

# World Journal of *Clinical Cases*

*World J Clin Cases* 2022 June 16; 10(17): 5518-5933



### MINIREVIEWS

- 5518** Occult hepatitis B — the result of the host immune response interaction with different genomic expressions of the virus  
*Gherlan GS*
- 5531** Pulmonary complications of portal hypertension: The overlooked decompensation  
*Craciun R, Mocan T, Procopet B, Nemes A, Tefas C, Sparchez M, Mocan LP, Sparchez Z*
- 5541** Ethical review of off-label drugs during the COVID-19 pandemic  
*Li QY, Lv Y, An ZY, Dai NN, Hong X, Zhang Y, Liang LJ*

### ORIGINAL ARTICLE

#### Case Control Study

- 5551** Gut peptide changes in patients with obstructive jaundice undergoing biliary drainage: A prospective case control study  
*Pavić T, Pelajić S, Blažević N, Kralj D, Milošević M, Mikolasevic I, Lerotic I, Hrabar D*

#### Retrospective Cohort Study

- 5566** Longitudinal assessment of liver stiffness by transient elastography for chronic hepatitis C patients  
*Mezina A, Krishnan A, Woreta TA, Rubenstein KB, Watson E, Chen PH, Rodriguez-Watson C*

#### Retrospective Study

- 5577** Clinical evaluation of prone position ventilation in the treatment of acute respiratory distress syndrome induced by sepsis  
*Xia WH, Yang CL, Chen Z, Ouyang CH, Ouyang GQ, Li QG*
- 5586** Three-dimensional arterial spin labeling and diffusion kurtosis imaging in evaluating perfusion and infarct area size in acute cerebral ischemia  
*Jiang YY, Zhong ZL, Zuo M*
- 5595** Intrathecal methotrexate in combination with systemic chemotherapy in glioblastoma patients with leptomeningeal dissemination: A retrospective analysis  
*Kang X, Chen F, Yang SB, Wang YL, Qian ZH, Li Y, Lin H, Li P, Peng YC, Wang XM, Li WB*
- 5606** Hepatic epithelioid hemangioendothelioma: Clinical characteristics, diagnosis, treatment, and prognosis  
*Zhao M, Yin F*
- 5620** Difference between type 2 gastroesophageal varices and isolated fundic varices in clinical profiles and portosystemic collaterals  
*Song YH, Xiang HY, Si KK, Wang ZH, Zhang Y, Liu C, Xu KS, Li X*

- 5634** Assessment of incidental focal colorectal uptake by analysis of fluorine-18 fluorodeoxyglucose positron emission tomography parameters

*Lee H, Hwang KH, Kwon KA*

### Observational Study

- 5646** "Zero ischemia" laparoscopic partial nephrectomy by high-power GreenLight laser enucleation for renal carcinoma: A single-center experience

*Zhang XM, Xu JD, Lv JM, Pan XW, Cao JW, Chu J, Cui XG*

- 5655** High Eckardt score and previous treatment were associated with poor postperoral endoscopic myotomy pain control: A retrospective study

*Chen WN, Xu YL, Zhang XG*

- 5667** Higher volume growth rate is associated with development of worrisome features in patients with branch duct-intraductal papillary mucinous neoplasms

*Innocenti T, Danti G, Lynch EN, Dragoni G, Gottin M, Fedeli F, Palatresi D, Biagini MR, Milani S, Miele V, Galli A*

### Prospective Study

- 5680** Application of a new anatomic hook-rod-pedicle screw system in young patients with lumbar spondylolysis: A pilot study

*Li DM, Li YC, Jiang W, Peng BG*

### META-ANALYSIS

- 5690** Systematic review of Yougui pills combined with levothyroxine sodium in the treatment of hypothyroidism

*Liu XP, Zhou YN, Tan CE*

### CASE REPORT

- 5702** Allogeneic stem cell transplantation-A curative treatment for paroxysmal nocturnal hemoglobinuria with PIGT mutation: A case report

*Schenone L, Notarantonio AB, Latger-Cannard V, Fremeaux-Bacchi V, De Carvalho-Bittencourt M, Rubio MT, Muller M, D'Aveni M*

- 5708** Gray zone lymphoma effectively treated with cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab chemotherapy: A case report

*Hojo N, Nagasaki M, Mihara Y*

- 5717** Diagnosis of spontaneous isolated superior mesenteric artery dissection with ultrasound: A case report

*Zhang Y, Zhou JY, Liu J, Bai C*

- 5723** Adrenocorticotrophic hormone-secreting pancreatic neuroendocrine carcinoma with multiple organ infections and widespread thrombosis: A case report

*Yoshihara A, Nishihama K, Inoue C, Okano Y, Eguchi K, Tanaka S, Maki K, Fridman D'Alessandro V, Takeshita A, Yasuma T, Uemura M, Suzuki T, Gabazza EC, Yano Y*

- 5732** Management of the palato-radicular groove with a periodontal regenerative procedure and prosthodontic treatment: A case report

*Ling DH, Shi WP, Wang YH, Lai DP, Zhang YZ*

- 5741** Combined thoracic paravertebral block and interscalene brachial plexus block for modified radical mastectomy: A case report  
*Hu ZT, Sun G, Wang ST, Li K*
- 5748** Chondromyxoid fibroma of the cervical spine: A case report  
*Li C, Li S, Hu W*
- 5756** Preterm neonate with a large congenital hemangioma on maxillofacial site causing thrombocytopenia and heart failure: A case report  
*Ren N, Jin CS, Zhao XQ, Gao WH, Gao YX, Wang Y, Zhang YF*
- 5764** Simultaneous multiple primary malignancies diagnosed by endoscopic ultrasound-guided fine-needle aspiration: A case report  
*Yang J, Zeng Y, Zhang JW*
- 5770** Neuroendocrine tumour of the descending part of the duodenum complicated with schwannoma: A case report  
*Zhang L, Zhang C, Feng SY, Ma PP, Zhang S, Wang QQ*
- 5776** Massive hemothorax following internal jugular vein catheterization under ultrasound guidance: A case report  
*Kang H, Cho SY, Suk EH, Ju W, Choi JY*
- 5783** Unilateral adrenal tuberculosis whose computed tomography imaging characteristics mimic a malignant tumor: A case report  
*Liu H, Tang TJ, An ZM, Yu YR*
- 5789** Modified membrane fixation technique in a severe continuous horizontal bone defect: A case report  
*Wang LH, Ruan Y, Zhao WY, Chen JP, Yang F*
- 5798** Surgical repair of an emergent giant hepatic aneurysm with an abdominal aortic dissection: A case report  
*Wen X, Yao ZY, Zhang Q, Wei W, Chen XY, Huang B*
- 5805** Heterotopic ossification beneath the upper abdominal incision after radical gastrectomy: Two case reports  
*Zhang X, Xia PT, Ma YC, Dai Y, Wang YL*
- 5810** Non-alcoholic Wernicke encephalopathy in an esophageal cancer patient receiving radiotherapy: A case report  
*Zhang Y, Wang L, Jiang J, Chen WY*
- 5816** New approach for the treatment of vertical root fracture of teeth: A case report and review of literature  
*Zhong X, Yan P, Fan W*
- 5825** Ultrasound-guided microwave ablation as a palliative treatment for mycosis fungoides eyelid involvement: A case report  
*Chen YW, Yang HZ, Zhao SS, Zhang Z, Chen ZM, Feng HH, An MH, Wang KK, Duan R, Chen BD*
- 5833** Pulp revascularization on an adult mandibular right second premolar: A case report  
*Yang YQ, Wu BL, Zeng JK, Jiang C, Chen M*

- 5841** Barrett's esophagus in a patient with bulimia nervosa: A case report  
*Gouda A, El-Kassas M*
- 5846** Spontaneous gallbladder perforation and colon fistula in hypertriglyceridemia-related severe acute pancreatitis: A case report  
*Wang QP, Chen YJ, Sun MX, Dai JY, Cao J, Xu Q, Zhang GN, Zhang SY*
- 5854** Beware of gastric tube in esophagectomy after gastric radiotherapy: A case report  
*Yurttas C, Wichmann D, Gani C, Bongers MN, Singer S, Thiel C, Koenigsrainer A, Thiel K*
- 5861** Transition from minimal change disease to focal segmental glomerulosclerosis related to occupational exposure: A case report  
*Tang L, Cai Z, Wang SX, Zhao WJ*
- 5869** Lung adenocarcinoma metastasis to paranasal sinus: A case report  
*Li WJ, Xue HX, You JQ, Chao CJ*
- 5877** Follicular lymphoma presenting like marginal zone lymphoma: A case report  
*Peng HY, Xiu YJ, Chen WH, Gu QL, Du X*
- 5884** Primary renal small cell carcinoma: A case report  
*Xie K, Li XY, Liao BJ, Wu SC, Chen WM*
- 5893** Gitelman syndrome: A case report  
*Chen SY, Jie N*
- 5899** High-frame-rate contrast-enhanced ultrasound findings of liver metastasis of duodenal gastrointestinal stromal tumor: A case report and literature review  
*Chen JH, Huang Y*
- 5910** Tumor-like disorder of the brachial plexus region in a patient with hemophilia: A case report  
*Guo EQ, Yang XD, Lu HR*
- 5916** Response to dacomitinib in advanced non-small-cell lung cancer harboring the rare delE709\_T710insD mutation: A case report  
*Xu F, Xia ML, Pan HY, Pan JW, Shen YH*
- 5923** Loss of human epidermal receptor-2 in human epidermal receptor-2+ breast cancer after neoadjuvant treatment: A case report  
*Yu J, Li NL*

**LETTER TO THE EDITOR**

- 5929** Repetitive transcranial magnetic stimulation for post-traumatic stress disorder: Lights and shadows  
*Concerto C, Lanza G, Fisticaro F, Pennisi M, Rodolico A, Torrisi G, Bella R, Aguglia E*

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## Gitelman syndrome: A case report

Shi-Yuan Chen, Ning Jie

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### Abstract

#### BACKGROUND

Gitelman syndrome (GS) is an autosomal recessive salt-losing renal tubulopathy arising from mutations in the thiazide-sensitive Na-Cl cotransporter gene. Due to its low incidence and lack of awareness, GS can be easily misdiagnosed or missed in diagnosis.

#### CASE SUMMARY

A 24-year-old male presented with > 4 years of repeated limb weakness without any treatment. The previous day, the patient was bitten by ants and showed weakness of the lower limbs. The patient had hypokalemia (1.66-2.83 mmol/L), hypomagnesemia (0.4 mmol/L), hypocalciuria (1.51-2.46 mmol/d), metabolic alkalosis (7.47-7.54), normal blood pressure, and increased activity of aldosterone and plasma renin activity (PRA) (PRA 6.4 and 16.45 ng/mL/h and aldosterone 330.64 and 756.82 pg/mL in the supine and upright position, respectively). In addition, *SLC12A3* gene mutation with GS was diagnosed. Oral and intravenous supplementation with potassium and magnesium was initiated. Serum magnesium returned to 0.48 mmol/L and serum potassium returned to 3.08 mmol/L, alleviating the patient's fatigue symptoms.

#### CONCLUSION

GS should be considered in patients with hypokalemia complicated with hypomagnesemia. Genetic testing is essential to confirm the diagnosis.

**Key Words:** Gitelman syndrome; Limb weakness; Hypokalemia; Hypomagnesemia; Hypocalciuria; Genetic testing; Case report

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**Core Tip:** Gitelman syndrome (GS) is easily misdiagnosed or missed in diagnosis due to its low incidence and lack of awareness. Herein, we present a rare case of GS in a young man with limb weakness. This case demonstrates that attention should be focused on GS in patients with hypokalemia complicated with hypomagnesemia. Genetic testing is helpful in confirming the diagnosis.

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## INTRODUCTION

Gitelman syndrome (GS) is characterized by low blood potassium, low blood magnesium, low blood chloride, low urinary calcium, normal or low blood pressure, alkalosis, and activation of the renin-angiotensin-aldosterone system (RAAS), which are the clinical manifestations of autosomal recessive salt-losing renal tubular disease, also known as familial hypokalemia and hypomagnesemia[1]. The incidence of GS is low and is reported to be approximately 1/40000 in Europeans[2], and 10.3/10000 in Japanese[3] based on the heterozygous carrier rate, and is easily misdiagnosed or missed in diagnosis. We here report a case of GS diagnosed and treated in the Department of Endocrinology, Longhua District Central Hospital, Shenzhen, China.

## CASE PRESENTATION

### Chief complaints

A 24-year-old male presented with > 4 years of repeated limb weakness and a relapse of 1 d.

### History of present illness

Four years ago, the patient developed limb weakness and fatigue, especially in the lower limbs, which could be relieved spontaneously after rest. He could walk and hold objects with both hands. During the period without a specific diagnosis and treatment, the above symptoms occasionally occurred without aggravation but could be relieved spontaneously after rest. One day ago, the patient was bitten by ants and showed weakness in the lower limbs. His blood potassium level was 1.66 mmol/L when examined in the Emergency Department. Following oral and intravenous potassium supplementation and intravenous magnesium supplementation, his blood potassium was reexamined and was found to be 2.22 mmol/L, and the patient was admitted to our department with hypokalemia.

### History of past illness

The patient had no medical history.

### Personal and family history

No member of the patient's immediate or extended family reported similar symptoms. He denied the use of any herbal medicine, diuretics, or laxatives.

### Physical examination

Physical examination revealed a thin man, 156 cm in height, and 33.5 kg in weight. His temperature was 36.5 °C, respiratory rate was 20 breaths/min, and blood pressure was 116/53 mmHg with a regular heart rate of 100 bpm. Thyroid palpation revealed that his thyroid was normal. Chest auscultation revealed that his lungs were clear and heart sounds were normal. Muscle strength of his left lower limb was grade 4, and that of the right lower and both upper limbs was grade 5.

### Laboratory examinations

Laboratory investigations carried out at the time of presentation are summarized in Table 1. We confirmed the persistence of a hypokalemic state secondary to renal potassium wasting, while serum potassium levels remained at approximately 1.66–2.83 mmol/L, and urinary potassium excretion was increased from 102.43 to 120.08 mmol/d. Intriguingly, we observed hypomagnesemia (0.4 mmol/L), hypocalciuria (1.51–2.46 mmol/d), and metabolic alkalosis (7.47–7.54). Urinalysis did not show any alterations. Serum creatinine and creatinine clearance were slightly higher than normal. Glycosylated hemoglobin and plasma cortisol were within the normal range. Echocardiography and renal ultrasound did not show any abnormalities. Liver function, thyroid function, and other biochemical parameters were normal. Secondary hyperreninemic hyperaldosteronism was detected in the supine and upright



Table 1 Laboratory examinations

	Value or range	Normal range
Urinary pH	8.5	5.0-8.4
Urinary specific gravity	1.01	1.021-1.03
Urinary protein	Negative	Negative
BUN, mmol/L	4.62	3.1-8
CR, mmol/L	76.3	57-97
pH	7.47-7.54	7.35-7.45
HCO <sub>3</sub> <sup>-</sup> , mmol/L	24.1-27.7	22-26
Serum magnesium, mmol/L	0.4	0.7-1.0
Serum potassium, mmol/L	1.66-2.83	3.5-5.3
Serum sodium, mmol/L	132.6-139.3	137-147
Serum calcium, mmol/L	2.21-2.36	2.11-2.52
Serum phosphorus, mmol/L	0.69	0.85-1.51
Urinary potassium, mmol/d	102.43-120.08	25-100
Urinary calcium, mmol/d	1.51-2.46	130-260
Glycosylated hemoglobin, %	5.5	4-6
Parathyroid hormone, pg/mL	8.67	14.5-87.1
Cor, nmol/L (8 a.m.)	287.17	6-10 a.m.: 133-537
Cor, nmol/L (4 p.m.)	151.73	4-8 p.m.: 68.2-327
ACTH, pmol/L (8 a.m.)	12.94	8 a.m., 4 p.m.: 2-14
ACTH, pmol/L (4 p.m.)	3.5	8 a.m., 4 p.m.: 2-14

BUN: Blood urea nitrogen; CR: Complete response; Cor: Cortisone; ACTH: Adreno-cortico-tropic-hormone.

positions (PRA 6.4 and 16.45 ng/mL/h and aldosterone 330.64 and 756.82 pg/mL, respectively) (Tables 2 and 3).

### Imaging examinations

Computed tomography revealed hyperplasia at the junction of the left adrenal gland and calcification of the diverticulum in the right renal pelvis. Electrocardiography showed sinus rhythm and low T wave level.

## FINAL DIAGNOSIS

The patient was diagnosed with hypokalemia, hypomagnesia, hypocalciuria, alkalosis, low serum chlorine, increased renin-angiotensin-aldosterone activity, normal blood calcium, and normal blood pressure. The detection of *SLC12A3* gene mutation confirmed the diagnosis of GS.

### Genetic testing

The Guangzhou KingMed Center for Clinical Laboratory tested the genes of this patient, including the exon sequence of *SLC12A3* gene. The DNA extracted from the samples was tested by gene sequencing, and possible gene mutations were identified by comparing with the reference sequence. Two pathogenic mutations related to GS (Table 3) were detected: heterozygous rs768527231 Exon1 missense mutation C.248G>A (p.Asg83Gln), which is included in the dbSNP147 database, and Exon21 nonsense mutation C.2532G>A (p.Trp844\*), confirming the diagnosis of GS (Figure 1).

Table 2 Results of postural stimulation test			
Position	Aldosterone/(pg/mL)	Renin/(ng/mL/h)	ARR
Clinostatism	330.64 (40.0-310.0)	6.4 (0.15-2.33)	5.36 (0-30)
Orthostatism	756.82 (10.0-160.0)	16.45 (1.31-3.95)	4.6 (0-30)

ARR: Aldosterone renin ratio.

Table 3 Genetic testing							
Gene	Zone	Reference sequence	Location	cDNA level	Protein level	Status	Classification of variation
SLC12A3	16q13	NM_000339.2	Exon1	c.248G>A	p.Arg83Gln	Heterozygosis	Suspicious pathologically
SLC12A3	16q13	NM_000339.2	Exon21	c.2532G>A	p.Trp844*	Heterozygosis	Pathological

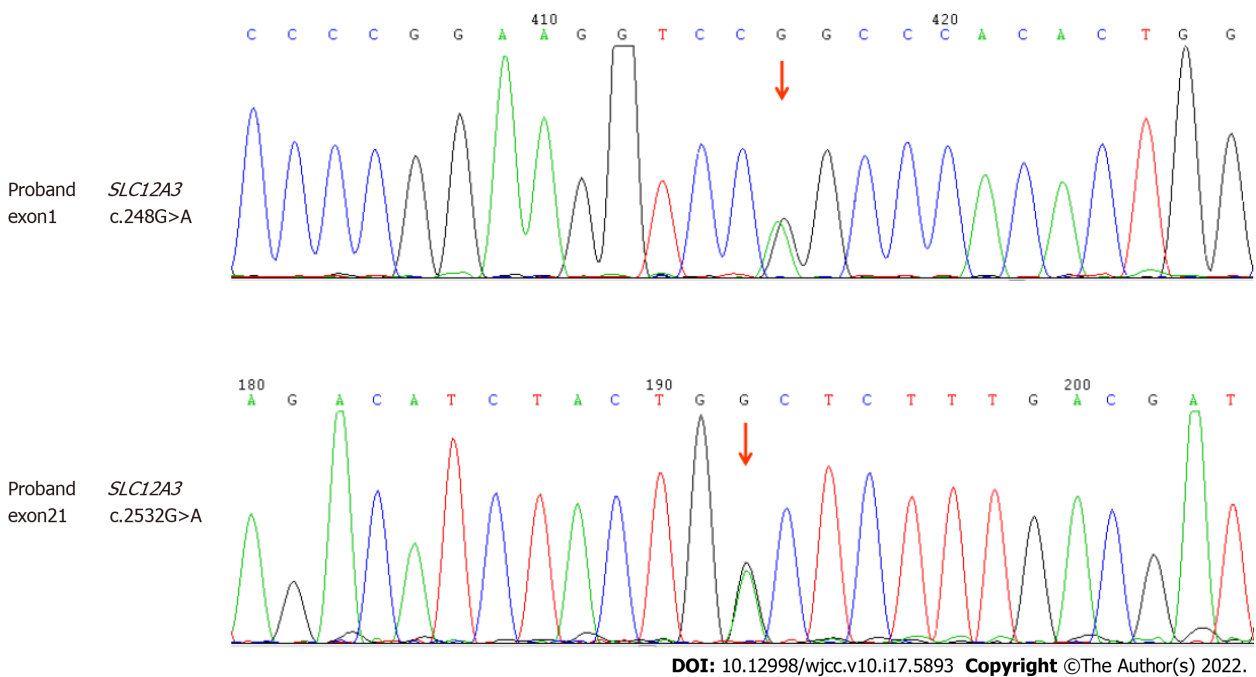


Figure 1 Exon sequencing of pathogenic genes.

TREATMENT

Oral and intravenous supplementation with potassium and magnesium was initiated.

OUTCOME AND FOLLOW-UP

After treatment, the patient’s serum magnesium returned to 0.48 mmol/L, and serum potassium returned to 3.08 mmol/L. As a result, his fatigue symptoms were alleviated.

DISCUSSION

Hypokalemia is a common electrolyte disorder in clinical practice. Severe hypokalemia can lead to life-threatening reactions, such as dyspnea and arrhythmia. There are several causes of hypokalemia that can lead to insignificant limb weakness symptoms and can be easily ignored by patients; therefore, the diagnosis is challenging.

According to the etiopathogenesis, potassium deficiency due to inadequate intake and increased potassium excretion, hypokalemia, metastatic hypokalemia, and dilutive hypokalemia are included. The common causes of potassium deficiency in hypokalemia are inadequate potassium intake and excessive potassium loss in the digestive tract and kidney. Metastatic hypokalemia occurs when potassium is transferred from extracellular to intracellular, resulting in hypokalemia, in which the total amount of potassium is not deficient.

The diagnosis and differential diagnosis of hypokalemia was carried out. The patient was a young male with recurrent fatigue. Repeated blood potassium (3.5 mmol/L) and synchronous 24 h urine potassium excretion increased to > 25 mmol/d, indicating renal potassium loss. The patient had a normal appetite, adequate potassium intake, no history of using diuretics or a large dosage of insulin, and no long-term nausea, vomiting, and diarrhea; therefore, gastrointestinal loss was not considered. Metastatic hypokalemia was not supported as hyperthyroidism was absent and the patient's blood glucose was normal. The patient had significantly elevated aldosterone levels, which excluded exogenous mineralocorticoid hyperplasia, Cushing syndrome, adrenal congenital 17- $\alpha$ /11- $\beta$  hydroxylase deficiency, and Liddle syndrome. The patient's blood pressure was normal, renin activity was increased, and no renal mass was observed. Primary aldosteronism and renin tumors were excluded. The patient did not have renal artery stenosis or proteinuria, and blood gas analysis suggested metabolic alkalosis. Therefore, renal tubular acidosis, renal artery stenosis, and chronic kidney disease were not considered. The patient developed the disease as an adult and was thin and small since childhood, which was related to long-term hypokalemia, with hypomagnesia, hypochloremia, and hypocalciuria. Genetic testing suggested a heterozygous variation in the *SLC12A3* gene. Two pathogenic mutations related to GS were detected in the *SLC12A3* gene region of the patient, including heterozygous rs768527231 Exon1 missense mutation C.248G > A (p.agsg83gln), which is included in the dbSNP147 database, and the Exon21 nonsense mutation C.2532g > A (p.TP844\*)[5], which was expected to change the amino acid position 844 of the encoded protein from Trp to stop codon, leading to protein translation terminated in advance. Based on these findings, the diagnosis of GS was established.

Furthermore, GS is an autosomal recessive genetic disorder, first described as an individual condition by Gitelman *et al* in 1966. GS can be attributed to structural and/or functional abnormalities of the sodium-chloride cotransporter (NCCT) due to the loss-of-function mutation in the gene *SLC12A3*, encoding the thiazide diuretic sensitive NCCT located in the distal renal tubules[6].

Reduced sodium chloride reabsorption, blood volume, and renal salinization lower the blood pressure, activating the RAAS system and increasing aldosterone and renin levels, leading to hypokalemia and metabolic alkalosis. Decreased urinary calcium in GS patients may be associated with abnormal Na<sup>+</sup>/Cl<sup>-</sup> combined transport, weakening the intracellular Cl<sup>-</sup> superactivation, increasing CA<sup>2+</sup> back absorption, and decreasing urinary calcium[4].

The decrease in serum magnesium level may be caused by increased Na<sup>+</sup> reabsorption under the action of aldosterone, which results in the formation of luminal side negative potential and increases the level of urinary magnesium through increased Mg<sup>2+</sup>/Na<sup>+</sup> exchange. This phenomenon may be related to the inactivation of transient receptor potential cation channel 6 (TRPM6) located at the apical domain of the distal convoluted tubules and brush border of the duodenal magnesium-transporter cells, resulting in decreased blood magnesium[7,8,10]. Simultaneously, hypomagnesemia can reduce the release of parathyroid hormone[7].

The mainstay of treatment for GS includes individualized lifelong administration of potassium and magnesium supplements (a strategy implemented in the present patient) combined with aldosterone antagonists and/or potassium-sparing agents, such as spironolactone, amiloride, and eplerenone to induce clinical remission.

A worldwide consensus[1,9] suggested that GS patients' blood potassium and magnesium levels should be maintained at > 3.0 mmol/L and > 0.6 mmol/L, respectively.

This patient was mainly treated with potassium chloride and magnesium sulfate. After treatment, the patient's clinical symptoms were relieved, but blood potassium did not reach the normal level; hence, regular follow-up was essential. GS is an autosomal recessive hereditary disease. Riveira-Munoz *et al* [11] suggested that the nature/position of *SLC12A3* mutation, combined with male gender, is a determining factor in the severity of GS. Therefore, investigation of the family by lineal gene testing is essential.

## CONCLUSION

GS can be easily misdiagnosed or missed in diagnosis due to its low incidence and lack of awareness. Therefore, it is necessary to consider the possibility of GS in patients with clinical hypokalemia, low urinary calcium and low blood magnesium, and improve genetic screening for accurate diagnosis.

## FOOTNOTES

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