



Persistent Hypokalemic Paralysis in a Patient with Graves' Disease and Gitelman Syndrome

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Thyrotoxic periodic paralysis (TPP) is a potentially life-threatening condition. Graves' disease accounts for the majority of cases of TPP. However, another diagnosis should be considered when repeated hypokalemic paralysis occurs in patients that maintain a euthyroid status. In this study, we report a case of persistent hypokalemic paralysis in a patient with Graves' disease and Gitelman syndrome and provide a brief review of Gitelman syndrome focused on challenges with diagnosis and management when it is accompanied by TPP.

Key Words: Hypokalemic periodic paralysis, Graves' disease, Gitelman syndrome

Introduction

Thyrotoxic periodic paralysis (TPP) is a potentially life-threatening condition, and the presentation often is misleading and leads to challenging diagnosis.¹⁾ Additionally, hypokalemic periodic paralysis can occur in patients without thyrotoxicosis. Previously, we reported two cases of hypokalemic periodic paralysis after low-dose glucocorticoid injection.²⁾

For most cases of TPP, Graves' disease also is present. Almost all patients completely recover from paralysis with potassium chloride supplementation and proper management. However, it is important to consider other diagnoses for cases with repeated hypokalemic paralysis that occur despite a euthyroid status.

We recently observed hypokalemic periodic paralysis in a patient with Graves' disease and a novel diagnosis of genetically confirmed Gitelman syndrome. In this article, we provide a brief review of Gitelman syndrome focused on the challenges of diagnosis and management when accompanied by TPP.

Case Report

A 42-year-old man was admitted to the emergency department with lower extremity paralysis that started three hours prior to his presentation. He did not have any significant past medical history. He was alert and oriented to person, place, and time. His vitals on presentation included a blood pressure of 120/80 mmHg, heart rate of 90 beats per minute, respiratory rate of 16 per minute, and temperature of 36.7°C. Physical examination revealed lower extremity motor weakness of grades 2/5 with no sensory deficit. The thyroid gland was palpable and slightly enlarged. The rest of the physical examination showed no abnormalities.


Laboratory tests revealed multiple abnormalities including hypokalemic metabolic alkalosis and thyrotoxicosis. Initial serum potassium level was 2.0 mEq/L (reference range: 3.5–5.5). Serum calcium and magnesium levels were 10.0 mg/dL (range: 8.4–10.2), and 1.5 mg/dL (range: 1.5–2.6), respectively. Thyroid stimulating hormone (TSH) level was <0.003 μ IU/mL

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(range: 0.35–4.94), free T4 level was 1.99 ng/dL (range: 0.70–1.48), and T3 level was 299.65 ng/dL (range: 58–159). Anti-thyroperoxidase (TPO) antibody was 13.95 IU/mL (range: 0–34). Anti TSH receptor antibody level was increased to 2.07 IU/L (range: 0–1.75), and thyroid-stimulating antibody bioassay showed an increase to 156.6% (range: 0–140). Table 1 provides an overview of the initial laboratory tests.

An EKG (electrocardiogram) was performed, and the results showed changes consistent with hypokalemia, including flattened T waves and enlarged U waves with a prolonged QT interval (Fig. 1). A chest X-ray

and computed tomography of the head without contrast showed no acute abnormalities. The thyroid scan showed homogeneous and slightly increased uptake of technetium-99m pertechnetate in both lobes (Fig. 2: 3.2% radioactive thyroid uptake). Ultrasound results showed heterogeneous enlargement of the excess thyroid with increased vascularity. Based on the results of these tests, TPP was diagnosed in this patient with Graves' disease.

The potassium level increased to 4.1 mEq/L after intravenous and oral replacement, and motor abilities progressively recovered after maintaining normal po-

Table 1. Laboratory data, including basal hormone values

Test variables	Result	Reference range
Sodium (mEq/L)	140	135–150
Potassium (mEq/L)	2.0	3.5–5.5
Chloride (mEq/L)	97	98–106
Calcium (mg/dL)	10.0	8.4–10.2
Magnesium (mg/dL)	1.5	1.5–2.6
Phosphorus (mg/dL)	3.7	2.5–4.5
pH	7.516	7.36–7.41
pCO ₂ (mmHg)	39.0	35–48
pO ₂ (mmHg)	81.4	83–108
HCO ₃ (mM/L)	30.8	18–23
O ₂ saturation (%)	96.3	95–98
TSH (μ IU/mL)	<0.003	0.35–4.94
T3 (ng/dL)	299.65	58–159
Free T4 (ng/dL)	1.99	0.70–1.48
Plasma renin activity (ng/mL/h)	5.07	0.17–5.38
Aldosterone (ng/dL)	17.36	3.0–16.0
		(in supine position)
Urine calcium (mg/dL)/creatinine (mg/dL)	6.4/101.35=0.063	

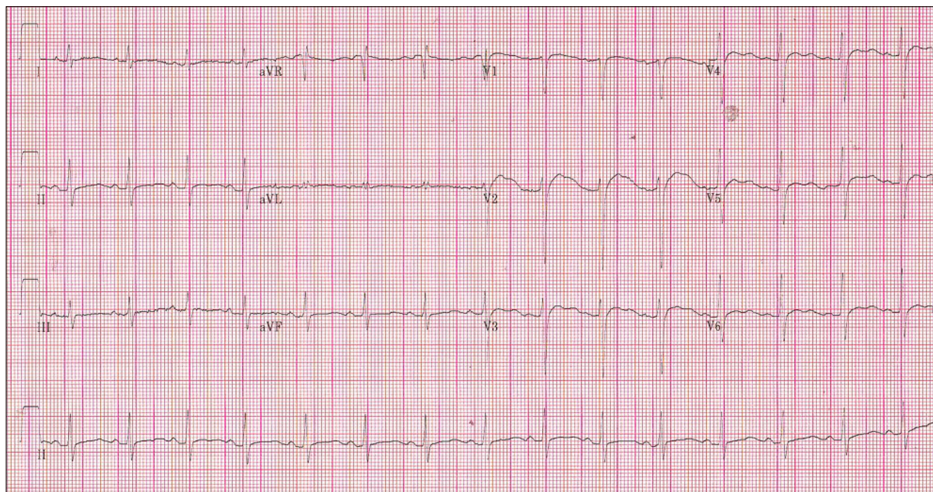


Fig. 1. EKG with changes indicative of hypokalemia.

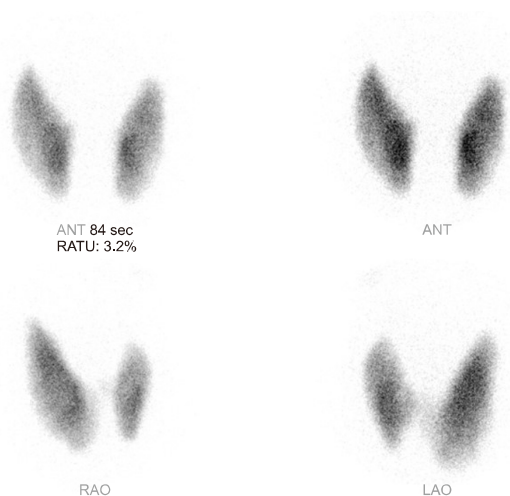


Fig. 2. Thyroid scan showing an enlarged thyroid gland and diffusely increased uptake of technetium-99m pertechnetate throughout both lobes (3.2% radioactive thyroid uptake).

tassium level. The patient started taking 10 mg/day of methimazole orally. On day 4, muscle power recovered completely, and he was discharged on 10 mg/day of methimazole and oral potassium replacement. The dose of methimazole was reduced gradually to 5 mg/day.

However, on follow-up, the patient complained of repeated muscle weakness, even though a euthyroid state had been established after 1.5 months of methimazole. Laboratory assessment indicated that his potassium level had decreased to 2.1 mEq/L. Because the severe hypokalemic condition persisted, the initial diagnosis was re-evaluated, and the possibility of coexistence of TPP and Gitelman syndrome was considered. We reviewed the initial laboratory tests and found hypokalemia, low normal limit of magnesium level, and hypocalcemia with metabolic alkalosis. Gitelman syndrome was confirmed based on genetic analysis of the SLC12A3 gene. An SLC12A3 gene mutation was detected in the 1,868th nucleotide with a T to C mutation, which resulted in the change of leucine to proline.

The patient was given oral potassium and magnesium replacement with spironolactone. On follow-up, the patient's potassium level was maintained above 4.3 mEq/L, and the serum magnesium level increased to 2.3 mEq/L. No additional instances of paralysis

have been repeated.

Discussion

In this study, we report persistent hypokalemic paralysis in a patient with the coexistence of Graves' disease and Gitelman syndrome. Previously, similar cases have been mostly reported in Asia, especially Japan^{3,4} and China.⁵ Most of them encountered the diagnostic challenges as our case. Compared with previous reports, our case showed lower potassium level (2.0 mEq/L) and less severe thyrotoxicosis. Therefore, early consideration of additional diseases might provide an accurate diagnosis without delay in our patient.

The exact mechanism of TPP is not understood. It is hypothesized that patients with TPP have an underlying channelopathy that is related to mutations in the KCNJ18 gene that encode Kir2.6, a skeletal muscle-specific Kir channel protein.^{6,7} Under thyrotoxic conditions, the protein stimulates tissue responsiveness to beta-adrenergic signaling and increases sodium-potassium ATPase activity and drives potassium uptake into cells and results in hypokalemia.⁸

Although any form of thyrotoxicosis can lead to TPP, Graves' disease is a leading cause. Treatment of TPP in Graves' disease is based primarily on potassium supplementation and regular doses of thionamide. Almost all patients completely recover from paralysis after proper management.

In comparison, Gitelman syndrome is an autosomal recessive, salt-loss tubulopathy that results from mutations in the SLC12A3 gene on chromosome 16q13,^{9,10} which encodes the thiazide-sensitive NaCl cotransporter.¹¹ This syndrome is characterized by hypokalemic metabolic alkalosis with hypomagnesemia and hypocalcemia caused by defective tubular reabsorption.^{12,13} Hyperreninemic hyperaldosteronism that results from volume contraction without hypertension can be observed.¹⁴ Clinical confirmation of suspected patients is based on molecular genetic testing, which should be performed in all patients.¹⁵ The diagnosis can be confirmed based on the detection of biallelic inactivating SLC12A3 mutations.^{9,10}

The estimated prevalence of Gitelman syndrome is 1 in 40,000, with a possibility of a much higher prevalence in Asian populations.^{16,17)} Additionally, there is a wide spectrum of clinical manifestations from asymptomatic to severe forms. Some patients only experience mild symptoms such as tiredness, while others have seizures, tetany, muscle weakness, paresthesia, arrhythmias, and impaired quality of life.¹⁸⁾ Given that a substantial proportion of patients who are asymptomatic or have mild symptoms are not diagnosed, the actual prevalence of Gitelman syndrome might be underestimated.

According to an expert consensus statement, a liberal salt intake with oral magnesium and potassium supplements is a foundation for treating Gitelman syndrome.¹⁵⁾ The most critical challenge of treatment is the recurrence of hypokalemia. In a patient with recurrent and symptomatic hypokalemia, potassium-sparing diuretics (e.g., spironolactone, amiloride, eplerenone) that block the distal tubule sodium-potassium exchange are an add-on option.^{19,20)} In limited cases, the use of renin-angiotensin system blockers (angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers) can be considered with caution.²¹⁾ Although urinary prostaglandin E2 level in Gitelman syndrome usually is normal, some cases have reported that prostaglandin synthase inhibitors (e.g., indomethacin) are effective in some patients.^{22,23)}

The symptoms of Gitelman syndrome, including muscle weakness and electrolyte disorders such as severe hypokalaemia, are very similar to those of TPP in Graves' disease. Thus, clinicians should consider the coexistence of Gitelman syndrome in a patient with recurrent hypokalemic episodes in Graves' disease. Moreover, when evaluating cases of muscle weakness with hypokalemia, assessment of serum and urinary excretion of electrolytes and the acid-base status should be performed in addition to evaluation of thyroid function.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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