

## Concurrence of thyrotoxicosis and Gitelman's syndrome-associated hypokalemia-induced periodic paralysis

Shinsaku Imashuku,<sup>1</sup>

Tomoko Teramura-Ikeda,<sup>1</sup> Naoko Kudo,<sup>1</sup> Shigehiro Kaneda,<sup>1</sup> Toshihiro Tajima<sup>2</sup>

<sup>1</sup>Division of Pediatrics, Takasago-seibu Hospital, Takasago; <sup>2</sup>Department of Pediatrics, Hokkaido Graduate School of Medicine, Sapporo, Japan

### Abstract

A 16-year-old Japanese boy with a history of truancy had been treated at a psychiatric clinic. When the patient was referred to us for hypokalemia-associated paralysis, the diagnosis of thyrotoxic hypokalemic periodic paralysis was made, common in Asian men. Subsequently, the patient was found to have persistently high plasma renin and aldosterone levels. Thus, solute carrier family 12 member 3 gene (*SLC12A3*) analysis was performed. A novel missense homozygous mutation CTC->CAC at codon 858 (L858H) was found for which the patient was homozygous and his non-consanguineous parents heterozygote. These findings indicated that the patient developed hypokalemia-associated paralysis concurrently with thyrotoxicosis and Gitelman's syndrome. This case underscores the importance of careful examinations of adolescents with complaints of truancy as well as of precise determinations of the causes of hypokalemia-associated paralysis.

### Introduction

Hypokalemia-induced periodic paralysis in adolescents comprises sporadic or familial thyrotoxic hypokalemic periodic paralysis (THPP) secondary to thyrotoxicosis,<sup>1-4</sup> and the hereditary syndrome of Gitelman.<sup>5-9</sup> THPP is a common complication of hyperthyroidism in Asian men and manifests as recurrent episodic muscle weakness with hypokalemia and thyrotoxicosis. THPP is caused by ion channel defects that result in the rapid shift of potassium into cells under hyperthyroid conditions. In sporadic cases, this is due to Na<sup>+</sup>/K<sup>+</sup>-ATPase channel activation because of high thyroxine levels.<sup>1,3</sup> In familial cases, it is due to an association of mutation in the *KCNJ3* (voltage-gated potassium channel) gene.<sup>2,4</sup> In contrast, Gitelman's syndrome has been attributed to mutations in the solute carrier family 12 mem-

ber 3 gene (*SLC12A3*) encoding thiazide-sensitive Na<sup>+</sup>/Cl<sup>-</sup> cotransporter of the distal tubule, respectively.<sup>5-9</sup> Gitelman's syndrome is an autosomal recessive disorder that commonly presents in older children or young adults and manifests clinically as hypokalemic hypomagnesemic hypocalciuria with metabolic alkalosis. It is thought to be a milder variant of Bartter's syndrome, which presents earlier in life.<sup>7</sup> To confirm the diagnosis of Gitelman's syndrome, renal clearance studies and/or TSC gene mutational analysis are required.<sup>6,8,10</sup>

The case of a Japanese male adolescent with concurrent THPP and Gitelman's syndrome is reported here.

### Case Report

A 16-year-old Japanese boy was treated at a psychiatric clinic for general malaise and truancy. He complained of being unable to wake up in the morning, probably because of late nights or insomnia, and had no desire to attend school for reasons that were unclear to his parents. Specific factor(s) that could explain this, such as bullying or peer group pressure, were not detected. He did not clearly describe his symptoms as weakness or fatigue. When he was first referred to us, we noticed mild hypokalemia (serum K; 2.6 mEq/L; reference values 3.6-5.0 mEq/L) but also euthyroidism and no weakness. Two years later, the patient returned due to fatigue and hypokalemia (serum K; 2.4 mEq/L). Three months later, he had a near paralytic episode, where he could not move his arms, associated with severe hypokalemia (serum K; 1.7 mEq/L). On admission, the patient, who was 160 cm tall (-1.0 SD) and weighed 50 kg (-1.0 SD), had normal blood pressure (120/80 mmHg) but exhibited hyperthyroidism. The laboratory data were as follows: WBC 12,980/μL, Hb16.0 g/dL, platelet counts 345,000/μL, AST 24 IU/L, ALT 36 IU/L, BUN 10.4 mg/dL, creatinine 0.66 mg/dL, serum Na 141 mEq/L, Cl 93 mEq/L, Mg 2.0 (reference values, 1.8-2.4) mg/dL, TSH 0.002 (0.436-3.78) μIU/mL, free T3 12.8 (2.1-4.1) pg/mL, free T4 4.9 (1.0-1.7) ng/dL, and anti-TSH receptor antibody (TRAb) 56.8% (<15%). The urine calcium-creatinine ratio was reduced to one-tenth (0.022) of the reference value. Blood gas analysis revealed HCO<sub>3</sub><sup>-</sup> and BE levels of 39.9 (24±2) mmol/L and 14.6 (0±2) mmol/L, respectively. Thus, the patient had metabolic alkalosis. He also showed high renin activity of 15.5 (0.2-2.7) ng/mL/hr in the supine position but normal aldosterone levels of 89 (30-159) pg/mL in the supine position. Thus, he was tentatively diagnosed with THPP and started on anti-thyroid propylthiouracil (PTU) (300 mg/day) and oral KCl (2400 mg/day). He

Correspondence: Shinsaku Imashuku, Division of Pediatrics and Hematology, Takasago-seibu Hospital, 1-10-41 Nakasuji, Takasago, 676-0812 Japan.

Tel. +81.79.447.0100 - Fax: +81.79.447.0180

E-mail: shinim95@mbox.kyoto-inet.or.jp

Key words: hypokalemic periodic paralysis, thyrotoxicosis, Gitelman's syndrome, adolescents, truancy.

Contributions: SI, TTK, NK, SK, took care of the patient; TT performed a gene mutation analysis; SI wrote a paper.

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responded well and his serum K levels improved to >3.6 mEq/L within 5 months. Within 6 months, he became euthyroid with normal anti-TRAb levels and returned to school. His past history before adolescence was insignificant. In particular, he lacked apparent polyuria or nocturnal enuresis in early childhood. He had a healthy sister and no family member had thyroid disease.

However, the serum K levels of the patient failed to reach >4.0 mEq/L in the follow-up period, even after euthyroidism was achieved. Moreover, persistently high plasma renin activity in the upright position of 15.8-30.1 (0.2-3.9) ng/mL/hr was noted. His aldosterone concentrations in the upright position were also high at 433-642 (28.9-307) pg/mL. This suggested that he might also have Gitelman's syndrome.

At the age of 20 years, the patient complained again of insomnia. Thus, the *SLC12A3* genes of the patient and his parents were analyzed with written informed consent. The patient had the missense homozygous mutation CTC->CAC at codon 858 (L858H). Both parents, who were not consanguineous, were heterozygous for this mutation (Figure 1). The patient was diagnosed with Gitelman's syndrome and has been doing well on spironolactone (50-100 mg/day), magnesium oxide (250 mg/day) and NSAID (naproxen 100 mg/day), in addition to maintenance doses of PTU and KCl (2400 mg/day).

## Discussion

The patient was first diagnosed with THPP due to its high incidence in Asian men but later developments suggested that Gitelman's syndrome may have been masked. In particular, although his hyperthyroidism and symptoms resolved with PTU and KCl treatment, he continued to exhibit persistently high renin-aldosterone status, metabolic alkalosis and hypocalciuria. Eventually, *SLC12A3* gene sequence analysis confirmed that he had Gitelman's syndrome in addition to THPP. The hypokalemia and muscle paralysis exhibited by this patient probably resulted from the sudden intracellular shift of potassium that occurs in

THPP<sup>3</sup> and from the loss of potassium due to the malfunctioning renal tubular electrolyte transporters that characterize Gitelman's syndrome.<sup>5-9</sup> However, although two hypokalemia-inducing mechanisms were operating simultaneously in this patient, his symptoms were no worse than those of patients with THPP or Gitelman's syndrome alone. A literature survey failed to identify any previous cases of concurrent THPP and Gitelman's syndrome. Notably, although more than 100 Gitelman's syndrome-associated *SLC12A3* gene mutations have been reported to date,<sup>7,9</sup> and L623P occurs frequently in Japan, presumably due to a founder effect,<sup>9</sup> the L858H mutation of our patient has not been reported previously. THPP-related gene analysis could not be performed because of the lack of family history for thyroid disease.

In summary, the patient had concurrent THPP and Gitelman's syndrome. Adolescents with a history of truancy should be tested carefully for such conditions. Moreover, it should be underscored that the causes of hypokalemia-associated periodic paralysis are complex and that caution should be exercised, even when the patient appears to have THPP and it is common in his residential area.

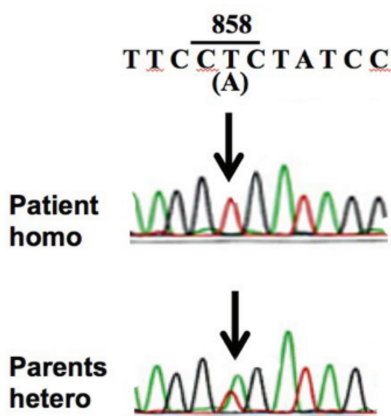


Figure 1. Sequence analysis revealed that the patient had the homozygous mutation CTC->CAC at codon 858 (L858H) in the alleles encoding the *SLC12A3* gene. Both parents were heterozygous for this mutation.

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