—Case Reports—

A Case of Gitelman Syndrome that Was Difficult to Distinguish from Hypokalemic Periodic Paralysis Caused by Graves' Disease

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A 21-year-old man presented with hyperthyroidism and hypokalemia and was treated for thyrotoxic hypokalemic periodic paralysis caused by Graves' disease. Thyroid function soon normalized but hypokalemia persisted. Laboratory data revealed hyperreninemic hyperaldosteronism and metabolic alkalosis consistent with Gitelman Syndrome. The patient was found to have a previously unreported compound heterozygous mutation of T180K and L858H in the SLC12A3 gene, and Gitelman Syndrome was diagnosed. He was started on eplerenone to control serum potassium level. Alternative diagnoses should be considered when electrolyte imbalances persist after disease resolution.
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Key words: eplerenone, Gitelman syndrome, thyrotoxic hypokalemic periodic paralysis, hypokalemia, SLC12A3 gene

Introduction

Thyrotoxic hypokalemic periodic paralysis (THPP) mainly affects Asian males and manifests as recurrent episodic hypokalemia, thyrotoxicosis, and muscle weakness[1]. In THPP, proximal muscles are more greatly affected than distal muscles[2]. Hypokalemia in THPP results primarily from marked shifts in intracellular potassium (K).

Gitelman syndrome (GS) was first described by Gitelman and colleagues in 1966[3] and is similar to Bartter syndrome (BS) in that both are autosomal recessive disorders characterized by hypokalemia, metabolic alkalosis, and normal blood pressure despite hyperreninemic hyperaldosteronism. In general, age at onset is older for GS than for BS, and GS can be distinguished from BS by the presence of hypomagnesemia and hypocalciuria. However, type III BS is difficult to distinguish from GS by laboratory findings alone, because patients with type III BS also have hypomagnesemia and hypocalciuria. In these cases, genetic analysis is required[4].

In most cases, GS is caused by homozygous or compound heterozygous loss-of-function mutations in the solute carrier family 12 member 3 (SLC12A3) gene that encodes the thiazide-sensitive sodium chloride cotransporter (TSC)[5–8]. In GS, hypokalemia is caused by decreased tubular reabsorption of K. Here, we report a case of GS complicated by Graves' disease (GD) in a young Japanese man, which was difficult to distinguish from THPP caused by GD.

Case Report

A 21-year-old Japanese man developed slowly progressive myalgia in both lower extremities. Three months after onset of symptoms, he could not ascend stairs without using a handrail, because of muscle weakness. He presented to our hospital for evaluation.

His height was 168.5 cm and he weighed 59.0 kg (body mass index, 20.8 kg/m^2). A review of systems showed a 4 kg weight loss, thyroid gland enlargement, and muscle weakness in both lower limbs. His vital signs were blood pressure 140/60 mm Hg, pulse rate 126 bpm, body temperature 36.8°C, respiratory rate 12 breaths per minute,

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Table 1 Laboratory data, including basal hormone values

Blood gases		Biochemistry	
pH	7.466	AST	24 U/L
pCO_2	47.7 mmol/L	ALT	37 U/L
HCO_3	33.6 mmol/L	LD	174 U/L
BE	8.4 mmol/L	γGT	33 U/L
Complete blood chemistry		T-Bil	1.3 mg/dL
WBC	6,900 /μL	TP	6.9 g/dL
RBC	608×10^4 /μL	Alb	4.4 g/dL
Hb	16.9 g/dL	UA	8.4 mg/dL
Ht	47.5 %	BUN	12.2 mg/dL
Plt	33.4×10^4 /μL	Cr	0.59 mg/dL
Hormones		Na	142 mmol/L
TSH	0.006 μIU/mL	Cl	93 mmol/L
FT3	17.49 pg/mL	K	2.1 mmol/L
FT4	5.09 ng/dL	Ca	10.6 mg/dL
TRAb	(+)	P	4.3 mg/dL
TSAb	(+)	Mg	1.8 mg/dL
Cortisol	14.2 μg/dL	CK	313 U/L
PRA	15 ng/mL/hr	TC	141 mg/dL
Aldosterone	199.0 pg/mL	LDL-C	83 mg/dL
Urine analysis		HDL-C	47 mg/dL
Na	67.5 mmol/L	TG	57 mg/dL
Cl	86.4 mmol/L	CRP	0.25 mg/dL
K	45.9 mmol/L	PG	106 mg/dL
Cr	133.5 mg/dL	HbA1c	5.5 %

pCO_2, partial pressure of carbon dioxide; HCO_3, bicarbonate; BE, base excess; WBC, white blood cells; Hb, hemoglobin; Ht, hematocrit; Plt, Platelets; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TRAb, thyrotrophin receptor antibody; TSAb, thyrotrophin receptor antibody; PRA, plasma renin activity; Na, sodium; Cl, chlorine; K, potassium; Cr, creatinine; AST, aspartate aminotransferase; ALT, alamine aminotransferase; LD, lactate dehydrogenase; γGT, γ-glutamyl-transferase; T-Bil, total bilirubin; TP, total protein; Alb, albumin; UA, uric acid; BUN, blood urea nitrogen; Ca, calcium; P, phosphorus; Mg, magnesium; CK, creatine kinase; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; CRP, C-reactive protein; PG, plasma glucose; HbA1c, hemoglobin A1c

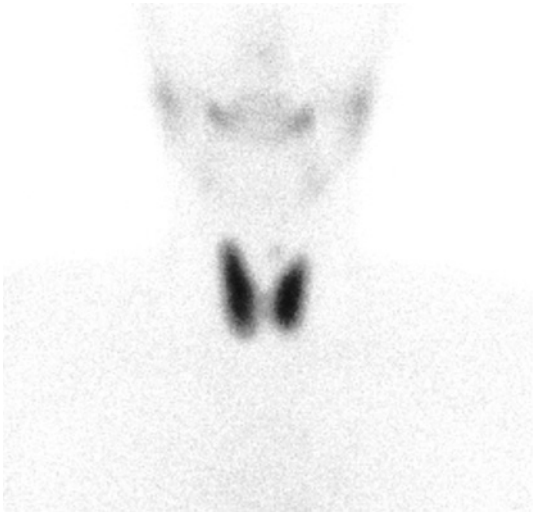

Fig. 1 Technetium scan showing elevated, bilateral, diffuse uptake of radioactive tracer (6.5%).

and SpO_2 96% in room air.

Laboratory data, including baseline hormone levels, are shown in **Table 1**. The results showed hyperthyroidism (free T4, 17.49 ng/dL; free T3, 5.09 pg/mL) and hypokalemia (serum K, 2.1 mmol/L), and an electrocardiogram showed QT elongation. He was hospitalized with a tentative diagnosis of THPP.

He was treated with potassium iodide (50 mg/day), propranolol (30 mg/day), and oral KCl (4,800 mg/day). On hospital day 2, serum K had corrected from 2.1 to 3.6 mmol/L, and his muscle weakness had resolved. On day 4, technetium-99m pertechnetate thyroid scintigraphy revealed diffuse elevated tracer uptake at 6.5%, consistent with GD (**Fig. 1**), and methimazole (15 mg/day) was administered. When he was discharged, on day 8, serum K level had improved to 3.6 mmol/L, and serum free T4 and free T3 levels had declined to 3.49 ng/dL and 8.43 pg/mL, respectively.

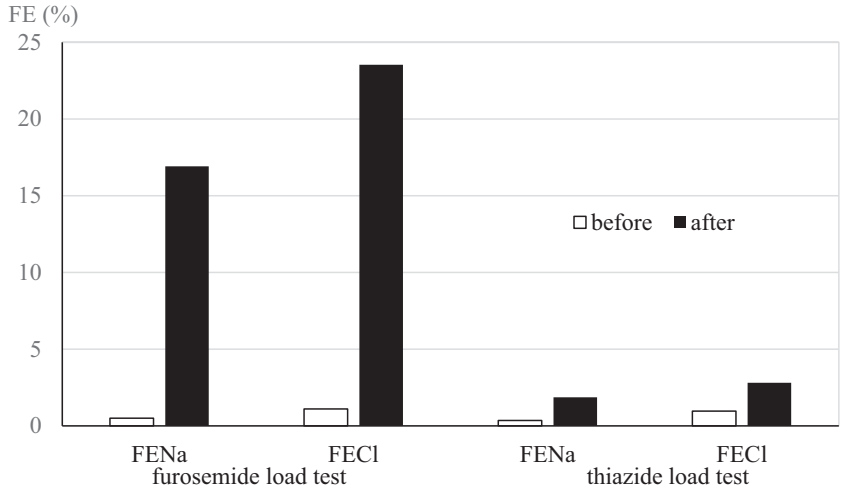

Fig. 2 Fractional excretion of Na (FENa) and Cl (FECl) during two diuretic-loading tests. Open bars: before furosemide or thiazide loading; closed bars: after furosemide or thiazide loading.
[FENa] (%) = ([urine Na] / [serum Na]) × ([urine Cr] / [serum Cr]) × 100
[FECl] (%) = ([urine Cl] / [serum Cl]) × ([urine Cr] / [serum Cr]) × 100

After discharge, the patient reached a euthyroid state within 5 weeks, and the methimazole dose was gradually reduced. However, his serum K level failed to normalize despite daily supplementation with 7,200 mg oral KCl. He did not take laxatives or diuretics and had no history of vomiting or diarrhea. The presence of hyperreninemic hyperaldosteronism and metabolic alkalosis suggested a renal tubular disease such as GS or BS. We suspected GS because of his hypocalciuria (fractional excretion of calcium, 0.49%) but could not exclude BS. He was thus rehospitalized for a furosemide-loading test and thiazide-loading test.

The patient underwent two diuretic-loading tests, as described by Tsukamoto *et al*.[9]. After an overnight fast, he was instructed to drink 1,200 mL (20 mL/kg body weight) of water within 30 minutes, after which he received an intravenous infusion of 0.45% saline. When urinary flow reached >20 mL/min, samples of serum and urine were obtained to calculate maximum free-water clearance. Furosemide (20 mg intravenously) or hydrochlorothiazide (100 mg orally) was administered thereafter. Samples were collected when urinary flow was at maximum level.

Fractional excretions of Na (FENa) and Cl (FECl) during the two diuretic-loading tests are shown in **Figure 2**. The patient had a good response (maximal diuretic-induced increase in FECl; ΔFECl) to furosemide and a weak response to thiazide, which suggested GS. Thus, we performed gene sequencing analysis of the SLC12A3 gene after receiving the consent of the patient and his parents. He had a compound heterozygous mutation of c.539C>G (T180K) in exon 4 and c.2573T>A (L858H) in exon 22. The T180K mutation was derived from his father, and the L858H mutation was derived from his mother (**Fig. 3**). Both mutations have been previously identified in GS patients[10]. However, this compound heterozygous mutation has not been reported previously.

Genetic diseases such as GS require long-term medical treatment. To minimize adverse effects, we administered eplerenone, which has greater selectivity than spironolactone for the aldosterone receptor. Eplerenone and KCl doses were adjusted on the basis of carefully monitored serum K levels and blood pressure. Serum K levels were maintained within the normal range with 50 mg eplerenone and 1,800 mg oral KCl (**Fig. 4**). The eplerenone dose was increased to 100 mg, and oral KCl was discontinued. However, serum K level gradually decreased, and low-dose oral KCl was restarted, which resulted in near-normal K levels (3.2-3.4 mmol/L).

Discussion

On the basis of his clinical findings, THPP was initially diagnosed in our patient. THPP generally affects young Asian males. In Japan, the incidence of THPP in thyrotoxic patients is 1.9%[11]. In contrast, the incidence of THPP in thyrotoxic North American Caucasians is 0.1% to 0.2%[11]. Our patient was treated with anti-thyroid drugs and oral potassium, and he reached a euthyroid state within 5 weeks. However, he required 7,200 mg of oral KCl per day to normalize his serum K levels. The pres-

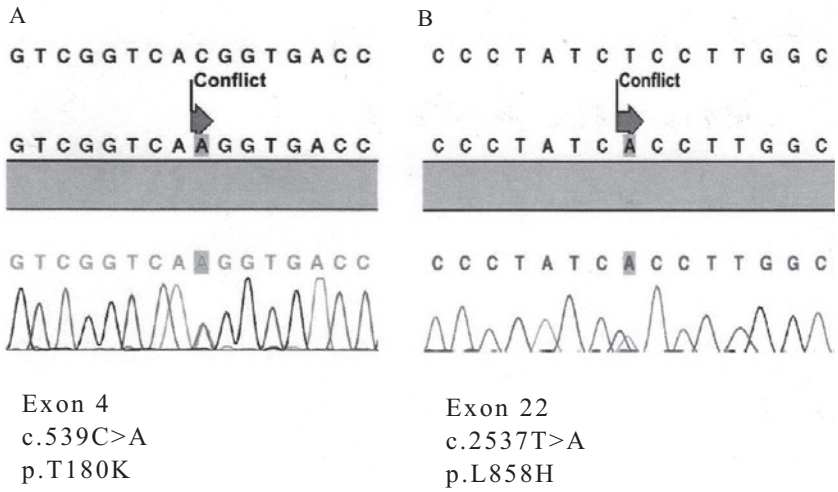

Fig. 3 Gene sequence analysis of SLC12A3. A and B, Results of direct sequencing of PCR fragments in exon 4 (A) and exon 22 (B). (A) Heterozygous point mutation of ACG to AAG in residue 180. This single nucleotide substitution causes a change of threonine to lysine at codon 539. (B) Heterozygous point mutation of CTC to CAC in residue 2,864. This single nucleotide substitution causes a change of leucine to histidine at codon 858.

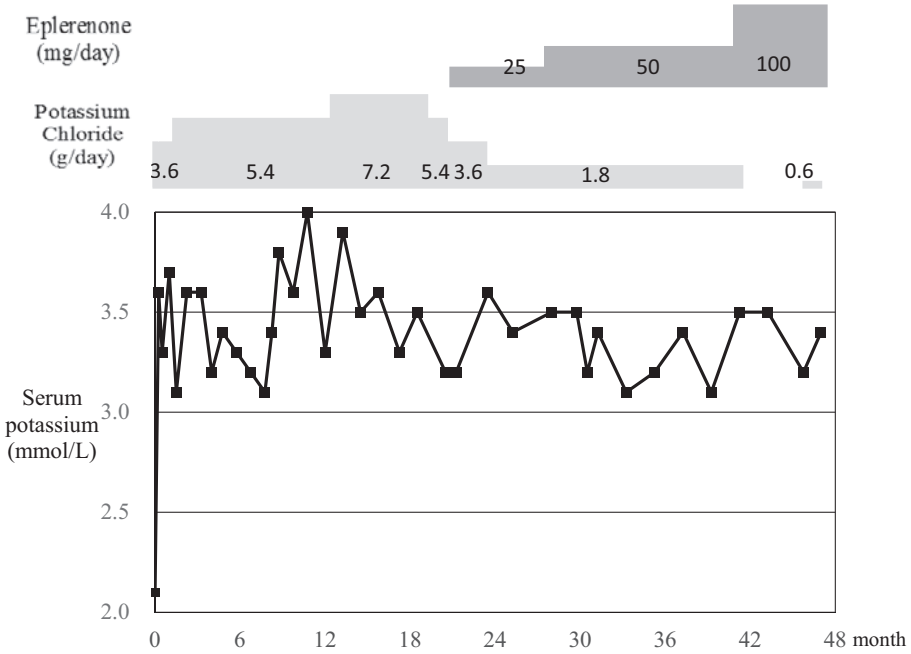

Fig. 4 Clinical course. Serum K level was maintained within the normal range during treatment with eplerenone and oral KCl.

ence of hyperreninemic hyperaldosteronism and metabolic alkalosis suggested GS or BS, and GS was subsequently diagnosed. Refractory hypokalemia in our patient probably resulted from a loss of K due to abnormal TSC[12–16]. A similar case of concurrent GD and GS was reported by Imashuku *et al*.[17].

Because the laboratory findings for GS and BS are similar, furosemide- and thiazide-loading tests are commonly used to differentiate these diseases. In our patient, the thiazide-loading test resulted in a ΔFECl of 1.85%. A ΔFECl of 2.3% is the cutoff point for GS diagnosis (sensitivity 93%, specificity 100%, as reported by Colussi *et al.*)[18]. However, Nozu *et al*.[4] reported that seven of nine patients with type III BS had a ΔFECl of 2.3% or greater, suggesting that loading tests alone cannot differentiate GS from type III BS. Molecular diagnosis is therefore re-

quired for definitive diagnosis.

GS is caused by mutations in the SLC12A3 gene, which encodes the apical TSC[4]. At present, more than 100 distinct mutations, including deletions, insertions, nonsense, missense, frameshift, and splice site mutations, have been identified in patients with GS[14]. In our patient, sequence analysis revealed a compound heterozygous mutation comprising T180K and L858H. Single mutations of T180K and L858H have previously been reported[10], but no compound heterozygous mutation has been previously described.

Treatment with eplerenone and oral KCl was started. Eplerenone rather than spironolactone was selected because the latter binds to several types of steroid hormone receptors, thereby causing multiple adverse effects[19]. Previous studies reported that spironolactone significantly increased HbA1c and plasma cortisol levels as compared with placebo[20,21]. In contrast, eplerenone has a lower affinity for other types of steroid hormone receptors, like the androgen and progesterone receptors (less than 1/100 of that for the aldosterone receptor)[19]. Our patient was started on low-dose eplerenone (25 mg/day), to decrease the risks of hypotension and hyperkalemia. The dose was gradually increased as the dose of oral KCl was decreased.

GS often causes hypomagnesemia. In our patient, however, serum magnesium remained in the normal range. Normomagnesemia was reported in some patients with GS caused by TSC mutations[13,22–26]. Nakamura *et al*.[26] reported that two of five patients with GS had normal magnesium levels; both patients were male. Moreover, Lin *et al*.[25] reported that male patients in two families with molecularly proven GS were normomagnesemic, whereas female patients had hypomagnesemia, even though each family member had the same TSC mutation. Although both these reports were small, the findings suggest that gender affects electrolyte profile in GS.

In conclusion, we described a patient with concurrent GD and GS who had a previously unreported compound heterozygous mutation, as indicated by a literature search. Eplerenone improved intractable hypokalemia, and no obvious adverse effects were observed. When electrolyte imbalances persist despite disease resolution, other disorders that cause hypokalemia should be considered.

Conflict of Interest: None declared.

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