

# Thyrotoxic Periodic Paralysis: Case Report and Review of the Literature

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## Abstract

Thyrotoxic periodic paralysis, a major subtype of hypokalemic paralysis, is a potentially reversible metabolic disorder characterized by acute muscle weakness and severe hypokalemia. It occurs mainly in people of Asian descent. We describe a 25-year-old Asian man with a history of attacks of transient weakness who presented with acute paralysis of the upper and lower extremities. At presentation, the patient was bradycardic with normal systolic blood pressure. Electrocardiography showed abnormal U waves. Although the clinical symptoms were not compatible with thyrotoxicosis, laboratory work-up yielded low levels of potassium and phosphorus. Findings on further evaluation by thyroid uptake scan were consistent with diffuse toxic goiter. Correction of the hypokalemia reversed the acute attack, and subsequent treatment with beta blockers prevented further attacks.

Hyperthyroidism has been shown to stimulate Na-K-ATPase, inducing cellular potassium uptake. It may therefore predispose individuals to paralytic episodes by increasing their susceptibility to the hypokalemic action of epinephrine or insulin. Hypophosphatemia may also be observed.

In view of the increasing number of immigrants from Asia, clinicians should be alert to the possibility of hyperthyroidism as an etiologic factor in periodic paralysis in this and other ethnic groups.

**MeSH Words:** Hypokalemic periodic paralyses, thyrotoxicosis, familial periodic paralysis

## Introduction

The presentation of acute weakness poses a diagnostic dilemma for emergency physicians. Hypokalemic paralysis is a potentially reversible metabolic disorder characterized by acute muscle weakness and severe hypokalemia. Thyrotoxic periodic paralysis (TPP), a major subtype of hypokalemic paralysis, is caused by a massive

intracellular shift of potassium, though obvious signs and symptoms of hyperthyroidism are often absent.[1] Major complications are sometimes severe, including fatal ventricular arrhythmias and respiratory failure.[2] The incidence of TPP is highest in the Asian population, although global migration has led to an increased incidence among other ethnic groups and in Western countries.

We describe a man of Asian descent who presented to a large, urban medical center in the United States with acute muscle paralysis and areflexia. Although the patient did not exhibit overt signs or symptoms of hyperthyroidism, values on thyroid function tests were elevated.

### Case Report

A 25-year-old man of Asian descent presented to the emergency department for evaluation of pain and paralysis in the upper and lower extremities. The patient reported that the previous evening he had experienced a mild, crampy pain in both legs that was aggravated by ambulation. He retired to bed and later awoke with severe pain and weakness in all extremities.

Barely able to crawl to the bathroom, he had called a neighbor who, in turn, notified the Emergency Medical Service. The patient described similar episodes during the past three years, though not to this extent. The pain often began at night and improved the following morning. He had visited a walk-in clinic three years before but was told nothing was wrong. The last episode had occurred one week before, but it resolved spontaneously after 3 hours. The patient denied any fever, chills, nausea, vomiting, diarrhea, chest pain or shortness of breath. He described a normal appetite with regular fluid intake. He had last eaten the evening before presentation. He denied any foreign travel, and had been living in the United States for the past seven years. The patient also denied use of alcohol, illicit drugs or any medications other than multivitamins. There was no history of recent trauma or illness, except for appendicitis treated by appendectomy nine years previously. A capillary glucose check performed by the Emergency Medical Service at the scene registered 40 mg/dL. 25 grams of glucose was administered.

On physical examination, the patient was afebrile, awake, and alert. Arterial pressure was 126/53 mmHg; heart rate 56 beats/min; and respiratory rate 16 breaths/min with an oxygen saturation of 100% in room air. The lungs were clear bilaterally on auscultation. A grade 2 holosystolic ejection murmur was noted. The patient was dysarthric and areflexic, and exhibited 0/5 strength in the proximal upper and lower extremities bilaterally. Sensory

examination revealed no abnormalities. There was no atrophy. Cranial nerves II through XII were grossly intact.

The laboratory test results are listed in Tables 1 and 2. The initial AccuCheck reading was 266 mg/dL. Arterial pH measured 7.38, and ionized calcium level was 1.47 mmol/L. Urine drug screen was negative. A portable chest radiograph did not reveal any acute findings. Computed tomography scan of the brain without contrast was normal. An electrocardiogram performed at presentation showed U waves in the precordial leads (Figure 1).

The patient was treated with 40 mEq potassium chloride p.o. Initial fluids infused were 0.45% NS with 50 mEq potassium chloride per liter at 250 cc/hour. One gram magnesium sulfate was administered intramuscularly. Prior to his arrival, 800 cc of normal saline had been infused, and 40 mEq K-Dur was given p.o. 2 hours later. In addition, 2 packets of NeutraphosK were administered p.o., and an intravenous drip of 11.2 mmol sodium phosphate was started; infusion was continued for 6 hours.

At 5 hours after presentation to the emergency room, the patient's heart rate increased to 114 beats/min, and it remained near that value thereafter. By this time, the patient was able to move his left hand and right foot. Arterial systolic pressure had fallen to 88 mmHg, and after administration of 2 liters of normal saline, it rose to 98 mmHg. On repeated electrocardiography, the U waves had disappeared.

At 7 hours after presentation, serum potassium measured 5.5 mmol/L and phosphorus, 2.1 mg/dL. The patient remained awake and alert with continued improvement in mobility of both upper and lower extremities. His speech returned to normal. Prophylactic treatment with 500 mg Levaquin (levofloxacin) was administered intravenously, and the patient was admitted to the Internal Medicine Service for further evaluation.

The following morning, potassium level was stable at 4.8 mmol/L. The patient reported no further paralysis or pain. Neurologic examination at this time demonstrated 5/5 muscle strength in all four extremities. Deep tendon reflexes were elicited.

We considered an infectious etiology unlikely, given the patient's improvement following potassium and phosphate replacement. On hospitalization day 2, evaluation of the patient's thyroid function had shown a thyroid stimulating hormone level of <0.06 UIU/ml and free thyroxine level of 4.05 ng/dL. No human immunodeficiency virus antibody was detected. Echocardiography revealed a normal left ventricular size, normal systolic function, and mild pulmonary hypertension. Arterial blood pressure had been normotensive throughout hospitalization on the Internal Medicine Service, though heart rate did not return to sinus rhythm until day 3. On day 4, treatment with propranolol 20 mg. twice a day was started.

An endocrinologist consulted on day 3 recommended additional tests, which revealed a total triiodothyronine (T3) level of 2.93 ng/ml and thyroid stimulating immunoglobulin level of 111% of baseline (reference range 125 or less). Thyroid uptake scan showed a mildly enlarged thyroid gland with diffuse, homogeneous radiotracer uptake. There was no evidence of hot or cold nodules. Thyroid uptake measured 97%. These findings were consistent with diffuse toxic goiter, and treatment with methimazole 30 mg. po daily was added on day 5. Repeated thyroid function tests were scheduled in 6 weeks with possible radioactive ablation of the thyroid.

Serum potassium level normalized on day 1 on the Internal Medicine Service and remained within normal range thereafter. Twenty-four hour urine potassium and creatinine levels were also within normal range. No further measurements of serum phosphorus were conducted. Normal saline was infused at 100 cc/hr during the patient's entire hospitalization. A regular diet was ordered and was well tolerated. The signs and symptoms of pain and paralysis did not recur following potassium and phosphorus correction.

The patient was discharged in good condition on day 5. He was clinically euthyroid. He was prescribed propranolol 20 mg. po twice daily and methimazole 30 mg. po daily.

### Discussion

The periodic paralyses are a heterogeneous group of primary or secondary muscle diseases characterized by episodes of transient, flaccid

muscle weakness occurring at irregular intervals. In hypokalemic periodic paralysis (HPP), a rare disorder, potassium levels drop to below 3.0 mEq/L. Familial HPP, transmitted by autosomal dominant mode, is more common in Western countries, whereas HPP associated with thyrotoxicosis in the absence of a family history of periodic paralysis or hyperthyroidism, and its unique subtype, sporadic periodic paralysis, are more common in Asia [3-8], predominantly in males.[1] One report found a 15 to 20% risk of thyrotoxic periodic paralysis (TPP) in hyperthyroid Chinese subjects.[9] Although researchers have sought a genetic predisposition, about 95% of cases appear to be sporadic.[1]

Our patient did not exhibit clinical symptoms compatible with thyrotoxicosis, but he was found to be hyperthyroid on laboratory work-up. He had no known family history of hyperthyroidism or neuromuscular disease.

The physiologic basis of flaccid weakness is inexcitability of the muscle membrane. Severe attacks of periodic paralysis are often precipitated by strenuous exercise, stress, or a high carbohydrate meal -- all of which are associated with increased release of epinephrine or insulin.[10] Catecholamines can promote potassium entry into the cells, primarily by increasing Na-K-ATPase activity. Accordingly, hyperthyroidism is a hyperadrenergic state in which beta-2-adrenergic stimulation in muscle cells directly induces cellular K<sup>+</sup> uptake by increasing cAMP, leading to activation of Na-K-ATPase.[6, 11] Thyroid hormone also directly stimulates Na-K-ATPase and increases the number and sensitivity of beta-receptors.[4, 10, 12] Excess thyroid hormone may therefore predispose individuals to paralytic episodes by increasing their susceptibility to the hypokalemic action of epinephrine or insulin.[4] Studies have shown that thyrotoxic patients with periodic paralysis have higher than normal sodium pump activity.[13] It is noteworthy that ATPase activity may be increased by androgens and inhibited by estrogens. This could explain the male predilection in TPP.[14-16] Furthermore, many patients with TPP, like ours, do not exhibit symptoms of hyperthyroidism during an attack. [4, 8, 17] In our patient, systolic blood pressure never rose above 139 mmHg during the whole hospitalization period, and heart rate was bradycardic at his presentation to the emergency department.

Hypophosphatemia is also commonly observed in HPP [6]. Severe hypophosphatemia, defined as a serum phosphate level below 1.5 mg/dL, can affect cardiac function and induce generalized skeletal muscle weakness.[18] Catecholamines can cause an intracellular shift of inorganic  $P_i$  to their effect on potassium. Studies have shown that exogenous epinephrine administration induces acute hypophosphatemia. In patients with TPP, serum phosphate levels frequently normalize spontaneously, without the administration of exogenous phosphate.[19-21] In our case, the severe hypophosphatemia concomitant with paralysis prompted our initiation of phosphate repletion as part of the initial management. Subsequently, phosphate levels measured 2.1 mg/dL.

Hypokalemia due to an acute shift of potassium into cells, without a total body  $K^+$  deficit, is a major diagnostic factor in HPP. Therefore, in patients with suspected HPP, clinicians should determine whether renal wasting is contributing to the hypokalemia.[22] The traditional approach to distinguishing between extrarenal and renal causes of hypokalemia consists of measuring urine potassium concentration or potassium excretion rate in 24-hour samples. However, because therapy with potassium chloride is required promptly, obtaining a 24-hour urine sample for measuring  $K^+$  excretion is not practical. Rather, a spot urine determination prior to potassium repletion should be made.[23] In addition to renal loss, increased gastrointestinal loss must be considered when seeking the cause of the hypokalemia. In our patient, gastrointestinal and renal causes of potassium loss were excluded by history and physical examination. Although the differential diagnosis of hypokalemia is extensive, the range of causes of acute hypokalemic paralysis is much narrower. (Table 3) [7]

When treating severe hypokalemia in patients with HPP, it is important to check that body stores are normal so that the  $K^+$  is given to normalize the plasma  $K^+$  concentration and not to replete a  $K^+$  deficit.[6] During attacks, oral supplementation of potassium is preferable to intravenous supplementation, which should be restricted to patients who are nauseated or unable to swallow. The value of aggressive potassium replacement is questionable because no correlation has been observed between the dose of KCl administered and recovery time.[6,10]

However, there is a danger of excessive  $K^+$  administration because  $K^+$  is rapidly released from cells when the paralysis subsides, leading to the development of hyperkalemia, which poses another risk of cardiac arrhythmia.[6] In a study of 24 episodes of TPP, Manoukain et al. found that rebound hyperkalemia occurred in 30-45% of patients, especially when more than 90 mmol of KCl was administered within 24 hours.[10] In our patient, repeated measurements of  $K^+$  yielded a value of 5.5 mmol/L at 7 hours after treatment was started, but it decreased to 4.8 mmol/L the following morning.

The implication of increased adrenergic activity in the pathogenesis of TPP has led to the use of non-selective beta-blockers as an alternative therapeutic agent in acute attacks owing to their favorable effect on serum  $K^+$  levels (beta-2 effect) and heart rate (beta-1 effect).[6] Lin et al. [24] reported that some cases of TPP were rapidly terminated with oral propranolol (3-4 mg/kg) alone, without supplemental potassium: The paralysis improved, and serum  $K^+$  and phosphate levels rose to normal range within several hours. There was no rebound hyperkalemia.[6,8,24] In our patient, however, nonselective beta blockers were initially contraindicated by the presence of bradycardia and transient hypotension. Moreover, thyroid function tests had not yet been conducted. Nevertheless, control of hyperthyroidism remains the definitive treatment for TPP.[4]

Preventive treatment consists of the restoration of euthyroidism in thyrotoxic patients and the administration of a beta-adrenergic blocker. Beta blockers can reduce the severity and number of attacks and, in most cases, limit the fall in plasma potassium concentration. Other preventive measures include  $K^+$ -sparing diuretics, acetazolamide, and a low-carbohydrate diet.[4,16]

Given the growing number of Asian immigrants worldwide, this case and review of the literature are intended to raise clinician awareness of the disorder and its method of diagnosis and management.

### Conclusion

A severe degree of hypokalemia with paralysis is a potentially life-threatening emergency. In

approaching the patient with HPP, the clinician must determine if the cause derives from an enhanced shift of potassium into cells or from excessive renal wasting. Serum phosphate should be measured, because hypophosphatemia may lead to a combination of respiratory, cardiac, and skeletal muscle dysfunction. In view of the increasing number of immigrants from Asia, clinicians should be alert to the possibility

of hyperthyroidism as an etiologic factor in periodic paralysis in this population. Clinical features of thyroid dysfunction may be clinically silent, lending to the importance of monitoring thyroid function tests. In addition to recognizing the presence of hyperthyroidism, definitive treatment includes discretionary use of potassium supplementation and non-selective beta blockers.

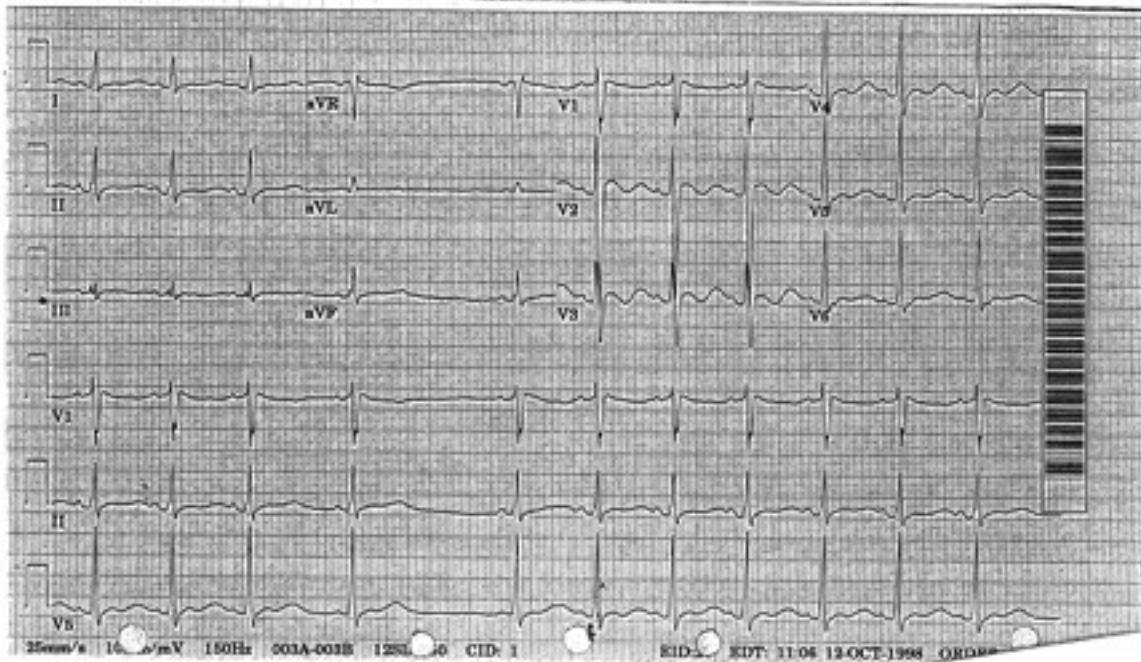


Figure 1. Initial electrocardiogram in a patient with HPP showing U wave in precordial leads V2-V4.

Table 1. Laboratory values at presentation in patient with thyrotoxic periodic paralysis

Parameter	Value	Range
Sodium (mEq/l)	142	135-148
Potassium (mmol/l)	<1.5	3.5-5.3
Chloride (mEq/l)	106	96-107
CO2 (mEq/l)	19	21-31
BUN (mg/dl)	14	6-20
Glucose (mg/dl)	138	60-99
Creatinine (mg/dl)	0.5	0.5-1.2
Calcium (mg/dl)	9.6	8.5-10.5
Magnesium (mg/dl)	1.5	1.58-2.55
Phosphorus (mg/dl)	0.8	2.7-4.5
CPK (U/l)	77	<171

BUN, blood urea nitrogen; CPK, creatinine phosphokinase

Table 2. Complete blood count in patient with thyrotoxic periodic paralysis

Parameter	Value	Range
WBC (k/ul)	11.8	4.6-10.2
Hemoglobin (g/dl)	15.7	14.1-18.1
Hematocrit (%)	49.1	43.5-53.7
Platelets (k/ul)	317	142.0-424.0
% Granulocytes	88.5	37.0-80.0
% Lymphocytes	8.4	10.0-50.0
% Monocytes	2.9	0-12
% Eosinophils	0.2	0-7
% Basophils	0.0	0-3

Table 3. Etiology

Hypokalemic paralysis – Causes and Differential Diagnosis	
<b>Intracellular shift of potassium</b>	
Familial hypokalemic periodic paralysis	
Thyrotoxic periodic paralysis	
Barium poisoning	
<b>Serum potassium deficit</b>	
<i>Renal loss</i>	
<i>Renal tubular acidosis</i>	
Type I (distal) renal tubular acidosis	
Medullary sponge kidney	
Toluene exposure	
Sjogren syndrome	
Type II (proximal) renal tubular acidosis	
Fanconi syndrome	
<i>Primary hyperaldosteronism</i>	
Conn syndrome	
<i>Pseudohyperaldosteronism</i>	
Licorice ingestion	
<i>Other renal</i>	
Nephrotic syndrome	
Acute tubular necrosis	
Diabetic ketoacidosis	
Chlorothiazide	
Ureterosigmoidostomy	
<i>Gastrointestinal loss</i>	
Celiac disease	
Tropical sprue	
<i>Salmonella</i> enteritis	
<i>Yersinia</i> enterocolitis	
Short bowel syndrome	

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**Authorship:** Dr. Becker is Chief Resident and Drs. Peckler and Paula are Attending Physicians in the Department of Emergency Medicine, University of South Florida. All Authors contributed to the conception of the article, collaborating in the revision and editing process

**Competing interests:** None declared

**Funding:** None declared

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