in 1966[2].** 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]. Here, we report the first case of liquorice-induced severe hypokalemia rhabdomyolysis with GS and diabetes.

Yours faithfully

Luyang Yang on behalf of the authors

Correspondence to: Jinhua Yin, MD, Assistant Professor, Department of Endocrinology, First Hospital of Shanxi Medical University, Shanxi Medical University, No. 85, South Jiefang Road, Taiyuan, Shanxi

Province030001, China. yinjjhh@163.com.

Telephone:+86-351-4639756

Fax:+86-351-4639758