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Title	Gitelman's syndrome with hyperphosphatemia, effectively responding to single oral magnesium oxide administration
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Citation	Medicine, 98(28), e16408 https://doi.org/10.1097/MD.0000000000016408
Issue Date	2019
Doc URL	https://hdl.handle.net/2115/78821
Rights(URL)	https://creativecommons.org/licenses/by-nc/4.0/
Type	journal article
File Information	Gitelman_s_syndrome_with_hyperphosphatemia,.67.pdf

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Clinical Case Report

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Gitelman's syndrome with hyperphosphatemia, effectively responding to single oral magnesium oxide administration

A case report

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Abstract

Rationale: The Gitelman's syndrome (GS) is characterized by metabolic alkalosis, hypokalemia, hypomagnesemia, and hypocalciuria. However, the involvement of this deranged electrolyte balance in patients with GS in parathyroid hormone action has not been known.

Patient concerns: We report a 34-year-old woman with muscle weakness and tetany/seizures caused by electrolyte imbalance. She had hyperphosphatemia and hypocalciuric hypocalcemia in addition to severe hypomagnesemia with low potassium in the absence of metabolic alkalosis. We identified 2 heterozygous mutations in the solute carrier family 12 member 3 gene in this case (c.1732G>A, p.Val578Met and c.2537_38delTT, p.846fs) by targeted sequence for all causative genes of salt-losing tubulopathies.

Diagnoses: A diagnosis of GS. Hypocalcemia and hyperphosphatemia were suggested to relate with the secondary obstruction of appropriate parathyroid hormone release following severe hypomagnesemia in GS.

Interventions: She was treated with single oral magnesium oxide administration.

Outcomes: The electrolyte imbalance including hypocalcemia and hyperphosphatemia were resolved with a remission of clinical manifestations.

Lessons: These observations, in this case, suggest that even severe hypomagnesemia caused by GS was associated with resistance to appropriate parathyroid hormone secretion. Through this case, we recognize that secondary hypoparathyroidism would be triggered by severe hypomagnesemia in GS.

Abbreviations: GS = Gitelman's syndrome, PTH = parathyroid hormone, *SLC12A3* = solute carrier family 12 member 3, TSC = thiazide-sensitive Na-Cl cotransporter.

Keywords: Gitelman's syndrome, hyperphosphatemia, hypocalciuric hypocalcemia, hypomagnesemia, parathyroid hormone

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Editor: N/A.

Written informed consent was obtained from the patient for the publication of this case report.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2019) 98:28(e16408)

Received: 9 January 2019 / Received in final form: 9 May 2019 / Accepted: 13 June 2019

http://dx.doi.org/10.1097/MD.0000000000016408

1. Introduction

The presence of electrolyte imbalance, including hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria with normal serum calcium levels, are prominent features in Gitelman's syndrome (GS).[1–3] A defect of the thiazide-sensitive Na-Cl cotransporter (TSC) causes such electrolyte imbalance through decreased reabsorption of sodium and chloride at the renal distal tubule, leading to inappropriate renal potassium wasting. These electrolyte imbalance are resolved through a liberal salt intake together with oral administration of potassium.[1,4] GS is an autosomal recessive disorder caused by the solute carrier family 12 member 3 (*SLC12A3*) gene mutation. This gene encodes TSC and magnesium channels in the thiazide-sensitive segment of the renal distal convoluted tubule.[2,5] A wide variety of more than 400 *SLC12A3* mutations in patients with GS have been identified.[6–9]

Hypomagnesemia is frequently associated with coexisting electrolyte imbalance, including hypokalemia and hypocalcemia. Hypocalcemia is secondary to hypoparathyroidism induced by hypomagnesemia.[10,11] However, hyperphosphatemia and associated hypoparathyroidism due to hypomagnesemia

concomitant with GS have not been known. We here report a rare case of a patient with GS in addition to severe hyperphosphatemia and inappropriately normal parathyroid hormone (PTH) levels complicated by severe hypomagnesemia. Furthermore, we detected 2 heterozygous pathogenic variants in *SLC12A3* gene, leading to GS, utilizing targeted sequence for all salt-losing tubulopathy causative genes. Single oral magnesium oxide administration improved her clinical symptoms of tetany and electrolyte imbalance. These findings suggest an association between severe hypomagnesemia caused by GS and the absence of appropriate PTH action.

2. Case report

A 34-year-old woman in previous good health was admitted to hospital complaining of muscle weakness and tetany/seizures for 1 year. On admission, the patient was 162.8 cm tall and weighed 53.7 kg, with a body mass index of 20.3 kg/m^2. Her blood pressure was 112/78 mm Hg. She showed Chvostek's sign, but no physical signs or digestive symptoms, including anorexia nervosa, vomiting, or diarrhea. She had not taken any medications, such as laxatives, diuretics, street drugs. She had also not attempted to lose weight. She was a nonsmoker nor alcohol drinker, and she had no allergies. The family history was negative for electrolyte imbalance or other forms of endocrinopathy. Her parents were not consanguineous.

Severe hypomagnesemia, hypocalcemia, and hyperphosphatemia in addition to hypokalemia without metabolic alkalosis were observed (Table 1). Urinary calcium excretion was decreased, whereas urinary magnesium was elevated compared with low serum values. Her plasma renin and aldosterone levels remained within the normal range. The serum creatinine level and glomerular filtration rate were normal. Her intact PTH level was relatively low in consideration of severe hypocalcemia. The serum alkaline phosphatase level was normal. The laboratory findings were indicative of GS, except for hypocalcemia, hyperphosphatemia, and hypokalemia without metabolic alkalosis. A renal function test using furosemide or thiazide is desirable when GS is suspected.[12] Therefore, we performed a renal function test in our case for assessment of the renal reabsorption rate of chloride in the distal tubule in morning fasting according to the described protocol.[12] Her renal reabsorption rate of chloride in the distal tubule was markedly decreased using furosemide (from 68.4% to 10.4%), but not by thiazide administration (70.4% to 63.5%), which led to the final diagnosis of GS. To alleviate the symptoms of muscle weakness and tetany/seizure, she had adequate electrolyte supplementation therapy of 8.5% calcium gluconate (20 ml/d) and magnesium sulfate (40 mEq/d) infusion. These supplementations were tapered within 2 days of admission. She has taken no supplementation since day 7 after admission. The clinical course was uneventful. She had a regular diet. Her serum potassium level returned to the normal range, and muscle weakness and tetany disappeared, although her serum calcium and magnesium levels persisted at 2.2 mmol/l and 0.7 mmol/l, respectively, which slightly exceed the lower limit of the normal range. Without any additional potassium gluconate and calcium replacement therapy, her serum potassium, calcium, magnesium, and phosphorus levels during oral administration of a low dose of magnesium oxide (0.6 g/d) were all within the normal range after discharge from our hospital (Fig. 1). Additionally, intact PTH levels were normalized (from 6.1 to 8.2 pmol/l) after hypomagnesemia was corrected.

Table 1

Electrolyte balance and other biochemical laboratory data on admission.

	Patient's value	Reference range
Plasma sodium, mmol/l	142	136–148
Plasma potassium, mmol/l	2.9	3.8–5.0
Plasma chloride, mmol/l	103	98–108
Plasma corrected calcium, mmol/l	1.3	2.2–2.5
Plasma phosphorus, mmol/l	2.0	0.8–1.5
Plasma magnesium, mmol/l	0.3	0.7–1.0
Serum creatinine, μmol/l	70.7	31.8–93.7
Estimated glomerular filtration rate	65.4	
Fractional excretion of K (%)	4.8	
Fractional excretion of Ca (%)	0.4	2.0–4.0
Fractional excretion of P (%)	13.0	10–20
The ratio of tubular maximum reabsorption of phosphate	2.4	2.5–4.5
Fractional excretion of Mg (%)	9.3	1.4–1.8
Plasma renin activity, ng/ml/h	0.2	0.3–2.9
Aldosterone, pg/ml	68.3	29.9–159.0
Intact parathyroid hormone, pmol/l	6.1	1.0–6.9
pH	7.36	7.35–7.45
Bicarbonate, mmol/l	21.2	23–38

Genetic analysis was performed using the patient's peripheral blood lymphocytes. It was first screened by targeted sequence including all salt-losing tubulopathy causative genes followed by Sanger sequence. As a result, she had 2 heterozygous mutations in the *SLC12A3* gene, one of which has been reported previously as a GS disease-causing mutation (c.1732G>A, p.Val578Met).[13] The other heterozygous mutation (c.2537_38delTT, p.846fs) has not been previously reported (Fig. 1).

Our case report was waived from the ethical approval or institutional review board of Hokkaido University Hospital, based upon their policy to review all intervention and observational study except for a case report. Written informed consent was obtained from the patient for the publication of this case report. The presented data are anonymized and risk of identification is minimal.

3. Discussion

This is the first report to show a rare case of an adult woman with GS who presented with a combination of hyperphosphatemia and hypocalciuric hypocalcemia. These conditions were suspected to be secondary to hypoparathyroidism induced by hypomagnesemia. GS is characterized by electrolyte imbalance, including hypokalemia, hypomagnesemia, hypocalciuria, metabolic alkalosis, and hyperreninemic hyperaldosteronism. This imbalance is mimicked by the condition of patients who are taking thiazide diuretics, the affected transporter in GS being the exact target of thiazides.[14] Hypokalemia with metabolic alkalosis in patients with GS is associated with decreased reabsorption of sodium at the TSC. Subsequently, increased potassium losses occur via the renal outer medullary potassium channel and are largely driven by secondary aldosteronism.[14] Hypomagnesemia then develops during chronic thiazide administration because transient receptor potential channel subfamily M member 6 downregulation might be involved in hypomagnesemia accompanying TSC inhibition or inactivation.[15] Hypocalciuria with normal serum calcium levels,

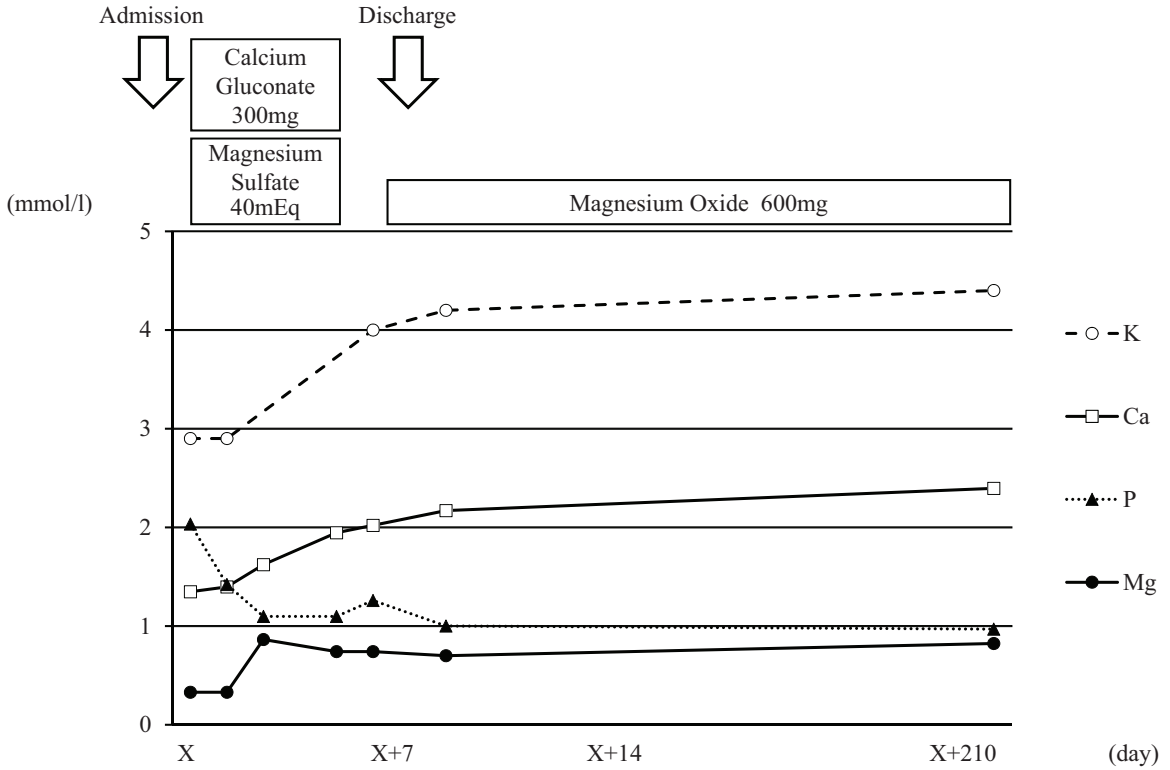

Figure 1. Clinical course of GS patient. Supplementation therapy of calcium gluconate and magnesium sulfate infusion was tapered within 2 days of admission. Electrolyte imbalance during oral administration of a low dose of magnesium oxide was within the normal range after discharge. GS = Gitelman's syndrome.

but not hypocalcemia, is a prominent feature in GS.[1] Enhanced passive calcium transport in the proximal tubule, rather than active calcium transport in distal convolution, leads to thiazide-induced hypocalciuria. The time-dependent effect of a single thiazide leads to development of hypocalciuria and a compensatory increase in sodium reabsorption secondary to natriuresis.[15] It is known that hypocalciuric hypocalcemia is widely related with renal disease, vitamin D malabsorption, pancreatitis, administration of drugs, and hypoalbuminemia. However, those kinds of pathogenesis were excluded in our case. Additionally, the severity of hyperphosphatemia in our case failed to meet features of GS. Although little has been known about renal regulation of phosphate homeostasis, a tendency towards renal phosphate wasting not related to altered circulating levels of either 25-hydroxyvitamin D or PTH is suggested in GS.[16] Therefore, our case of GS coexisted with atypical clinical features of hyperphosphatemia and hypocalciuric hypocalcemia.

Generally, clinical conditions that exhibits both hypocalciuric hypocalcemia and hyperphosphatemia have been suspected the pathophysiology of hypoparathyroidism. Hypomagnesemia is a cause of hypoparathyroidism.[17] Under the hypomagnesemic state, renal and skeletal resistance to PTH action is increased and adenylate cyclase activity in parathyroid cells is inhibited, leading to blunted secretion of PTH.[18] Our case with GS may have presented with hypocalciuric hypocalcemia and hyperphosphatemia because sustained very low magnesium levels by GS led to resistance to PTH action and disturbed secretion of PTH. This absence of PTH action resulted from chronic hypomagnesemia as shown by a relative increase in intact PTH levels (from 6.1 to 8.2 pmol/l) after replenishing magnesium stores, although serum calcium levels arose to the normal range (from 1.3 to 2.1 mmol/l). Hypomagnesemia is associated with removing ATP inhibition of potassium channels by a decline in intracellular ATP activity, presumably leading to hypokalemia.[19] Despite the deranged electrolyte balance in our patient with GS, all manifestations were resolved by supplementation of single oral administration of magnesium without potassium.

In patients with GS, severe hypomagnesemia impairs PTH response to peripheral stimuli and induces severe hypocalcemia.[5] Additionally, disturbed secretion of PTH leads to a blunted relationship among PTH levels, ionized calcium concentrations, and calcitriol.[4] Plasma phosphate and urinary fractional phosphate excretion are generally normal in the absence of PTH action.[14] Therefore, hyperphosphatemia and associated hypoparathyroidism due to hypomagnesemia concomitant with GS have not been determined.

The genotyping study of our patient detected the variant c.1732G>A (p.Val578Met) and the variant c.2537_38delTT (p.846fs), both in heterozygosity, in the *SLC12A3* gene. The variant c.1732G>A (p.Val578Met) was described in other patients with GS.[13] The other variant, a heterozygous 2-bp (TT) deletion at 2537–2538 (Fig. 2), was a novel mutation in patients with GS. This deletion would result in a frameshift that alters codon 846 to encode a stop signal, and it is predicted to lead to loss of the latter half of the intracellular carboxy terminus. Because of a lack of functional studies, this variant has undetermined significance. However, a frameshift usually shows a more severe phenotype than missense mutations and in-frame deletion mutations in human inherited disorders.[20] The presence of this novel mutation of c.2537_38delTT (p.846fs) may have

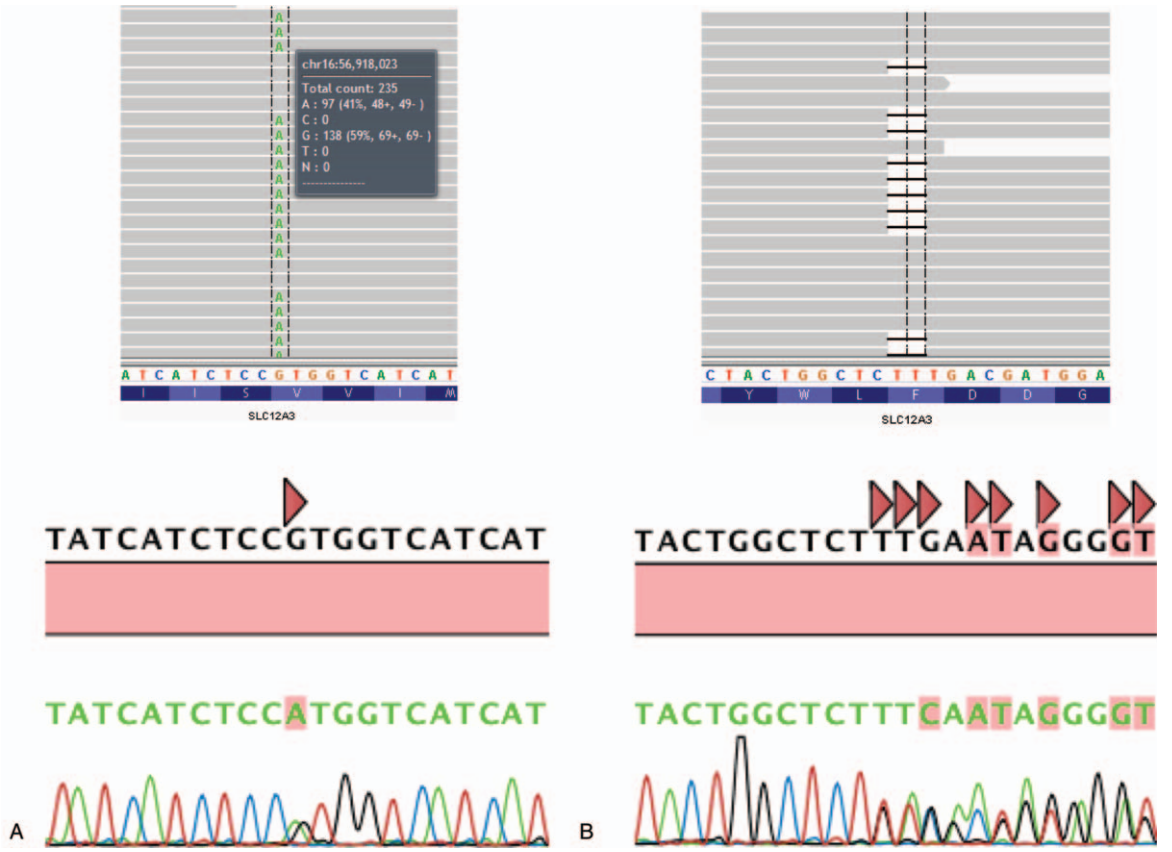

Figure 2. *SLC12A3* gene mutations identified in this patient by targeted sequence confirmed by Sanger method. Targeted sequence results (upper panels) and Sanger sequence results with DNA sequence chromatograms (lower panels) from this patient are shown. (A) A heterozygous transition (G>A) at nucleotide 1732 that is located in exon 14, resulting in a Val to Met substitution at amino acid 578. (B) A heterozygous deletion (TT) at nucleotide 2537–2538 that is located in exon 21, resulting in a frameshift at amino acid 846. *SLC12A3* = solute carrier family 12 member 3.

been associated with the remarkably severe magnesium depletion by GS in our case.

In conclusion, our observations suggest that severe hypomagnesemia caused by GS is associated with the absence of PTH action. This case emphasizes the importance of taking into consideration the possibility of GS in a patient who shows hypocalcemia and hyperphosphatemia, as well as the importance of replacement therapy of magnesium in this electrolyte imbalance.

Acknowledgment

We thank Ellen Knapp, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Author contributions

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References

[1] Gitelman HJ, Graham JB, Welt LG. A new familial disorder characterized by hypokalemia and hypomagnesemia. Trans Assoc Am Physicians 1966;79:221–35.
[2] Scheinman SJ, Guay-Woodford LM, Thakker RV, et al. Genetic disorders of renal electrolyte transport. N Engl J Med 1999; 340:1177–87.
[3] Blanchard A, Bockenhauer D, Bolignano D, et al. Gitelman syndrome: consensus and guidance from a kidney disease: improving global outcomes (KDIGO) controversies conference. Kidney Int 2017;91: 24–33.
[4] Bianchetti MG, Bettinelli A, Casez JP, et al. Evidence for disturbed regulation of calciotropic hormone metabolism in gitelman syndrome. J Clin Endocrinol Metab 1995;80:224–8.
[5] Simon DB, Nelson-Williams C, Bia MJ, et al. Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. Nat Genet 1996;12:24–30.
[6] Cruz DN, Shaer AJ, Bia MJ, et al. Yale Gitelman's and Bartter's Syndrome Collaborative Study GroupGitelman's syndrome revisited: an evaluation of symptoms and health-related quality of life. Kidney Int 2001;59:710–7.
[7] Colussi G, Bettinelli A, Tedeschi S, et al. A thiazide test for the diagnosis of renal tubular hypokalemic disorders. Clin J Am Soc Nephrol 2007;2:454–60.
[8] Lemmink HH, Knoers NV, Károlyi L, et al. Novel mutations in the thiazide-sensitive NaCl cotransporter gene in patients with Gitelman syndrome with predominant localization to the C-terminal domain. Kidney Int 1998;54:720–30.

[9] Lin SH, Shiang JC, Huang CC, et al. Phenotype and genotype analysis in Chinese patients with Gitelman's syndrome. J Clin Endocrinol Metab 2005;90:2500–7.
[10] Pantanetti P, Arnaldi G, Balercia G, et al. Severe hypomagnesaemia-induced hypocalcaemia in a patient with Gitelman's syndrome. Clin Endocrinol (Oxf) 2002;56:413–8.
[11] Agus ZS. Hypomagnesemia. J Am Soc Nephrol 1999;10:1616–22.
[12] Tsukamoto T, Kobayashi T, Kawamoto K, et al. Possible discrimination of Gitelman's syndrome from Bartter's syndrome by renal clearance study: report of two cases. Am J Kidney Dis 1995;25:637–41.
[13] Monkawa T, Kurihara I, Kobayashi K, et al. Novel mutations in thiazide-sensitive Na-Cl cotransporter gene of patients with Gitelman's syndrome. J Am Soc Nephrol 2000;11:65–70.
[14] Graziani G, Fedeli C, Moroni L, et al. Gitelman syndrome: pathophysiological and clinical aspects. QJM 2010;103:741–8.
[15] Nijenhuis T, Vallon V, van der Kemp AW, et al. Enhanced passive Ca2+ reabsorption and reduced Mg2+ channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. J Clin Invest 2005; 115:1651–8.
[16] Viganò C, Amoruso C, Barretta F, et al. Renal phosphate handling in Gitelman syndrome – the results of a case-control study. Pediatr Nephrol 2013;28:65–70.
[17] Chase LR, Slatopolsky E. Secretion and metabolic efficacy of parthyroid hormone in patients with severe hypomagnesemia. J Clin Endocrinol Metab 1974;38:363–71.
[18] Abbott L, Nadler J, Rude RK. Magnesium deficiency in alcoholism: possible contribution to osteoporosis and cardiovascular disease in alcoholics. Alcohol Clin Exp Res 1994;18: 1076–82.
[19] Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. J Am Soc Nephrol 2007;18:2649–52.
[20] Nozu K, Iijima K, Kanda K, et al. The pharmacological characteristics of molecular-based inherited salt-losing tubulopathies. J Clin Endocrinol Metab 2010;95:E511–8.