

# Thyrotoxic Periodic Paralysis

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**T**hyrotoxic periodic paralysis (TPP) is a rare syndrome characterized by muscular weakness and paralysis in the predisposed thyrotoxic patient. The incidence of this disease in a largely white, North American hyperthyroid study population is approximately 0.1%; however, it is 10 times that in matched Asian populations.<sup>1</sup> Although patients with TPP are almost uniformly males of Asian descent, cases have been reported in persons of Polynesian, African, Hispanic, Greek, and American Indian descent.<sup>2-5</sup> Although most of the literature regarding TPP comes from countries with large Asian populations, the rapid increase in ethnic diversity in the Western and European nations has led to an increase in reports where it was once exceedingly rare.<sup>6</sup>

The paralysis is reversible once the hypokalemic and hyperthyroid states are corrected. However, failure to recognize the unique clinical characteristics of TPP may lead to a delayed diagnosis, missed diagnosis, or iatrogenic error resulting in recurrences, arrhythmias, respiratory failure, and death.<sup>7-9</sup> This article describes the case of a young Thai man, recently diagnosed with hyperthyroidism, who presented with an acute paralysis. The clinical characteristics, pathophysiology, management, and complications of TPP are reviewed.

## CASE PRESENTATION

### Patient Presentation

A 28-year-old Thai man arrived at the emergency department (ED) in the early morning hours with the complaint of being unable to stand. The previous afternoon, he had noticed a diffuse muscular ache, especially in his thighs. When he attempted to rise from his desk, he found that his legs collapsed under his own weight.

His weakness had become progressively worse over the preceding days, reaching the point of a paralytic crisis on the morning of presentation. Additionally, he stated that over the previous few days he had experienced excessive sweating, heat intolerance, palpitations, and 2 to 4 loose bowel movements per day. The patient was

nauseated and vomited once prior to arrival. The past medical history and family history were unremarkable.

### Outpatient Evaluation 6 Days Earlier

Six days earlier, the patient visited an outpatient primary care clinic, stating that he had been "ill" for the past 2 months. The review of systems was remarkable for fatigue, tremulousness, headaches, myalgias, polydipsia, and a 15-lb weight loss over the 2-month period, despite his voracious appetite. During this period he had intermittently felt very weak in the legs (especially walking up stairs); however, the episodes would resolve spontaneously.

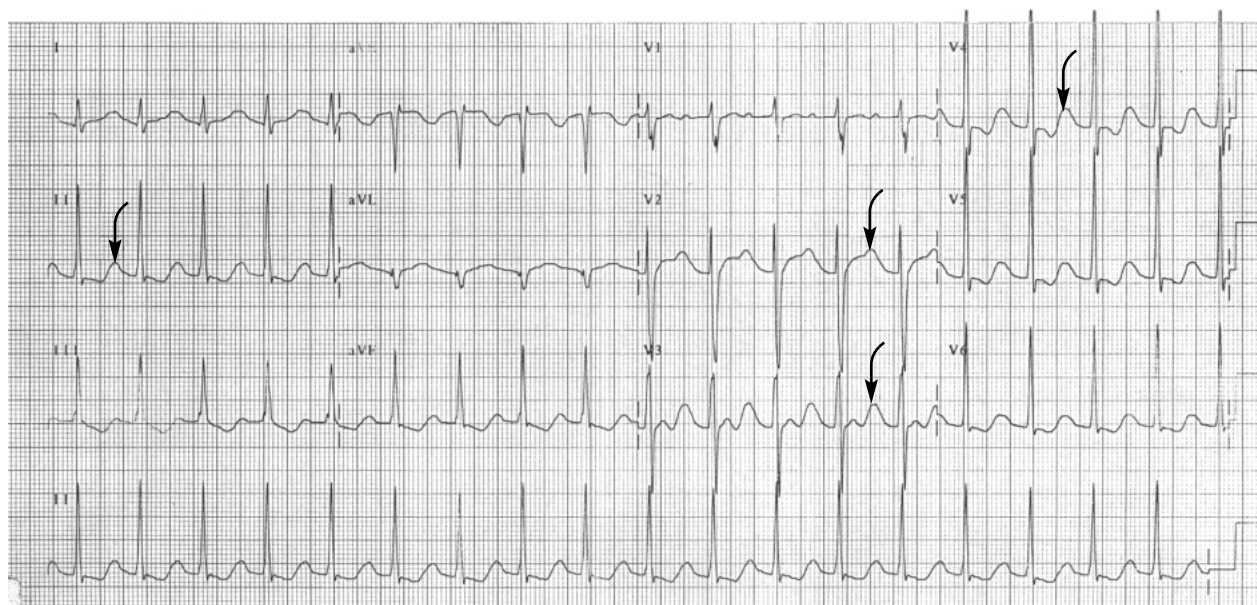
At that initial outpatient clinic evaluation, his laboratory results were notable for a thyroid-stimulating hormone level of 0.01  $\mu\text{U}/\text{mL}$  (normal, 0.4–4.20  $\mu\text{U}/\text{mL}$ ) and a hemoglobin level of 13.4 g/dL (normal, 13.5–17.1 g/dL). The remainder of the complete blood count was normal, as were the results of the serum electrolyte panel, urinalysis, and plasma levels of glucose, urea nitrogen, and creatinine. The following day he was informed of the abnormal thyroid test result and returned for a complete thyroid panel, which subsequently confirmed the diagnosis of hyperthyroidism. He was referred to an endocrinologist for management; however, his paralysis developed prior to that evaluation.

### Evaluation in the Emergency Department

Upon arrival to the ED, the patient had to be lifted from a wheelchair to the bed. The physical examination in the ED showed a pale, diaphoretic, acutely ill-appearing man with profound weakness. His vital signs were as follows: blood pressure, 144/79 mm Hg; pulse,

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**Figure 1.** Initial 12-lead electrocardiogram (ECG) of the case patient. At the time this ECG was performed, his serum potassium level was 1.7 mEq/L. The large U waves in lead II and leads V2 to V5 (arrows) are characteristic of TPP. Note in this ECG that the P waves are actually fused with the preceding U waves.

115 bpm; respiratory rate, 18 breaths/min; temperature, 36.1°C (97.1°F). The pertinent findings were a diffusely enlarged thyroid gland and an accentuated precordial thrust. He had no obvious exophthalmos or integumentary findings suggestive of hyperthyroidism. The neurologic examination demonstrated an awake, alert, and oriented young man with diffuse weakness. The girdle muscles and extremities were particularly weak, with the legs being more affected than the arms. The strength of the proximal muscle groups of the legs was graded at 1/5, whereas the strength of the muscles of the upper arms was graded at 2/5. Muscle strength was symmetrical bilaterally. Bilateral hand grip strength was only slightly diminished. The deep tendon reflexes were significantly diminished in the lower extremities. Cranial nerve function was intact. A fine tremor of the hands was noted. Sensation and mentation were within normal limits, and he exhibited no obvious emotional lability.

An electrocardiogram (ECG) was obtained, and it revealed a regular rhythm tachycardia and several findings consistent with severe hypokalemia, such as tall U waves in lead II and in the anterior leads (Figure 1). In addition, prominent ST segment depression in the inferior and lateral leads was evident. The ECG provided the first objective evidence that the patient's paralysis could be secondary to hypokalemia.

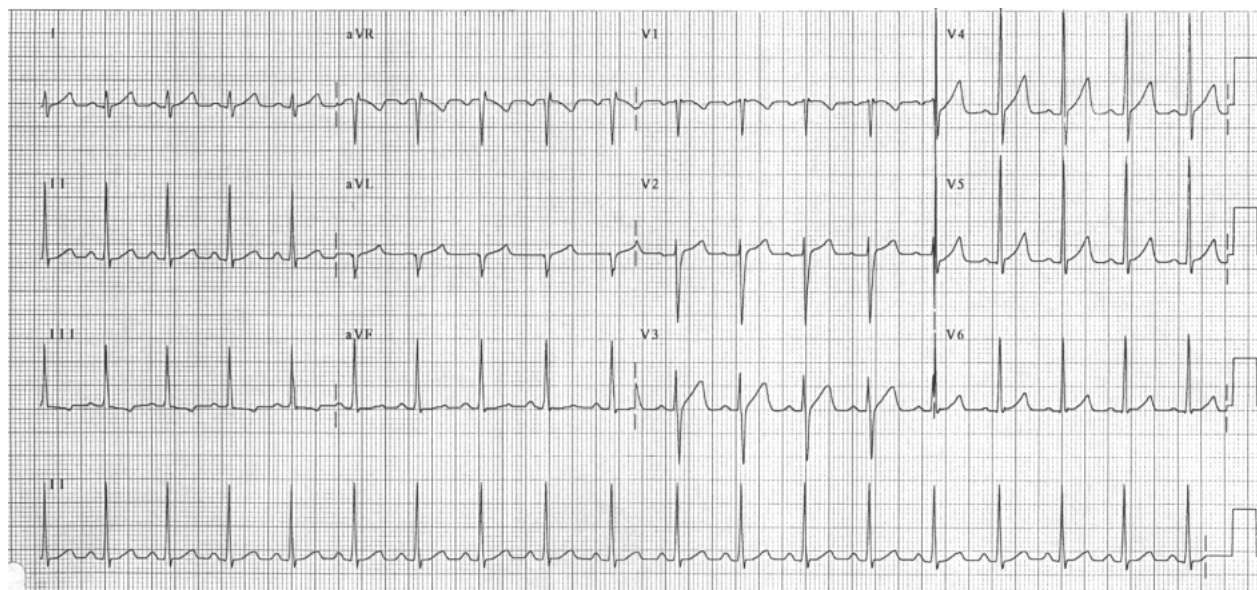
The initial electrolyte analysis was notable for a potassium level of 1.7 mEq/L (normal, 3.5–5.3 mEq/L). The

remainder of the electrolyte levels and the plasma levels of urea nitrogen, creatinine, and glucose were within normal limits. The calcium, magnesium, and phosphorus levels were normal. A complete blood count revealed a mild microcytic anemia. The muscle enzyme assay measured total creatine phosphokinase at 324 U/L (normal, 22–269 U/L). The thyroid-stimulating hormone level was less than 0.12  $\mu$ U/mL (normal, 0.35–5.50  $\mu$ U/mL), supporting the diagnosis of thyrotoxicosis.

#### Treatment and Outcome

The patient's treatment in the ED consisted of potassium chloride replacement. The patient received 40 mEq of potassium chloride by mouth and an additional 40 mEq of potassium chloride intravenously over 4 hours. Within 2 hours of therapy, he demonstrated dramatic improvement in his motor weakness, and he was able to ambulate unassisted. A second ECG, obtained 6 hours after initiation of potassium therapy, revealed a persistent sinus tachycardia with normal appearing P waves, no ST segment depression, and resolution of the U waves (Figure 2).

He was admitted to the internal medicine service for continued telemetry monitoring, serial potassium measurements, and treatment of his hyperthyroidism. A complete serum thyroid function evaluation was ordered upon admission with the following results: free thyroxine,



**Figure 2.** A second electrocardiogram of the case patient performed 6 hours after potassium replacement therapy was initiated shows a sinus tachycardia with resolution of the U waves and ST segment depression. Normal-appearing P waves are now clearly visible.

3.9 ng/dL (normal, 0.8–1.8 ng/dL); triiodothyronine uptake, 48.4% (normal, 22.5%–37%); total thyroxine, 13.9 µg/dL (normal, 4.5–10.9 µg/dL).

While in the hospital, the patient's thyrotoxicosis was treated with oral administration of propylthiouracil and propranolol. He was discharged the following day with a complete recovery of his paralysis and was scheduled for outpatient endocrine follow-up. At outpatient follow-up with an endocrinologist, it was decided that thyroid ablation with radioactive iodine would be attempted. Unfortunately, prior to the ablation procedure he experienced 2 milder paralytic crises. One year after ablation and with continued daily thyroid hormone replacement in the form of synthroid, he has had no further paralytic crises.

## DISCUSSION

Although the connection between hyperthyroidism and periodic paralysis was first described by Rosenfeld in 1902, TPP has remained a disorder rarely encountered in the continental United States.<sup>10</sup> Although more than 90% of patients with TPP are of Asian descent, the condition is not limited to this group.<sup>2</sup> The male-to-female ratio of patients with TPP has been reported as 20:1 or higher in North American series; however, the ratio is much higher in primarily Asian populations, making TPP in women a very rare clinical entity.<sup>10</sup> (Conversely, hyperthyroidism is primarily a disease of women.) An understanding of the

unique clinical features and differential diagnosis of TPP can significantly aid the clinician in proper diagnosis of this disease.

## Etiology and Pathophysiology

Because TPP is so strongly linked to gender and ethnic origin, a genetic predisposition undoubtedly exists. However, the exact mode of transmission has yet to be clearly defined. The pathophysiology of TPP is not completely understood and is currently a subject of scientific debate. It is probably multifactorial, involving at least hypokalemia and the hyperadrenergic state of thyrotoxicosis. Thyrotoxicosis causes increased binding and decreased inactivation of catecholamines at the tissue receptor site. The amplified stimulation of the  $\beta_2$ -adrenergic receptors on the muscle cells that results from the increased catecholamine activity is thought to lead in turn to increased  $\text{Na}^+\text{K}^+\text{-ATPase}$  activity.<sup>11</sup> The end result of the augmented  $\text{Na}^+\text{K}^+\text{-ATPase}$  activity is hypokalemia and a decrease in the ability of muscle cells to depolarize and contract when stimulated.<sup>9</sup>  $\text{Na}^+\text{K}^+\text{-ATPase}$  activity appears to be higher in patients with TPP than in those without the disease.<sup>12</sup> The  $\text{Na}^+\text{K}^+\text{-ATPase}$  pump is also activated by insulin and androgens, which may explain the relationship of paralytic attacks after high carbohydrate meals and the male predilection for the disease.<sup>13,14</sup>

Although hypokalemia is a hallmark and clearly a component of the disease, it is probably not the sole

**Table 1.** Differential Diagnosis of Acute Weakness

**Neuromuscular junction diseases**

Myasthenia gravis  
Organophosphate poisoning  
Botulism  
Eaton-Lambert syndrome

**Spinal cord diseases**

Transverse myelitis  
Poliomyelitis  
Metastatic tumor  
Primary tumor  
Amyotrophic lateral sclerosis

**Polyneuropathies**

Guillain-Barré syndrome  
Tick paralysis  
Paralytic seafood poisoning

**Primary acute myopathies**

Periodic paralysis  
Electrolyte abnormalities  
Myoglobinuria  
Polymyositis  
Alcoholic myopathy  
Muscular dystrophy

**Psychiatric and functional disorders**

Malingering  
Conversion disorder  
Munchausen syndrome

and ultimate mediator of the paralytic attacks. Propranolol has been found to prevent paralytic attacks in patients with TPP who have serum potassium levels typically associated with paralysis.<sup>4</sup> The finding that metoprolol, a selective  $\beta_1$ -adrenergic antagonist, does not protect patients from the attacks is consistent with the specific role of  $\beta_2$ -adrenergic receptors in mediating the catecholamine-induced  $\text{Na}^+, \text{K}^+$ -ATPase activity in skeletal muscle.<sup>15</sup>

**Clinical Features and Diagnosis**

TPP is characterized clinically by an acute paralytic crisis accompanied by hypokalemia. The differential diagnosis of acute weakness is exhaustive and includes myopathies, neuropathies, electrolyte abnormalities, psychiatric disorders, and spinal and neuromuscular

diseases (Table 1).<sup>16–18</sup> Once it has been determined that the patient is hypokalemic, the differential diagnosis narrows to include TPP, familial periodic paralysis (FPP), barium poisoning, and a variety of potassium-deficit disorders.<sup>16</sup>

When the symptoms of hyperthyroidism are separated from the clinical presentation, TPP most closely resembles FPP, a more frequently encountered clinical entity. In fact, if hyperthyroidism has not been previously diagnosed, the patient's age, race, gender, and family history may provide the only clues to a diagnosis of TPP. In patients with TPP, a family history of similar syndromes is rarely present; in contrast, patients with FPP typically have a family history of periodic paralysis. Patients with TPP typically present in the third to fourth decade of life, whereas those with FPP present at or before adolescence. Because most hyperthyroid patients have been symptomatic for weeks to months prior to the paralytic crisis, a physical examination with a thorough review of systems may provide clues to the sometimes clinically occult thyrotoxic condition.<sup>17</sup>

There exists a seasonal predilection for the patient with TPP to experience a paralytic crisis during the warmer months. The vast majority of crises occur during the nighttime hours. High carbohydrate meals, physical exertion, cold exposure, infection, and even emotional stresses have been known to precipitate paralysis in the predisposed individual.<sup>19</sup>

Although variations exist, the paralytic crisis in TPP generally follows a characteristic pattern. The weakness is most predominant in the lower extremities and occurs to a lesser degree in the upper limbs. Proximal muscle groups tend to be more affected than distal muscle groups. Speech, ocular muscles, sensation, and cognition are spared. Respiratory function is rarely affected.<sup>19</sup>

Hypokalemia is the single most common electrolyte abnormality during an acute crisis. Unless the patient has a secondary complication of the crisis or thyrotoxicosis (eg, diarrhea or vomiting) hypokalemia will often be the only electrolyte abnormality. TPP associated with hypophosphatemia as well as hypokalemia was once thought to be rare; however, in a review of hospital records of 24 thyrotoxic paralytic crises that occurred over a period of 15 years, this combination occurred in 80% of cases.<sup>5,6</sup> Additionally, although calcium pump activity is decreased during paralysis in TPP patients, no consistent findings pertaining to serum calcium levels have been demonstrated. Serum muscle enzyme levels are usually normal. Thyroid function studies are uniformly diagnostic of thyrotoxicosis (ie, low thyroid-stimulating hormone with increases in free thyroxine, triiodothyronine uptake, and total thyroxine levels).

Cardiac disturbances in rate and rhythm are common in patients with TPP. The most common arrhythmias are sinus tachycardia, atrial flutter, atrial fibrillation, atrial and ventricular extrasystoles, paroxysmal supraventricular tachycardia, and, rarely, ventricular fibrillation.<sup>7,10</sup> Electrocardiographic findings during an acute paralytic crisis are typical of hypokalemia and include U waves (usually in leads V2 to V4), flattened T waves, QT prolongation, ST segment depression, and fusion of the P waves with the preceding U waves, giving the P wave a “tilted” appearance.<sup>10,20</sup>

### Management of TPP

The standard therapy for TPP is potassium-replacement therapy. Additionally, propranolol has proven to be a valuable adjunct to the remission of the acute phase of TPP and the prevention of recurrences until a euthyroid state is established.<sup>4</sup>

Potassium replacement treats the paralysis and also—and perhaps, more importantly—decreases the potential for arrhythmias. The paralysis, especially milder cases, frequently resolves spontaneously, and correction to a euthyroid state will always result in resolution of the paralysis. However, the most immediate life-threatening concerns are those of conduction blocks and arrhythmias. With this in mind, it should be emphasized that these patients do not have a total body depletion of potassium but, rather, have a distribution problem.<sup>21</sup>

Although most patients have a persistent hypokalemia, the serum potassium level occasionally has returned to the reference range by the time the patient is evaluated.<sup>22</sup> In one study, the initial serum potassium level at presentation ranged from 1.1 to 3.4 mmol/L.<sup>6</sup> As the paralysis and/or the thyrotoxicosis resolve, the intracellular potassium returns to the intravascular space. Numerous cases of severe rebound hyperkalemia during treatment have been reported. Therefore, if potassium replacement is initiated, it is important to use judicious doses and monitor potassium levels frequently during the treatment and recovery phase. For this reason, some authors have proposed that intravenous therapy be reserved for only the most unstable patients and those in whom oral replacement is not possible.<sup>23</sup> Anecdotal reports recommend potassium replacement doses in the range of 90 to 130 mEq over a 24-hour period, given in divided doses.<sup>6,17</sup>

The ultimate objective of therapy is to establish a euthyroid state, because the hypokalemia and paralysis appear to be thyrotoxicosis-dependent, and recurrences are virtually nonexistent if the patient is euthyroid.<sup>21</sup> Therapy aimed at this objective should be initi-

ated as soon as possible via medical, surgical, or ablation therapies. Most patients will respond to the standard therapies for hyperthyroidism, such as propylthiouracil or carbimazole.

Because TPP can closely resemble other disorders of acute paresis, it is this author’s recommendation that a TSH level be checked in those patients whose acute weakness remains undiagnosed. All patients who present in a TPP crisis should be admitted to the hospital for telemetry monitoring, initiation of treatment for the thyrotoxic condition, and serial potassium measurements until the threat of arrhythmias has resolved. Close outpatient follow-up for thyroid function studies and long-term management of the hyperthyroidism is important to prevent recurrences.

### SUMMARY

This article presents a case of acute paralysis and severe hypokalemia in a young Thai man, who was recently diagnosed as hyperthyroid. The patient demonstrated many of the salient features of this unique endocrine emergency, including acute paresis, severe hypokalemia, numerous symptoms of hyperthyroidism, and, ultimately, an ECG with findings consistent with severe hypokalemia. In addition, the patient—a young Asian male with no family history of periodic paralysis—had the characteristic profile of a patient with TPP. At present, thyrotoxic periodic paralysis is a disease that is rarely encountered outside largely Asian populations. The rare nature of the disease notwithstanding, as the world’s nations become more ethnically diverse, clinicians can expect to encounter this disease more frequently.

The emergency physician is often the first to see these patients. Therefore, it is imperative that he or she recognize the characteristic clinical features of TPP and distinguish them from those findings in other similar forms of paresis. Prompt diagnosis and the initiation of the appropriate management aimed at correction of both the hypokalemia and the thyrotoxic state will minimize the risk of an iatrogenic error, morbidity, and potential death. Complete resolution typically occurs with good supportive care, close monitoring, administration of  $\beta_2$ -adrenergic antagonists, and judicious potassium replacement. The correction of the patient’s thyrotoxicosis to an euthyroid state is the definitive cure. **HP**

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