

Depressive State and Paresthesia Dramatically Improved by Intravenous MgSO₄ in Gitelman's Syndrome

Mayumi ENYA¹⁾, Yoshinori KANO¹⁾, Tomoatsu MUNE¹⁾, Masayoshi ISHIZAWA¹⁾, Hiroshi SARUI¹⁾, Mayumi YAMAMOTO¹⁾, Noriyuki TAKEDA¹⁾, Keigo YASUDA²⁾, Minoru YASUJIMA³⁾, Shoji TSUTAYA³⁾ and Jun TAKEDA^{1, 4)}

Abstract

A 69-year-old woman was referred to our department for evaluation of hypokalemia, which had been treated by oral potassium for more than ten years. She complained of headache, knee joint pain, sleeplessness and paresthesia in extremities and, most prominently, depression. Laboratory data suggested Gitelman's syndrome, which is caused by mutations in the gene encoding the thiazide-sensitive Na-Cl cotransporter. Direct sequencing of the gene in this patient revealed homozygous mutation R964Q in exon 25. Intravenous supplement of MgSO₄ dramatically improved both the depression and the paresthesia, suggesting that hypomagnesemia played a role in the clinical manifestations.

(Internal Medicine 43: 410–414, 2004)

Key words: hypokalemia, hypomagnesemia, depressive state, gene testing, mutation

Introduction

Gitelman's syndrome (GS) was first characterized in 1966 by hypokalemia, metabolic alkalosis, and normal blood pressure under hyperreninaemic hyperaldosteronism, concomitant with hypocalciuria and hypomagnesaemia (1). GS was thought to be a variant of Bartter's syndrome, but is now recognized as an autosomal recessive disorder due to mutations in the gene (*SLC12A3*) encoding the thiazide-sensitive Na-Cl cotransporter (TSC) (2). This gene lies on chromosome 16q13 and has 26 exons encoding a polypeptide of 1,021 amino acids consisting of 12 transmembrane domains. TSC

is expressed in the renal distal convoluted tubule, molecular defects in which cause hypokalemia and hypocalciuria similar to that seen in patients treated with thiazide diuretics. Hypomagnesemia also is common in these patients, possibly due to magnesium wasting by urinary excretion.

The clinical symptoms of GS such as episodic muscular weakness, tetany, abdominal pain, and fatigue or joint pain are not as severe or as frequent as in Bartter's syndrome. Asymptomatic adults sometimes have hypokalemia, but the mildness of the symptoms hampers diagnosis. Here, we report a case of GS with severe depression and paresthesia lasting for more than ten years which was dramatically improved by intravenous magnesium sulfate (MgSO₄) treatment.

For editorial comment, see p 351.

Case Report

A 69-year-old woman presented with an egg-size mass in her left axilla in October 2001. She had had an operation for malignant melanoma on her back in 1988, and the mass was diagnosed as lymph node metastasis by excisional biopsy. She was admitted to the department of dermatology in our hospital for chemotherapy in February 2002, and then was moved to the third department of internal medicine for evaluation of hypokalemia of unknown origin in April 2002.

The patient had no history of chronic diarrhea, vomiting or diuretics use. She complained of headache, joint pain of bilateral knees, sleeplessness, and paresthesia in extremities. There was no history of tetany or palsy, but physical examination showed grip test at 7.2 kg bilaterally. She had an attack of muscle weakness after hospitalization, which was

From the ¹⁾Third Department of Internal Medicine, Gifu University School of Medicine, Gifu, ²⁾Center for Lifestyle-Related Diseases, Matsunami General Hospital, Gifu, ³⁾Department of Laboratory Medicine, Hirosaki University School of Medicine, Hirosaki and ⁴⁾Laboratory of Molecular Genetics, Department of Cell Biology, Institute for Molecular and Cellular Regulation, Gunma University, Maebashi

Received for publication July 31, 2003; Accepted for publication December 1, 2003

Reprint requests should be addressed to Dr. Mayumi Enya, the Third Department of Internal Medicine, Gifu University School of Medicine, 40 Tsukasamachi, Gifu 500-8705

Table 1. Summary of Laboratory Data

| | Variable | Normal range |
|--------------------------------|------------------------------------|--------------|
| Serum electrolyte levels | | |
| | Na | 143 |
| | K | 3.2 |
| | Cl | 103 |
| | Ca | 8.6 |
| | Mg | 0.7 |
| Urinary electrolyte excretions | | |
| | Na | 68 |
| | K | 65 |
| | Cl | 82 |
| | Ca | 27 |
| | (urinary Ca/Cr molar ratio = 0.15) | |
| | Plasma renin activity | 2.8 |
| | Plasma aldosterone concentration | 130 |
| | Serum pH | 7.455 |
| | Serum bicarbonate levels | 26.1 |

improved by intravenous drip of potassium chloride. Chvostek's sign and Trousseau's sign were negative. Blood pressure was 103/67 mmHg. Consciousness was clear, but she was generally inactive and unconcerned, lying all day in bed. A psychiatrist diagnosed a depressive state. Laboratory data are listed in Table 1. The plasma potassium level was low despite daily supplementation of 32 mEq potassium chloride, but urinary excretion of potassium was not decreased. The patient had hypomagnesemia, hypocalciuria, and metabolic alkalosis. Plasma renin and aldosterone levels were high. X-rays of bilateral knees revealed chondrocalcinosis of the menisci.

All these features are consistent with a diagnosis of GS. Bettinelli et al have described the following criteria: 1) hypomagnesemia (<0.65 mmol/l) in the presence of inappropriately high magnesium excretion (fractional excretion of magnesium >4.0%); 2) hypokalemia (<3.6 mmol/l) in the presence of inappropriately high potassium excretion (fractional excretion of potassium >16.0%); and 3) urinary calcium/creatinine molar ratio <0.10 (3). The laboratory data of the present case concur with these criteria except for the urinary calcium/creatinine molar ratio, which was 0.15. To evaluate distal nephron function, the effects of furosemide (FUR) and hydrochlorothiazide (HCT) were examined according to the study protocol described previously (4). We used 10 mg FUR injected intravenously and 100 mg HCT administered orally. After maximal diuresis induced by oral water intake and drip infusion of half of the saline, electrolyte excretion was evaluated as fractional clearance (FE_x, i.e., C_x/GFR) using creatinine clearance (C_{cr}) as GFR marker. After FUR administration, there were obvious increases in both FE_{Na} and FE_{Cl} but only small increases after HCT administration. Colussi et al reported that in healthy adults, differences in maximal Na and Cl excretion between before and after HCT administration were 2.52±1.14% and 3.64±1.30

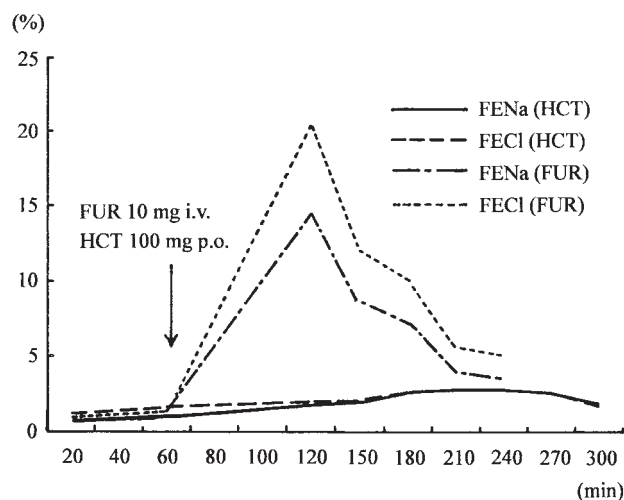


Figure 1. FUR test and HCT test. FE_{Na} and FE_{Cl} showed large increases after injection of 10 mg FUR, but little increase was seen after oral administration of 100 mg HCT.

%, respectively (5). In this case they were 1.7% and 1.2%. In addition, fractional free water clearance (C_{H₂O}/[C_{H₂O}+C_{Cl}]) as a fraction of distal delivery showed an abrupt change after FUR administration while HCT induced little effect (Figs. 1 and 2).

Genetic analysis was performed after obtaining informed consent. Direct sequencing of the exons and flanking introns of *SLC12A3* revealed homozygous mutation R964Q (CGG CAG) in exon 25, confirming the diagnosis of GS in this patient (Fig. 3). This mutation corresponds to R955Q that Simon et al reported in a Japanese patient (6); the different numbering of the amino acid residues may be due to possible splicing variation. We were unable to examine other family

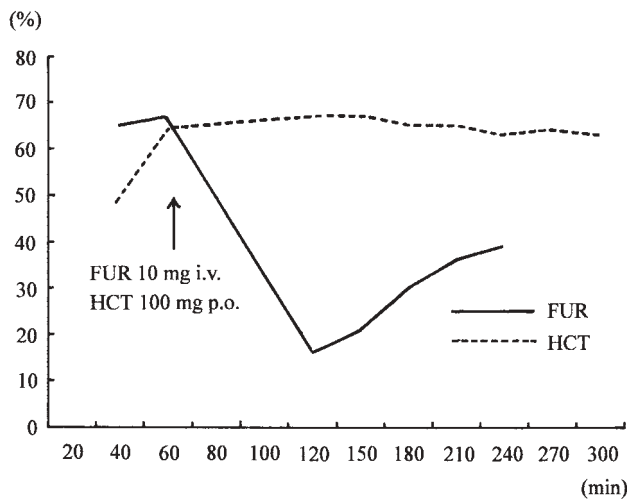


Figure 2. Fractional free water clearance. Fractional free water clearance showed an abrupt drop after 10 mg FUR administration compared to minimal change after 100 mg HCT. Before administration of diuretics, oral water intake and drip infusion of half of the saline induced maximally diluted diuresis. Urinary osmolality just before administration of FUR and HCT were 90 and 111 mOsm, respectively.

members.

Therapy with spironolactone (25 mg/day) and oral magnesium (magnesium oxide 1.5 g/day) was begun in addition to the potassium chloride supplementation (16 mEq/day). However, because of the severe diarrhea, the magnesium dosage had to be reduced to 0.5 g/day. For the persisting hypomagnesemia, intravenous drip infusion of magnesium sulfate (20 mEq/day) dissolved in 100 ml normal saline was performed for three days. As hypermagnesemia may cause Mg toxicity (specific symptoms so far reported are nausea, vomiting, muscle weakness, reduction of deep tendon reflexes, respiratory paralysis and cardiac arrest), $MgSO_4$ was administered for over two hours. On the second day of intravenous magnesium supplementation, the patient's depressive state improved dramatically, and she became quite active. The paresthesia in her extremities disappeared completely (Fig. 4). Intravenous drip infusion of magnesium at least once a week was required to maintain the serum magnesium level.

Discussion

Gitelman's syndrome has been considered a variant of Bartter's syndrome because of similarities in both clinical features and laboratory data. In 1996, Simon et al demonstrated complete linkage of GS to the locus including *SLC12A3* and identified mutations in this gene in GS patients (6). Thirty Japanese families have been described in the literature; the male to female ratio is 3 : 4 and the age at diagnosis ranges from 5 to 66 years with a mean of 28.4 years.

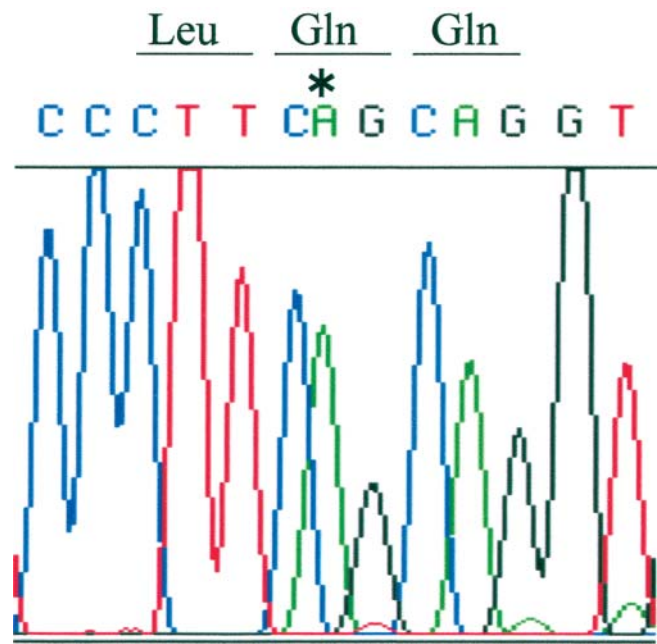


Figure 3. DNA sequence analysis in exon 25 of *SLC12A3*. The patient has a homozygous transition (G → A) in exon 25, resulting in an Arg (CGG) to Gln (CGA) substitution at residue 964.

Gene testing was performed in thirteen of these families to confirm the diagnosis, resulting in the identification of fifteen different mutations including four compound heterozygotes. The most frequent clinical symptoms observed in patients are tetany and cramp (n=8), followed by muscle weakness and paralysis (n=7) and fatigue (n=6). The others are numbness, nausea, vomiting, abdominal pain, diarrhea, joint pain, growth retardation, dyspnea, and unstable feeling (4, 7–22). The depressive state seen in this case is not common. The medical record shows that the patient had hypokalemia (2.5 mEq/l) in 1988, but the plasma magnesium level was not examined due to the absence of the typical symptoms.

Treatment with spironolactone and/or oral administration of potassium and magnesium is commonly performed in patients with GS. Spironolactone with supplementation of potassium chloride corrected the hypokalemia in this patient but did not relieve the symptoms. In contrast, intravenous magnesium supplementation promptly improved her condition, suggesting that the hypomagnesemia had played a major role in her clinical manifestations. Of patients who have received diagnostic gene testing, this is the only case of intravenous magnesium supplementation. Magnesium is an essential cation involved in a wide range of biological activities and plays crucial roles in many enzymatic systems. Hypomagnesemia, therefore, is associated with multiple non-specific clinical symptoms and signs (23), and the variety often results in confusion and controversy in diagnosis. As in this patient at an earlier stage, GS presents only mild clinical

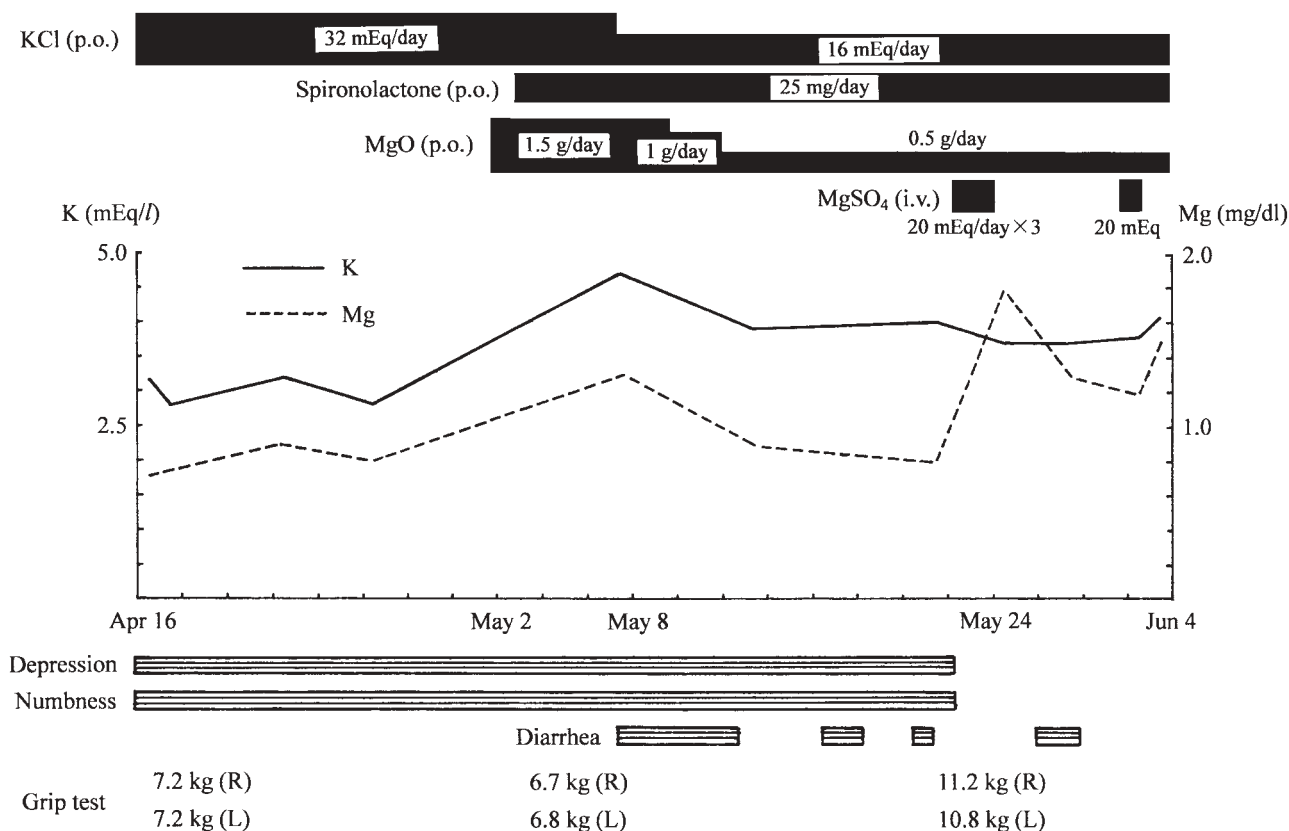


Figure 4. Clinical course. Depressive state and numbness dramatically improved after administration of intravenous supplement of MgSO₄.

features or remains asymptomatic. In addition, because serum magnesium is not measured routinely in clinics, many patients with GS are not diagnosed. Accordingly, patients with hypokalemia of unknown origin should be checked for the presence of hypomagnesemia and hypocalciuria.

To date, a number of different TSC mutations have been reported (2, 6, 18, 24–28). They include missense, frame-shift, nonsense and splice-site mutations distributed throughout the entire coding region of the protein. Our patient had a missense mutation in the intracellular carboxyl terminus that contains a putative cAMP-dependent protein kinase phosphorylation site, a putative protein kinase C phosphorylation site, and two putative casein kinase phosphorylation sites (2). Functional analysis of the mutant protein identified in our patient should clarify the physiological properties of this domain and lead to a better understanding of the pathogenesis, genotype/phenotype relationship, and therapeutic significance of magnesium supplementation.

References

- 1) Gitelman HJ, Graham JB, Welt LG. A new familial disorder characterized by hypokalemia and hypomagnesemia. *Trans Assoc Am Physicians* **79**: 221–235, 1966.
- 2) Mastroianni N, Fusco M, Zollo M, et al. Molecular cloning, expression pattern, and chromosomal localization of the human Na-Cl thiazide-sensitive cotransporter (SLC12A3). *Genomics* **35**: 486–493, 1996.
- 3) Bettinelli A, Bianchetti M, Borella P, et al. Genetic heterogeneity in tubular hypomagnesemia-hypokalemia with hypocalciuria (Gitelman's syndrome). *Kidney Int* **47**: 547–551, 1995.
- 4) Tsukamoto T, Kobayashi T, Kawamoto K, Fukase M, Chihara K. Possible discrimination of Gitelman's syndrome from Bartter's syndrome by renal clearance study: report of two cases. *Am J Kidney Dis* **25**: 637–641, 1995.
- 5) Colussi G, Rombola G, Brunari C, et al. Abnormal reabsorption of Na⁺/Cl⁻ by the thiazide-inhibitable transporter of the distal convoluted tubule in Gitelman's syndrome. *Am J Nephrol* **17**: 103–111, 1997.
- 6) 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* **12**: 24–30, 1996.
- 7) Imamura Y, Mori T, Miyabayashi M, Inoue K, Takeuchi M, Komiyama A. Two sibling cases of Gitelman syndrome. With particular interest in their clinical response to the treatment. *Nippon Shonika Gakkai Zasshi (J Jpn Pediatr Soc)* **100**: 1778–1784, 1996 (in Japanese).
- 8) Aoki T, Miyauchi Y, Ootsu M. A case of Bartter's syndrome showing various psychotic symptoms. *Seishin Igaku (Clin Psychiatry)* **39**: 265–270, 1997 (in Japanese).
- 9) Yoshimoto M, Tsutsui T, Kuroki S, Nishio T. Gitelman syndrome. Report of two cases. *Kobe City Hosp Bull* **36**: 87–90, 1997 (in Japanese).
- 10) Yoshida M, Fujiwara M, Hotsubo T. A case report of Gitelman syn-

- drome. *Rinsho Shoni Igaku (J Clin Pediatr)* **45**: 113–115, 1997 (in Japanese).
- 11) Takeuchi K, Kato T, Taniyama Y, et al. Three cases of Gitelman's syndrome possibly caused by different mutations in the thiazide-sensitive Na-Cl cotransporter. *Intern Med* **36**: 582–585, 1997.
 - 12) Hisakawa N, Yasuoka N, Itoh H, et al. A case of Gitelman's syndrome with chondrocalcinosis. *Endocr J* **45**: 261–267, 1998.
 - 13) Kawai H, Satomi A, Yoshimura G, Deura T. A case of Gitelman's syndrome. *Rinsho Taieki* **26**: 43–44, 1999 (in Japanese).
 - 14) Shiota J, Ito K, Nakamura Y, et al. A case with acute renal failure, rhabdomyolysis and tetanic convulsions, subsequent to intermittent vomiting. *Jin To Toseki (Kidney and Dialysis)* **47**: 743–747, 1999 (in Japanese).
 - 15) Kadomatsu K, Iwamoto M, Ozawa S, Akizuki T, Mizuiri E, Hasegawa A. A case of Gitelman's syndrome. *Nippon Naika Gakkai Zasshi (J Jpn Soc Intern Med)* **88**: 2230–2232, 1999 (in Japanese).
 - 16) Matsuki M, Ohara K, Hirokawa Y, et al. Mutations of three familial Gitelman's syndrome. *Horumon To Rinsho (Clin Endocrinol)* **48**: 164–169, 2000 (in Japanese).
 - 17) Kameoka K, Isotani N, Ito M, Furukawa K, Takamatsu J. A case of Gitelman's syndrome with quadriplasia from Basedow's disease. *Horumon To Rinsho (Clin Endocrinol)* **48**: 170–173, 2000 (in Japanese).
 - 18) Monkawa T, Kurihara I, Kobayashi K, Hayashi M, Saruta T. Novel mutations in thiazide-sensitive Na-Cl cotransporter gene of patients with Gitelman's syndrome. *J Am Soc Nephrol* **11**: 65–70, 2000.
 - 19) Tsuchiya H, Kamoi K, Soda S, Sasaki H, Kobayashi K, Hayashi M. Gitelman's syndrome first diagnosed as Bartter's syndrome. *Intern Med* **40**: 1011–1014, 2001.
 - 20) Tajima T, Kobayashi Y, Abe S, et al. Two novel mutations of thiazide-sensitive Na-Cl cotransporter (TSC) gene in two sporadic Japanese patients with Gitelman syndrome. *Endocr J* **49**: 91–96, 2002.
 - 21) Pantanetti P, Arnaldi G, Balercia G, Mantero F, Giacchetti G. Severe hypomagnesaemia-induced hypocalcaemia in a patient with Gitelman's syndrome. *Clin Endocrinol* **56**: 413–418, 2002.
 - 22) Yamashiki J, Terui K, Hirai Y, et al. Genetic analysis of a case of Gitelman's syndrome. *Nippon Naika Gakkai Zasshi (J Jpn Soc Intern Med)* **91**: 3503–3506, 2002 (in Japanese).
 - 23) Iannello S, Belfiore F. Hypomagnesemia. A review of pathophysiological, clinical and therapeutical aspects. *Panminerva Med* **43**: 177–209, 2001.
 - 24) Takeuchi K, Kure S, Kato T, et al. Association of a mutation in thiazide sensitive Na-Cl cotransporter with a familial Gitelman's syndrome. *J Clin Endocrinol Metab* **81**: 4496–4499, 1996.
 - 25) Mastroianni N, Bettinelli A, Bianchetti M, et al. Novel molecular variants of the Na-Cl cotransporter gene are responsible for Gitelman syndrome. *Am J Hum Genet* **59**: 1019–1026, 1996.
 - 26) Lemmink HH, Knoers N, Karolyi L, et al. Novel mutations in the thiazide-sensitive Na-Cl cotransporter gene in patients with Gitelman syndrome with predominant localization to the C-terminal domain. *Kidney Int* **54**: 720–730, 1998.
 - 27) Yahata K, Tanaka I, Kotani M, et al. Identification of a novel R642C mutation in Na/Cl cotransporter with Gitelman's syndrome. *Am J Kidney Dis* **34**: 845–853, 1999.
 - 28) Bettinelli A, Rusconi R, Ciarmatori S, et al. Gitelman disease associated with growth hormone deficiency, disturbances in vasopressin secretion and empty sella: a new hereditary renal tubular-pituitary syndrome? *Pediatr Res* **46**: 232–238, 1999.
-