

Thyrotoxic Periodic Paralysis: A Case Report and Literature Review

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Thyrotoxic periodic paralysis (TPP) is a rare presentation of thyrotoxicosis most commonly associated with Graves' disease. It is rare in Caucasians, but it affects approximately 2% of Asians (occurring in those of Chinese, Japanese, Vietnamese, Filipino, and Korean descent) with thyrotoxicosis of any cause. Typical thyrotoxic features may be absent despite biochemical thyrotoxicosis. Hypokalemia and muscle paralysis are the result of an acute intracellular shift of potassium and not due to total body potassium deficiency. TPP is a self-limiting condition that is easily corrected by treatment of the thyrotoxicosis. We present a case of a Filipino man, aged 47 years, who presented to the emergency department with acute bilateral lower extremity weakness and hypokalemia who was subsequently diagnosed with TPP due to Graves' disease.

Keywords: Hyperthyroidism; Graves' disease; Thyrotoxic Periodic Paralysis; Weakness

Hypokalemic thyrotoxic periodic paralysis (TPP) is a rare endocrine disorder characterized by the triad of thyrotoxicosis, hypokalemia, and acute muscle weakness, and it is most often encountered at night.¹⁻⁵ Although thyrotoxicosis affects females nine times more frequently than males, TPP occurs more commonly in men (male to female ratio ranging from 17:1 to 70:1), and it occurs in higher rates in males of Asian and Polynesian descent.^{1-3,5} The prevalence in North America is 0.1%–0.2%, but the incidence is expected to rise in the future in both Europe and North America due to immigration patterns.³

The pathophysiology of TPP is currently unknown, but thyroid hormone is thought to stimulate the sodium-potassium-adenosine triphosphatase (Na/K ATPase) pump, resulting in an intracellular potassium shift and resultant hypokalemia without total body potassium deficit.² Thyrotoxicosis of any cause can be associated with TTP, but Graves' disease is the most common.²

Case Presentation

A Filipino male, aged 47 years, presented to the emergency department with leg weakness. He described painless lower limb weakness rendering him unable to stand independently or walk. There was no history of trauma, recent illness, toxic ingestions, fever, heat intolerance, or palpitations. Review of systems was also negative for gastrointestinal, cardiovascular, and respiratory symptoms. His past medical history was significant for poorly controlled hypertension and anxiety. Due to hypertension, he was started on hydrochlorothiazide 25 mg PO daily, candesartan 4 mg PO daily, and amlodipine 5 mg PO daily 3 weeks prior to this current presentation. Family history was unremarkable.

On examination, he was alert, with a heart rate of 113 beats/minute and a blood pressure of 128/65 mmHg, and he was afebrile. There was bilateral proximal leg weakness with normal arm strength. Deep tendon reflexes were reduced in the legs and normal in the arms. Plantar reflexes were normal

Table 1. Thyroid function testing results of this patient revealing hyperthyroidism.

Thyroid Function Test	Patient's Result	Normal Value Range
Thyroid Stimulating Hormone	< 0.01 mIU/L	0.35 – 4.9 mIU/L
Free Thyroxine	21.9 pmol/L	0.0 – 19.0 pmol/L
Free Tri-iodothyronine	11.3 pmol/L	2.76 – 6.45 pmol/L

bilaterally. There were no sensory abnormalities, and cranial nerves were normal. Rectal tone and thyroid examination were normal.

Laboratory studies completed in the emergency department revealed hypokalemia of 1.9 mmol/L (normal 3.5-5.3 mmol/L). Other laboratory investigations including complete blood count, electrolytes, calcium, magnesium and phosphate, renal and liver tests were normal. An electrocardiogram showed sinus tachycardia and no U waves or ST changes.

The patient was admitted to a general medicine ward and placed on a cardiac monitor. Intravenous fluids and intravenous potassium replacement as well as oral potassium replacement were commenced, and his hydrochlorothiazide was discontinued. Correction of his potassium level was achieved within 36 hours, and this correlated with a resolution of his lower limb weakness.

Despite there being no features of hyperthyroidism on physical examination, thyroid function testing was consistent with biochemical thyrotoxicosis as shown in Table 1. A radioactive iodine thyroid uptake scan followed the laboratory testing, and this was consistent with Graves' disease. The scan showed increased radioactive iodine uptake of 35% at 4 hours (normal is 5%–14%) and 88% at 24 hours (normal is 8%–30%) with homogenous distribution of the tracer. Testing for thyroid stimulating hormone (TSH) receptor antibodies (TRAb) was negative.

The patient was discharged with a diagnosis of TPP due to Graves' disease, possibly triggered by the initiation of hydrochlorothiazide. At discharge, his potassium level was 4.3 mmol/L without potassium supplementation. His hydrochlorothiazide was discontinued, and he was started on methimazole. Discussion will be had with him regarding definitive therapy of his hyperthyroidism.

Discussion

TPP is an uncommon complication of thyrotoxicosis, most commonly associated with Graves' disease.² The exact mechanism is unknown, but it is thought to arise from direct and indirect stimulation of the Na/K ATPase pump by thyroid hormone.^{2,6} Thyroid hormone activates the thyroid response element in cellular nuclei, thereby inducing Na/K ATPase gene transcription.⁴ It also increases beta-adrenergic receptor sensitivity, which itself increases Na/K ATPase pump activity

in skeletal muscles.⁷ The end result from both of these processes is increased intracellular shift of potassium and depleted extracellular potassium stores.⁴ Eventually there is hyperpolarization of the muscle cell membranes, leading to muscle paralysis and clinical weakness.⁷ Young and middle aged adult men appear to be most affected by TPP,

which may be explained by testosterone's stimulatory effects on the Na⁺-K⁺ATPase, unlike estrogen, which decreases its activity.⁵

Attacks of muscle paralysis preferentially affect the proximal lower extremities and may be precipitated by high carbohydrate meals, vigorous exercise, alcohol ingestion, trauma, infection, stress, and medications such as insulin and diuretics.^{1,2} The development of TPP is also associated with genetic mutations (eg, KCNE3) and certain leukocyte antigen subtypes (A2BW22, AW19B17, B5, BW 46, DRw8), which increase Na/K ATPase pump activity or modify other potassium channels in skeletal muscle cells.⁷ As there was no history of high carbohydrate or alcohol ingestion, vigorous exercise, stress, trauma, or infection in our patient, the initiation of hydrochlorothiazide was the most likely trigger for TPP in his case. TPP is rare, and other potential diagnoses should be considered including familial hypokalemic periodic paralysis, myasthenia gravis, Guillain-Barre Syndrome, infectious and inflammatory myopathies, transverse myelitis, cord compression, and other electrolyte abnormalities.² These causes can be excluded based on the history, physical examination, and other investigations. Assessing thyroid function distinguishes TPP from other causes of hypokalemic periodic paralysis, as outlined in Table 2.

In patients with TPP, thyrotoxic symptoms and signs may be subtle or absent, as in our case, and the presenting complaint may be of weakness, paralysis, or other symptoms of hypokalemia.^{2,8} Our patient's hyperthyroidism was confirmed with biochemical laboratory testing, and his 24-hour thyroid scan was consistent with Graves' disease. While his TRAb was negative, this does not exclude a diagnosis of Graves' disease, which can be absent in a small minority of patients without overt symptoms, goiter, or classic ophthalmopathy and dermopathy, as in this case.⁹ Proponents of TRAb advocate that sensitive and specific assays, when available, can mitigate the need for radioactive iodine uptake (RAIU) and thyroid scan.¹⁰ However, a negative antibody test can occur, and clinical performance of TRAb testing has not been evaluated in patients with subclinical hyperthyroidism.¹⁰ RAIU and thyroid scan remain the gold standard to differentiate causes of thyrotoxicosis, with sensitivity and specificity over 95%.¹⁰ The joint guideline of the American Thyroid Association and the American Association of Clinical Endocrinologists recommends a thyroid uptake and scan as the primary differential diagnostic test for thyrotoxicosis

Table 2. Triggers of Extra-Cellular Hypokalemia In Periodic Paralysis

Increased Intra-Cellular Shift

- Increased Insulin
- Increased Beta-Adrenergic Activity
- Elevated Extra-Cellular pH
- Paradoxical Hypokalemia After Repletion
- Increased Hematopoietic Cell Production
- Hypothermia
- Barium, Cesium and Chloroquine Intoxification
- Antipsychotic Medication (Risperidone, Quetiapine)
- Familial Hypokalemia Periodic Paralysis
- Thyrotoxic Periodic Paralysis

Increased Gastro-Intestinal Losses

- Vomiting
- Diarrhea & Malabsorption Syndromes (Celiac Disease, Infectious, Short-Bowel Syndrome)
- Laxative Use
- Tube Decompression/Drainage
- Ingestion of Clay (Binds Potassium in the Gastro-Intestinal Tract)

Increased Urinary Losses

- Diuretic (Loop Diuretics, Thiazide Diuretics & Carbonic Anhydrase Inhibitors)
- Hyperaldosteronism
- Type 1 (Distal) Renal Tubular Acidosis
- Type 2 (Proximal) Renal Tubular Acidosis
- Hypomagnesemia
- Hypercalcemia
- Renal Tubular Injury
- Sjogren's Syndrome
- Bartter & Gitelman Syndrome
- Liddle's Syndrome
- Medication (amphotericin B, cisplatin)

Other Rare Causes

- Decreased Potassium Intake
- Dialysis
- Plasmapheresis

when the clinical presentation of thyrotoxicosis is not diagnostic of Graves' disease.⁹

In patients with TPP, the severity of muscle weakness is directly correlated to the degree of hypokalemia.⁵ To prevent cardiac arrhythmias, correction of the hypokalemia is imperative.² Potassium replacement therapy with close monitoring of serum potassium is the mainstay for the acute treatment of TPP.^{2,6} Intravenous potassium replacement may result in quicker correction of hypokalemia and faster

recovery of muscle strength compared to oral replacement.⁶ In most cases, < 50 mEq of potassium is required, and > 90 mEq in 24 hours can result in rebound hyperkalemia.⁸ Non-selective beta-blockers (eg, propranolol) can be used to attenuate the adrenergic overstimulation of the sodium-potassium ATPase pump if there is a poor response to potassium replacement.^{2,5} Our patient responded well to moderate doses of potassium without the need for beta blockers. Definitive treatment of TPP requires correction of the thyrotoxic state including with anti-thyroid medication, radioactive iodine thyroid ablation, or thyroidectomy.^{2,5,6}

In conclusion, TPP should be considered in all patients with muscle weakness, especially in middle aged males of Asian descent, who present with acute weakness or paralysis and hypokalemia. While TPP is currently rare in Europe and North America, current trends in human migration will likely result in a greater incidence of TPP in the future.³ Thyroid function testing should be completed in patients presenting with muscle weakness, even when overt symptoms and signs of thyrotoxicosis are absent. Management includes appropriate resuscitative measures with moderate doses of potassium replacement to prevent rebound hyperkalemia and beta blockers for intractable symptoms.^{2,5} Recurrent attacks may be mitigated by avoiding known triggers and restoration of a euthyroid state with appropriate treatment.^{2,5}

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