Clinical and Metabolic Features of Thyrotoxic Periodic Paralysis in 24 Episodes

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Background: Hypokalemia is a well-known, consistent finding in thyrotoxic periodic paralysis (TPP). It is less well known that hypophosphatemia and mild hypomagnesemia are often present in TPP and that rebound hyperkalemia can occur as a result of potassium therapy.

Objective: To report the prevalence of these electrolyte abnormalities in 24 episodes of TPP in 19 patients admitted to a single university-affiliated public hospital during a 15-year period.

Methods: The medical records of all patients admitted to the Santa Clara Valley Medical Center in San Jose, Calif, between August 1, 1982, and June 1, 1997, with any type of hypokalemic periodic paralysis were reviewed. In patients with TPP, serum potassium, phosphorus, and magnesium levels were evaluated during and after episodes of paralysis. The administered dose of potassium chloride, recovery time from hypokalemia, and prevalence of rebound hyperkalemia after recovery were also ascertained. Data are presented as mean ± SD.

Results: Hypokalemia was present in all 24 initial episodes of TPP, with serum potassium levels ranging from 1.1 to 3.4 mmol/L (mean, 1.9 ± 0.5 mmol/L). After recovery from hypokalemia, the maximum serum potassium level significantly increased, ranging from 4.0 to 6.6 mmol/L (mean, 4.9 ± 0.5 mmol/L; P<.001). In 10 (42%) of 24 episodes, rebound hyperkalemia (serum potassium level >5.0 mmol/L) was present. Recovery time did not correlate with the potassium chloride dose administered (r = 0.17). Initial serum phosphorus levels ranged from 0.36 to 0.97 mmol/L (mean, 0.61 ± 0.23 mmol/L) (1.1-3.0 mg/dL [mean, 1.9 ± 0.7 mg/dL]), with hypophosphatemia present in 12 (80%) of 15 episodes. Serum phosphorus levels significantly increased (P<.01), to 1.26 to 1.74 mmol/L (mean, 1.48 ± 0.16 mmol/L) (3.9-5.4 mg/dL [mean, 4.6 ± 0.5 mg/dL]), with or without phosphorus replacement therapy. A slight increase in serum magnesium levels after paralysis resolved was observed in all patients (P<.07). No further episodes of paralysis occurred in any patients after they became euthyroid.

Conclusions: Hypokalemia, hypophosphatemia, and mild hypomagnesemia are characteristic features of TPP. Hypokalemia occurred in 100% and hypophosphatemia in 80% of the episodes in our study. Rebound hyperkalemia is a potential hazard of potassium administration and occurred in 42% of 24 episodes.

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Thyrotoxic periodic paralysis (TPP) is an uncommon disorder characterized by simultaneous thyrotoxicosis, hypokalemia, and paralysis that occurs primarily in males of Asian descent, including patients of Japanese, Chinese, Vietnamese, Korean, Filipino, American Indian, and Hispanic ancestry.1-12 Although the association of thyrotoxicosis and periodic paralysis has been well known since 1931,13 TPP is often not recognized when first seen because of a lack of familiarity with the disorder in the United States, although the immigration of people from Asia and Latin America has increased. We retrospectively reviewed all case records of patients with TPP seen at Santa Clara Valley Medical Center, San Jose, Calif, during a 15-year period, and from these records we determined the prevalence of electrolyte abnormalities, including hypokalemia, rebound hyperkalemia, hypophosphatemia, and hypomagnesemia. We also examined diagnostic difficulties occurring, during which the patient is first seen, when TPP is often thought to be Guillain-Barré syndrome, spinal cord compression, familial periodic paralysis, or sporadic periodic paralysis.

RESULTS

CLINICAL PRESENTATION

All 19 patients with TPP were men of Asian descent (1 Korean, 3 Filipino, 6 Hispanic, and 8 Vietnamese patients), except 1 African American man, aged 20 to
PATIENTS AND METHODS

We reviewed medical records of 37 patients seen at Santa Clara Valley Medical Center from August 1, 1982, to June 1, 1997, with hypokalemic periodic paralysis. Santa Clara Valley Medical Center is a university-associated public teaching hospital with a sizable population of Asian, white, and Hispanic patients. Of the 37 patients, 30 had TPP, 6 had familial periodic paralysis (an autosomal-dominant disorder of euthyroid patients), and 1 had spontaneous periodic paralysis. Of the 30 patients with TPP, 19 were admitted to the hospital on 24 occasions during attacks and therefore had detailed metabolic data available for analysis. The remaining 11 patients with TPP had a typical history of periodic paralysis when they were thyrotoxic but did not seek medical attention and recovered spontaneously from their attacks after being treated for hyperthyroidism.

The medical charts of all 19 patients admitted to the hospital with TPP were reviewed and evaluated for initial symptoms; physical findings; and measurements of potassium (K), phosphorus (P), magnesium (Mg), and other electrolyte levels during and after paralysis. Electrocardiographic changes, recovery time from hypokalemia, occurrence of rebound hyperkalemia, and thyroid hormone test results were also evaluated. Recovery time used in this study is the time between the patient’s arrival at the hospital with paralysis and hypokalemia and the time of the first normal or elevated serum K level because these times were recorded for all patients in this retrospective review. This definition represents a maximum recovery time for the resolution of hypokalemia. Exact recovery time from paralysis was not recorded in the medical records for most patients, but we assume it is similar to the recovery time from hypokalemia. All episodes were reviewed for use of unnecessary diagnostic tests and for accuracy of clinical diagnosis at the initial encounter. Analysis of variance with the least significant difference was used to compare independent variables, with P<.05 as the criterion of significance.

Their extremities on awakening. One patient had onset of paralysis at 7 PM, and for the 2 remaining patients the time of onset was not specified.

Ten patients noted prodromal muscle pains, stiffness, or cramps in the thighs preceding paralysis by 1 hour to 3 days. On the day before paralysis, 5 patients had extensively exerted themselves, 4 patients had eaten large carbohydrate meals, 2 patients had attacks of diarrhea, 3 patients had abused alcohol, and 1 patient had an infection. Of 19 patients, 16 noted previous episodes of weakness in the extremities for which they did not seek medical attention and that resolved spontaneously, whereas 3 patients were admitted to the hospital with their first and only attack. Nevertheless, the attack that brought them to the hospital was described as the most severe. Five patients had a family history of thyroid disease. Only 1 patient had a history of an episode of paralysis in a first-degree relative. Episodes were equally distributed throughout the year, with 6 patients admitted in the winter and 6 during the summer.

Symptoms of hyperthyroidism at hospital admission included weight loss in 7 patients, palpitations in 3 patients, and heat intolerance in 2 patients. After thyroid function test results established a diagnosis of hyperthyroidism, patients were specifically questioned about the duration of thyrotoxicosis. Thyrotoxicosis was present in 17 patients for an average of 14 weeks (range, 8-24 weeks).

BIOCHEMICAL ABNORMALITIES

Laboratory data were analyzed for 24 episodes of TPP in 19 patients (Table 1). Available laboratory test results varied among patients; for example, serum P level was measured initially in 15 of 24 episodes of paralysis.

Initial serum K levels ranged from 1.1 to 3.4 mmol/L (mean, 1.9 ± 0.5 mmol/L). After administration of potassium chloride in a total dose ranging from 40 to 200 mmol, all patients had normalization of serum K levels within 1.5 to 10.0 hours. Most patients received both intravenous and oral potassium chloride, and several patients received either oral or intravenous potassium chloride. There was no correlation between potassium chloride dose and recovery time (r = 0.17) or potassium chloride dose and initial serum K level (r = −0.28). Maximum serum K levels of patients after treatment began ranged from 4.0 to 6.6 mmol/L. Ten (42%) of 24 episodes had rebound hyperkalemia, with a K level greater than 5.0 mmol/L. In 8 of 10 episodes, patients with hyperkalemia received 90 mEq or more of potassium chloride; in only 3 of 14 episodes, patients without rebound hyperkalemia received more than 90 mEq of potassium chloride (Table 2). A prolonged recovery time (>6.5 hours) was seen in only 3 of 24 episodes.

In 12 of 15 episodes, mild to moderate hypophosphatemia (0.36-0.77 mmol/L [1.1-2.4 mg/dL]) was noted when serum P level was measured within 1.5 hours of hospital admission or when it was measured while the K level was still low. Neutra-phos was administered in only 4 episodes; nevertheless, serum P level returned to normal or was slightly elevated after paralysis was resolved in all episodes evaluated. In 2 episodes, in which

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serum P levels were initially normal (0.81 and 0.94 mmol/L [2.5 and 2.9 mg/dL]), the levels increased to 1.29 and 1.55 mmol/L (4.0 and 4.8 mg/dL), respectively, after these patients recovered from paralysis. One patient had an initial serum P level of 0.97 mmol/L (3.0 mg/dL), measured about 1½ hours after hospital admission, but this patient was already improving from paralysis.

Serum Mg level was measured in 18 episodes during paralysis and in 13 episodes after paralysis. During paralysis episodes, all patients had low or low normal Mg levels (0.60-0.80 mmol/L [1.5-1.9 mg/dL]), measured about 1½ hours after hospital admission, but this patient was already improving from paralysis.

Serum Mg level was measured in 18 episodes during paralysis and in 13 episodes after paralysis. During paralysis episodes, all patients had low or low normal Mg levels (0.60-0.80 mmol/L [1.5-1.9 mg/dL]). Only 2 patients received supplemental magnesium sulfate, but Mg levels increased by 0.1 mmol/L or more ($0.24 \text{ mg/dL}$) in all patients who had it checked. Serum creatine phosphokinase levels were obtained in 18 episodes during paralysis. Twelve patients had elevated creatine phosphokinase values, 5 of which were of 1000 U/L or more. Creatine phosphokinase was fractionated in 4 patients, and 100% MM fraction of creatine phosphokinase was found in all patients. Thus, the severe paralytic myopathy seen in TPP was often associated with an elevated MM fraction of creatine phosphokinase. Serum calcium levels were normal in all measurements during and after paralysis. During paralysis, electrocardiograms were analyzed for 17 episodes. The most frequent abnormalities included sinus tachycardia, diffuse ST-T changes, flattening of T waves, prolonged QT intervals, and U waves.

All 19 patients were hyperthyroid during the 24 episodes of TPP. Fourteen patients who were seen after 1989 had serum thyrotropin levels of 0.08 µIU/L or less (normal, 0.20-5.39 µIU/L) and serum free thyroxine levels of 41.0 pmol/L or more (normal, 10.0-27.0 pmol/L) ($3.2 \text{ ng/dL}$ [normal, 0.8-2.1 ng/dL]). Five patients had elevated total thyroxine, triiodothyronine resin uptake, and total triiodothyronine levels. Radioiodine scans were consistent with Graves disease in 16 patients and a toxic nodule in 1 patient. Patients remained attack free as long as they took methimazole and propranolol hydrochloride or after radioiodine 131 treatment. Among 4 patients who were admitted to the hospital more than once, 2 were not recognized to be hyperthyroid when first seen and 2 were diagnosed as having hyperthyroidism but did not take their medications after discharge. Eighteen patients were eventually treated with radioiodine 131 therapy. None of the patients had paralytic episodes after a euthyroid state was achieved.

At hospital admission, most patients underwent multiple procedures and tests in a search for the cause of paralysis, including 3 lumbar punctures; 2 electromyograms; 2 nerve conduction velocity studies; 1 head computed tomographic scan; 2 head and 2 spine magnetic resonance imaging scans; 2 spine radiographs; se-

### Table 1. Serum Electrolyte Levels During and After 24 Episodes of TPP in 19 Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Episode No.</th>
<th>K(i), mmol/L</th>
<th>K(max), mmol/L</th>
<th>P(i), mmol/L†</th>
<th>P(f), mmol/L†</th>
<th>Mg(i), mmol/L</th>
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<td>5.2</td>
<td>0.58</td>
<td>1.74</td>
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</table>

Mean ± SD 1.9 ± 0.5 4.9 ± 0.5‡ 0.61 ± 0.23 1.49 ± 0.16§ 0.88 ± 0.04 0.84 ± 0.09| 

Normal range 3.5-5.0 0.81-1.55| 

†To convert P from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.3229.

§$P<.01$ for K(max) compared with K(i).

### Notes

*TPP indicates thyrotoxic periodic paralysis; K, potassium; P, phosphorus; Mg, magnesium; (i), initial serum electrolyte level obtained when first seen with paralysis; (max), maximum serum potassium level during hospitalization; (f), final serum electrolyte level before discharge; and ellipses, not available.

†To convert P from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.3229.

‡$P<.01$ for K(max) compared with K(i).

§$P<.07$ for Mg(f) compared with Mg(i).
We retrospectively studied 19 patients with TPP to evaluate clinical features, electrolyte changes, and outcomes of therapeutic interventions in this uncommon disorder. Clinical presentation of our patients was similar to that reported in the literature\textsuperscript{1-17} where there is a predominance of males with Asian heritage. Indeed, 4.3% to 8.2% of Japanese males\textsuperscript{1-2} and 12.9% of Chinese males\textsuperscript{1} who develop hyperthyroidism will manifest TPP compared with 0.11% of Japanese females\textsuperscript{1-2} and 0.17% of Chinese females.\textsuperscript{3} Thus, TPP rarely occurs in women, although occasionally a case is reported.\textsuperscript{4,12} We observed no episodes of TPP in women, although most patients seen at our hospital with thyrotoxicosis are women. Eighteen of our patients had Graves disease and 1 had a toxic adenoma. Thyrotoxic periodic paralysis has been described in patients with nonimmunologic thyroid diseases, such as toxic nodular goiter and toxic adenoma.\textsuperscript{5,6,11}

Of our 19 patients with TPP, 6 (32%) were Hispanic, which has been noted in previous studies,\textsuperscript{7,8,11-13} and 12 (64%) were Asian. Because the combined Hispanic and Asian population in the United States rose from 12% to 15% of the total US population between 1990 and 1998 (US Census Bureau estimate), it is likely that the incidence of TPP is increasing, particularly in regions such as Santa Clara county, where Hispanics and Asians combine to form 41% of the total population. None of our patients with TPP were white, and 1 patient was African American, which has been previously reported.\textsuperscript{11,12,16,17} An HLA association has been noted for Chinese, Japanese, Hispanic, and white males.\textsuperscript{4,6,12,18,19}

Similar to our study, others reported that attacks of paralysis tend to occur during the night,\textsuperscript{13,9,14,15} and that proximal muscles of the lower extremities are more affected than other muscle groups.\textsuperscript{5,11} Indeed, attacks of periodic paralysis occurring at night are so prevalent that the condition has been referred to in the literature as nocturnal paralysis and night palsy.\textsuperscript{20} Although exercise may actually attenuate paresis in TPP, it is a period of rest after exercise that precipitates paralysis.

All patients in our study had mild to severe hypokalemia (1.1-3.4 mmol/L) when first seen. Hypokalemia is considered to be the most consistent electrolyte abnormality in TPP and a hallmark of the syndrome, along with hyperthyroidism. It has been demonstrated that hypokalemia is a result of a K shift into cells and that it is not caused by total-body K depletion.\textsuperscript{6,11,21} Our patients received potassium chloride in a total dose of 40 to 200 mmol (mean, 89 mmol) and recovered from hypokalemia within 1.5 to 10.0 hours (mean, 4.8 hours) after arrival at the hospital. During previous episodes of weakness when the patients did not come to the hospital for treatment, the attacks commonly lasted from 3 to 48 hours, which is similar in duration to attacks reported by others.\textsuperscript{11,22} There was no correlation in our study between recovery time and potassium chloride dose ($r = 0.17$). Rebound hyperkalemia occurred in 42% of our 24 episodes of hospitalized patients with TPP, with a maximum serum K level of 6.6 mmol/L, and this phenomenon is well described in the literature.\textsuperscript{5,6,8-10,14,23-25}

Hypophosphatemia during paralysis in patients with TPP has been previously reported\textsuperscript{8,10,24,26,27} and may contribute to the muscle weakness\textsuperscript{28} along with hypokalemia. In our study, 12 (80%) of 15 episodes had decreased serum levels of P when first seen, and only 4 of the episodes (patients 7, 17, 23, and 24 in Table 1) received replacement therapy with neutra-phos. After resolution of the paralysis, there was a significant elevation of the serum P level, even in patients who did not receive a supplement ($P < .01$). A mild rebound hyperphosphatemia was seen in 3 (30%) of 10 episodes evaluated after resolution of paralysis, including 1 patient who received neutra-phos and developed the highest level of serum P (1.74 mmol/L [5.4 mg/dL]). Mild hyperphosphatemia after paralysis has been previously observed.\textsuperscript{24,27} Phosphorus is a major intracellular anion, and its influx

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
Episode No. & $K(i)$, mmol/L & $K(max)$, mmol/L & Dose of K, mEq† & Recovery Time, h‡ \\
\hline
1 & 2.5 & 4.0 & 40 & 5.5 \\
2 & 1.8 & 5.7 & 94 & 4.5 \\
3 & 2.3 & 4.8 & 116 & 3.0 \\
4 & 1.9 & 6.6 & 184 & 10.0 \\
5 & 1.6 & 4.7 & 30 & 3.0 \\
6 & 1.8 & 5.7 & 70 & 9.0 \\
7 & 2.0 & 4.9 & 200 & 3.5 \\
8 & 2.3 & 4.9 & 80 & 6.5 \\
9 & 3.4 & 4.7 & 40 & 2.0 \\
10 & 2.5 & 4.6 & 40 & 5.5 \\
11 & 1.7 & 4.4 & 52 & 1.5 \\
12 & 1.9 & 5.1 & 90 & 4.0 \\
13 & 1.6 & 5.4 & 140 & 10.0 \\
14 & 2.2 & 5.1 & 40 & 2.5 \\
15 & 1.5 & 5.9 & 108 & 6.0 \\
16 & 1.1 & 4.7 & 90 & 4.5 \\
17 & 1.8 & 4.0 & 80 & 4.0 \\
18 & 1.4 & 5.4 & 110 & 3.5 \\
19 & 1.7 & 4.5 & 110 & 4.5 \\
20 & 1.7 & 5.3 & 106 & 4.0 \\
21 & 1.7 & 4.2 & 60 & 2.5 \\
22 & 1.6 & 4.0 & 70 & 6.0 \\
23 & 1.9 & 4.5 & 70 & 5.0 \\
24 & 1.9 & 5.2 & 120 & 3.5 \\
Mean & 1.9 & 4.9 & 89 & 5.0 \\
\hline
\end{tabular}
\caption{Total Potassium (K) Administered and Time of Recovery From Hypokalemia}*
\end{table}

* Data are given for 24 episodes of paralysis in 19 patients with thyrotoxic periodic paralysis. See Table 1 for definitions of $(i)$ and $(max)$.
† Total K administered is the sum of K given by intravenous and oral routes in each patient.
‡ Recovery time is the time between arrival at the hospital and the first normal or elevated serum potassium level.

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into and efflux from the cell most likely occurs in conjunction with K transport. Hypophosphatemia and hypokalemia are well-known causes of rhabdomyolysis, and the mild elevation of creatine phosphokinase concentration in 12 (67%) of 18 episodes may be related to the low serum P and K levels.

Mild hypomagnesemia was noted in all of our patients during paralysis, with an increase of 0.1 mmol/L or more (≥0.24 mg/dL) after resolution of the paralysis, and this has been observed in several previous reports. Endogenous catecholamines during stress may contribute to hypomagnesemia without depleting total-body stores of Mg by causing an intracellular shift in Mg. In a previous study, 4 of 10 patients with TPP had an increase in skeletal muscle Mg content during paralysis. The mild elevation of serum alkaline phosphatase concentration in 80% of our patients most likely resulted from hyperthyroidism.

The most frequent electrocardiographic changes that we observed were ST segment depression with T wave flattening, sinus tachycardia, and U waves, which are typical in hypokalemia and thyrotoxicosis. Sinus arrest and second-degree atrioventricular block also have been described in patients with TPP, ventricular fibrillation, and ventricular tachycardia.

The pathophysiological effect of TPP remains unclear, although it likely involves defects in membrane-bound ion-transporting proteins, such as sodium, K-adenosine triphosphatase, or ion channel proteins. It is well known that attacks of paralysis no longer occur once thyrotoxicosis is cured; therefore, a necessary condition for the disorder is the presence of excessive thyroid hormones in serum. Nevertheless, it is not well understood what initiates attacks, why the attacks often resolve spontaneously, and why attacks occur predominantly in males of Asian descent. It has been shown that the presence of excessive amounts of thyroid hormone can induce increased electrolyte permeability of the muscle membrane to electrolytes, with influx of K into the cell associated with a failure in depolarization.

The events that lead to paralysis with hypokalemia and hypophosphatemia in patients with TPP are complex. They include hyperthyroidism, a genetic and racial predisposition, an exaggerated insulin response, a hyperadrenergic state, and probably other mechanisms leading to the intracellular shift of K and P. Episodes of paralysis occurred during the night in more than 80% of our patients with TPP. It has been shown that plasma glucose and insulin responses to meals are markedly higher in the evening than in the morning in control subjects. Such a phenomenon suggests a possible mechanism for the nocturnal preponderance of TPP; another explanation could be the circadian rhythmicity of many hormones reaching their peak levels during sleep.

Results of this study demonstrate that the diagnosis of TPP at the initial encounter is often delayed and confused with other more familiar causes of lower extremity paralysis, partially because of the subtleness of the thyrotoxicosis and partially because of an unfamiliarity with this disorder by physicians. When a young male of Asian descent is initially seen with severe lower extremity weakness or paralysis, TPP should be considered as the most likely diagnosis until proven otherwise. This is important because TPP is a curable disorder that resolves when a euthyroid state is achieved.

Although the cause of hypokalemia in TPP is not a total-body deficit but rather an intracellular shift of K, vigorous K replacement has been advocated for the treatment of paralysis and prevention of fatal arrhythmias. However, the value of vigorous replacement of K is questionable because there is no correlation between potassium chloride dose administered and recovery time. Spontaneous recovery from paralysis attacks with subsequent normalization of serum P and K levels occurs in many patients, which demonstrates that these electrolytes can shift from the intracellular space back to the extracellular space without replacement therapy.

For treatment of paralysis, it has been recommended that 27 mEq of potassium chloride be given every 2 hours orally for 6 hours and then every 4 hours with careful monitoring, based on a study of 51 patients. In another study, treatment with potassium chloride, 130 mEq orally or 20 mEq intravenously, in 100 cm³ of normal saline was recommended based on experience with 2 patients. More than 40% of our patients had rebound hyperkalemia, 80% of whom received more than 90 mEq of potassium chloride within 24 hours. Based on our results, K replacement therapy should be cautious and should not exceed 90 mEq of potassium chloride per 24 hours unless there is a reason for K loss, such as diarrhea, vomiting, or diuretic use. Nonselective beta-blockers such as propranolol may be useful to prevent attacks of paralysis once patients begin taking antithyroid medications but are not yet euthyroid. It is unclear whether potassium chloride supplementation can prevent attacks of paralysis in such patients.

In summary, we described clinical and metabolic features seen in 19 patients with TPP, an uncommon and curable disorder that is encountered with increasing frequency in American hospitals because of the rising number of Asian and Hispanic patients. Clinical features, biochemical abnormalities, pathophysiological effects, treatment, and the complications of treatment were addressed.

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