

CLINICAL REVIEW: Thyrotoxic Periodic Paralysis: A Diagnostic Challenge

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Context: The aim of this article was to review the clinical presentation, pathogenesis, and management of thyrotoxic periodic paralysis (TPP).

Evidence Acquisition: A MEDLINE search was conducted for articles published during the last 40 yr based on the key words thyrotoxic periodic paralysis and hypokalemic periodic paralysis. A total of 281 primary articles and 168 references of the retrieved articles were also reviewed.

Evidence Synthesis: TPP is a common complication of hyperthyroidism in Asian men but is increasingly seen in Western countries. Hypokalemia and muscle paralysis results from a sudden intracellular shift of potassium and is not due to potassium deficiency. Clinical features of hyperthyroidism in patients with TPP may be subtle. Immediate potassium supplementation prevents serious cardiopulmonary complications and may hasten the recovery of muscle weak-

ness. Nonselective β -adrenergic blockers can ameliorate and prevent recurrence of the paralytic attacks. This episodic paralysis will remit with definitive control of hyperthyroidism. Increased sodium-potassium ATPase pump activity and enhanced insulin response in patients with TPP is postulated to contribute to the hypokalemia. The genetic predisposition for TPP is not entirely clear. Association of polymorphisms of the calcium channel α 1-subunit gene with TPP has been noted.

Conclusions: Due to population mobility, TPP is increasingly common in Western countries. Early diagnosis and prompt treatment prevent life-threatening complications associated with hypokalemia and muscle weakness. Assaying of thyroid function in patients with hypokalemic paralysis distinguishes TPP from other forms of hypokalemic periodic paralysis. (*J Clin Endocrinol Metab* 91: 2490–2495, 2006)

THYROTOXIC PERIODIC PARALYSIS (TPP) is an alarming and potentially lethal complication of hyperthyroidism characterized by muscle paralysis and hypokalemia due to a massive intracellular shift of potassium. This condition mainly affects male patients of Asian descent. Many affected patients do not have obvious symptoms and signs of hyperthyroidism. Because the condition is rare in Caucasians, it is frequently overlooked and misdiagnosed on presentation. With increasing population mobility and admixture, TPP as the presenting feature of hyperthyroidism is more common in Western countries. Immediate therapy with potassium supplementation and β -adrenergic blockers can prevent serious cardiopulmonary complications and may hasten recovery of the periodic paralysis. Effective control of hyperthyroidism is indicated to prevent the recurrence of paralysis.

Epidemiology

TPP is a well-known complication of thyrotoxicosis in Asian populations, including Chinese, Japanese, Vietnamese, Filipino, and Koreans. The overall incidence of TPP in Chinese and Japanese thyrotoxic patients is 1.8 and 1.9%,

respectively (1, 2). The incidence is largely unknown in the West. In North America, the incidence rate of TPP was reported to be around 0.1–0.2% in thyrotoxic patients (3, 4). Sporadic cases of TPP have also been reported in other non-Asian populations such as Caucasians, Afro-Americans, American Indians, and Hispanics. The American Indians are thought to be at a higher risk of TPP (5) because there is evidence that their ancestors originated in Asia and migrated to North America between 11,000 and 23,000 yr ago (6).

Despite a much higher incidence of thyrotoxicosis in women, TPP predominantly affects males. In the Chinese, TPP occurs in 13% of male and 0.17% of female thyrotoxic patients, in a series published in 1967 (1), whereas in the Japanese, the incidence was 8.67 among male and 0.4% among female thyrotoxic patients in 1957 (2). Overall, the male to female ratio ranges from 17:1 to 70:1 (1, 2, 7, 8). Interestingly, a decline in the incidence of TPP has been reported in Japan, with the figures being 4.3% among male and 0.04% among female thyrotoxic patients in 1991 (9).

The number of TPP cases reported in Western countries has increased recently. A computer search revealed nine review papers and 72 case reports (41 Asians and 31 non-Asians) published between 1986 and 1995, whereas in 1996–2005, a total of 25 review papers and 67 case reports (24 Asians and 43 non-Asians) were published, suggesting that TPP is no longer an unusual condition in the Western medical arena.

Clinical Presentation

Patients are usually young adult males 20–40 yr of age, although occurrence of TPP in adolescents has also been

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Abbreviations: ECG, Electrocardiographic; EMG, electromyogram; FHPP, familial hypokalemic periodic paralysis; HLA, human leukocyte antigen; Na/K-ATPase, sodium-potassium-adenosine triphosphatase; SNP, single-nucleotide polymorphism; TPP, thyrotoxic periodic paralysis; TRE, thyroid hormone-responsive element.

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reported (10, 11). The attack is characterized by recurrent, transient episodes of muscle weakness that range from mild weakness to complete flaccid paralysis (Table 1). The proximal muscles are affected more severely than the distal muscles. Attacks usually first involve the lower limbs and progress to the girdle muscles and subsequently the upper limbs. Sensory function is not affected. The muscles affected may be asymmetrical. Although patients can present with tetraparesis that resembles other conditions such as Guillain-Barré syndrome, transverse myelitis, and acute spinal cord compression or hysteria, bowel and bladder function are never affected. Respiratory muscles are seldom involved but total paralysis of respiratory, bulbar, and ocular muscles has been reported in a severe attack (12–14). Patients may experience recurrent episodes of weakness that last from a few hours up to 72 h, with complete recovery in between the attacks. There may also be prodromal symptoms of aches, cramps, and stiffness of the affected muscles. In the majority of patients, deep tendon reflexes are markedly diminished or absent, although some patients may have brisk or normal jerks, even during paralysis (15).

Patients with TPP usually experience the attack a few hours after a heavy meal or in the early morning upon waking; more than two thirds of patients present to the emergency department between 2100 and 0900 h. Such timing of presentation led the condition to be initially described as nocturnal paralysis or night palsy (16). Patients may give a history of similar but milder attacks before presentation. Attacks are commonly precipitated by ingestion of carbohydrate-rich meals or sweet snacks, alcohol, or strenuous exercise. In these patients the paralysis can be induced by a high glucose load, insulin infusion, and exercise test. The weakness does not occur during exercise but during the resting period after exercise and may be aborted by resumption of the exercise. In subtropical regions, a seasonal variation is observed that is probably related to increase outdoor exercise or consumption of sweet drinks during summer (1, 8). TPP occurs only in the presence of hyperthyroidism and is abolished when thyroid hormone levels are normalized. Likewise the paralysis can be induced only when the patient is thyrotoxic, not euthyroid. The attacks of weakness are similar to those of familial hypokalemic periodic paralysis (FHPP) except for the presence of hyperthyroidism (Table 2). Nonetheless, whereas FHPP is an autosomal dominant con-

dition that affects mainly Caucasians (17, 18), TPP is a sporadic disease found mainly in Asian males, and the familial trait is rare (3, 19, 20).

Biochemical Features

Hyperthyroidism

Biochemical hyperthyroidism distinguishes patients with TPP from FHPP. Most patients with TPP have only mildly elevated serum thyroid hormone levels: a previous study reported only 10% of patients with mild thyrotoxic symptoms (8). Indeed, the hyperthyroidism may even be clinically silent (4). The subtlety of the features of hyperthyroidism together with the rarity of this condition makes TPP a difficult condition to diagnose at presentation.

The majority of cases of hyperthyroidism associated with TPP are due to Graves' disease, although other conditions including thyroiditis (7), toxic nodular goiter (21), toxic adenoma (4), TSH-secreting pituitary tumor (22), ingestion of T₄ (23), and inadvertent iodine excess (24) have also been implicated. TPP may be the presenting feature of Graves' disease, or present during relapse or after radioactive iodine therapy (25).

Electrolytes

The hallmark of TPP is hypokalemia. The presenting serum potassium level is usually less than 3.0 mmol/liter and can be as low as 1.1 mmol/liter. Occasionally if the patient is at the recovery stage of the paralysis, serum potassium can be normal. Hypokalemia occurs due to a massive shift of potassium into the cells rather than net loss from the body. It is not associated with urinary potassium loss because the urinary potassium excretion is normal or low, and the blood acid-base balance is normal (26, 27). Similarly, there is no excessive fecal loss of potassium. The degree of hypokalemia is correlated to the severity of paralysis but not to the clinical features of thyrotoxicosis or thyroid hormone levels. Fatal and life-threatening ventricular arrhythmia associated with hypokalemia has been reported (28–30).

In addition to hypokalemia, there may be hypophosphatemia and hypomagnesemia. Mild to moderate hypophosphatemia in the range of 0.36–0.77 mmol/liter has been reported in two thirds of cases in one series (31). Serum phosphate level returns to normal without supplementation when the patient recovers from the weakness. This is confirmed by the occurrence of rebound hyperphosphatemia after recovery from paralysis in patients prescribed phosphate supplementation (27, 32). The hypophosphatemia is likely due to intracellular shift that accompanies the potassium transport. Similarly, serum magnesium level is low or low normal but returns to normal spontaneously when the patient recovers from the paralytic attack (31). The hypomagnesemia is also due to intracellular shift, likely secondary to endogenous catecholamines released during stress rather than due to depletion of body stores (33).

Serum creatine phosphokinase of muscle origin is elevated in about two thirds of patients, particularly among those whose attacks are precipitated by exercise. The complication of rhabdomyolysis may occur in a severe attack (31).

TABLE 1. Clinical features of TPP

Feature
Adult young men
Sporadic
Recurrent acute paralysis with complete recovery
Limb > trunk involvement
Precipitated by heavy carbohydrate load, high-salt diet, alcohol, exertion
Family history of hyperthyroidism
Clinical features of hyperthyroidism
Hypokalemia
Normal acid-base balance
Low potassium excretion rate
Low phosphate excretion
EMG: low-amplitude compound muscle action potential with no change after epinephrine

TABLE 2. Distinguishing features between TPP and FHPP

	TPP	FHPP
Age (yr)	20–40	<20
Sex distribution	Predominantly male	Equal
Heredity	Sporadic	Autosomal dominant
Ethnicity	Asian, American Indian/Hispanic, Caucasian	Caucasian, Asian
Family history	History of thyrotoxicosis	History with hypokalemic paralysis
Clinical features of hyperthyroidism	Yes	No
Genetic predisposition	Associated with SNPs of $Ca_v1.1$ (–476A→G, intron 2 nt 57G→A, intron 26 nt 67A→G)	Mutations of $Ca_v1.1$ (R5258H, R1239H, R1239G), $Na_v1.4$ (R669H, R672G, R672H), $K_v3.4$ (R83H)

Electrodiagnostic studies

Electromyogram (EMG) performed during spontaneous weakness typically reveals myopathic changes with reduced amplitude of compound muscle action potentials (34). There is no notable change in the amplitude on epinephrine stimulation. Nerve conduction studies are normal with no peripheral nerve involvement. Similar to FHPP, exercise can induce weakness in patients with TPP, and an exercise test can reproduce the EMG abnormalities during paralysis. These impaired muscle responses improve when the patient becomes euthyroid.

TPP patients have significantly more electrocardiographic (ECG) abnormalities than patients with hypokalemic periodic paralysis due to other causes. Apart from serious ventricular arrhythmias and ECG changes associated with hypokalemia, other ECG abnormalities include rapid heart rate, high QRS voltage, and first-degree atrioventricular block (35).

Pathogenesis

The pathogenesis of TPP remains unclear. Hypokalemia is the consequence of a rapid and massive shift of potassium from the extracellular into the intracellular compartment, mainly into the muscles. This is believed to be related to increased sodium-potassium-adenosine triphosphatase (Na/K-ATPase) pump activity (Fig. 1). Potassium flux and

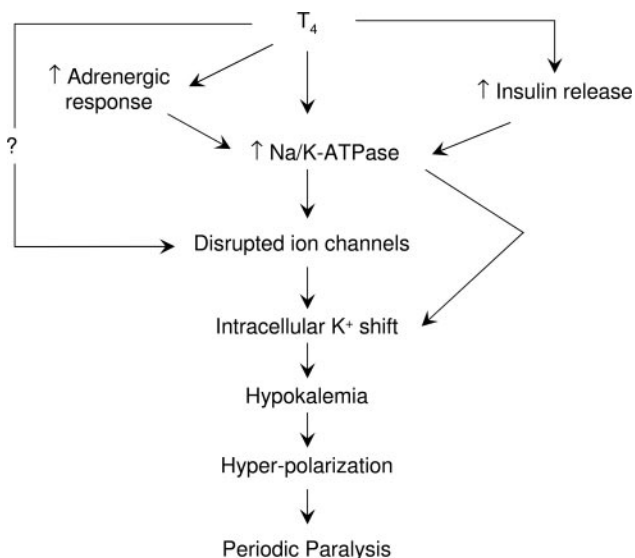


FIG. 1. Mechanisms for acute muscle weakness in thyrotoxic periodic paralysis.

sodium transport as well as Na/K-ATPase pump activity have been evaluated in patients with TPP. Studies were nonetheless performed in peripheral tissues such as red blood cells, leukocytes, and platelets because of the inherent difficulties in measuring ion transport in intact skeletal muscles during TPP. Overall, the data revealed an increased number as well as activity of the Na/K-ATPase pump in patients with thyrotoxicosis: patients with TPP had significantly higher pump activity than thyrotoxic patients without TPP (36–38). When thyrotoxicosis was controlled, Na/K-ATPase activity returned to a level similar to that of healthy controls.

Thyroid hormones can increase Na/K-ATPase activity in skeletal muscle, liver, and kidney to induce an influx of potassium into the intracellular space (39–42). Among the various Na/K-ATPase subunits, the α 1-, α 2-, β 1-, β 2-, and β 4-subunits are expressed in skeletal muscles (43, 44). Thyroid hormone-responsive elements (TREs) are present in the upstream region of these five genes, and thyroid hormones has been shown to increase Na/K-ATPase activity via both transcriptional and posttranscriptional mechanisms (45, 46). Apart from direct stimulation by thyroid hormones, catecholamine can also increase Na/K-ATPase activity in skeletal muscle (47). The enhanced β -adrenergic response in thyrotoxicosis further increases Na/K-ATPase activity and may explain why nonselective β -adrenergic blockers can abort or prevent paralytic attacks.

In addition to an increased adrenergic response, patients with TPP have an exaggerated insulin response during oral glucose challenge, compared with thyrotoxic patients without TPP (48, 49). Insulin-response sequences are present in the upstream region of Na/K-ATPase genes, and insulin has been shown to stimulate Na/K-ATPase activity (50). Hence, insulin can play a permissive role for the potassium shift in patients with TPP. The hyperinsulinemic response may explain the association of TPP with carbohydrate-rich meals and sweet snacks. Exercise releases potassium from the skeletal muscles, whereas rest promotes influx of potassium. This explains why paralytic attacks occur only during recovery from exercise and resumption of exercise can abort an attack (3).

Overall, it appears that patients with TPP have an underlying predisposition for activation of Na/K-ATPase activity, either directly by thyroid hormone or indirectly via adrenergic stimulation, insulin, or exercise. To determine whether this predisposition is genetically associated, a number of studies have addressed different candidate genes. The human leukocyte antigen (HLA) B46, DR9, and DQB1*0303

have been reported to be present at a higher prevalence among Hong Kong Chinese TPP patients, whereas HLA A2, Bw22, AW19, B17, and DRW8 are reported to be associated in Singapore Chinese and Japanese, respectively (51–53). However, it is uncertain whether these HLA genes are independently related to TPP because these HLA associations are also observed with Graves' disease *per se*.

In view of similarities between TPP and FHPP, the role of genes associated with FHPP has also been examined in patients with TPP (Table 2). The L-type calcium channel α_1 -subunit $Ca_v1.1$, also called the voltage-dependent calcium channel or dihydropyridine-sensitive L-type calcium channel receptor, which is associated with FHPP-1, was studied. None of the few mutation hot spots associated with FHPP was present in Asian or non-Asian patients with TPP (54, 55). However, certain single-nucleotide polymorphisms (SNPs) of $Ca_v1.1$, including nucleotide (nt) – 476, intron 2 nt 57, and intron 26 nt 67, were associated with TPP in southern Chinese (55). The location of these SNPs lies at or close to the TRE of the gene, and it is likely that they affect the binding affinity of TRE and modulate the stimulation of thyroid hormone on the $Ca_v1.1$ gene.

Similarly, mutations in other genes that encode for skeletal muscle ionic channels have also been examined. One TPP patient of Portuguese descent has been found to carry an R83H mutation in the $K_v3.4$ gene that encodes for voltage-gated potassium channel (56). In addition the R672G mutation of the voltage-gated sodium channel $Na_v1.4$ that is associated with FHPP-2 is reported in one pediatric Caucasian patient with thyrotoxicosis and paralysis (57). Interestingly, family members of these two probands also carry similar mutations and have hypokalemic paralysis without thyrotoxicosis. The authors postulated that there may be overlap of genetic predisposition between FHPP and TPP. However, these two mutations are not found in any of the 97 southern Chinese TPP patients studied (55), or in other series of Asian TPP patients (58, 59).

Because patients with TPP have increased Na/K-ATPase activity, the genes coding for the α_1 -, α_2 -, β_1 -, β_2 -, and β_4 -subunits of Na/K-ATPase were examined. No mutations were identified in the 5' upstream region and the coding region of these five genes in southern Chinese patients with TPP (59). Also, no association between the SNPs of these five genes and TPP could be detected (60). Similarly, polymorphism in the β_2 -adrenergic receptor gene is not associated with TPP in Korean patients (61). Thus, whether TPP patients truly have a genetic predisposition to activation of the Na/K-ATPase genes remains to be elucidated.

Treatment

During periodic paralysis and marked hypokalemia, immediate supplementation with potassium chloride (KCl) is warranted to prevent major cardiopulmonary complications. KCl is given iv or orally or both (Table 3). The dose of KCl required varies between 40 and 200 mmol. Recovery time was significantly shorter in those given iv KCl infusion than those given saline infusion alone (62). However, other studies have shown a lack of correlation between the dose of KCl given with the initial serum potassium level and the recovery

TABLE 3. Treatment of TPP

Treatment type
Emergency therapy
Potassium replacement
KCl 10 mEq/h iv and/or KCl 2 g every 2 h, orally
Monitor serum K^+ level, avoid rebound hyperkalemia
Propranolol 3–4 mg/kg, orally
Prevention of recurrent attacks
Avoid precipitating factors (heavy carbohydrate meals, high salt, alcohol, undue exertion) until euthyroidism is achieved
Propranolol 20–80 mg every 8 h, orally
Determine the cause of TPP
Definitive therapy of hyperthyroidism with antithyroid drugs/thyroidectomy/radioiodine

of muscle weakness (8, 31). Excessive potassium replacement may result in rebound hyperkalemia during recovery of the paralysis when potassium is shifted back into the intravascular compartment. It was reported that 40% of patients given iv KCl at a rate of 10 mmol/h developed rebound hyperkalemia greater than 5.5 mmol/liter (62). Thus KCl supplementation should be given at a slow rate unless there are cardiopulmonary complications. Use of potassium supplements is not useful for prophylaxis against further paralytic attacks and should not be given to patients between attacks.

Oral or iv propranolol, a nonspecific β -adrenergic blocker, has also been proposed as an alternative treatment to ameliorate the paralysis without rebound hyperkalemia and raise the serum levels of potassium and phosphate. Three case reports showed that iv propranolol rapidly reversed the paralysis in patients with TPP who failed to respond to potassium replacement (63–65). Similarly, high-dose oral propranolol (3–4 mg/kg orally) alone has been reported to rapidly abort the paralysis (66). Propranolol, but not the selective β_1 -blocker metoprolol, also effectively prevented recurrence of paralytic attacks or inhibited paralysis induced by a carbohydrate load. At a dose of 40 mg four times a day, propranolol prevented paralysis in carbohydrate-induced TPP in about two thirds of cases by inhibiting the activity of Na/K-ATPase (67). In view of the small number of case reports on the use of β -blockers alone, more controlled studies are needed to determine their efficacy, compared with potassium supplementation in the emergency treatment of TPP.

Because TPP does not recur once the patient is euthyroid, adequate control of hyperthyroidism is the mainstay of therapy. The cause for the hyperthyroidism should be identified. Definitive treatment with radioactive iodine or thyroidectomy should be given to patients with hyperthyroidism due to Graves' disease, multinodular goiter, or toxic adenoma. Patients should avoid precipitating factors including heavy carbohydrate intake, high-salt diet, alcohol ingestion, and undue exertion until thyrotoxicosis is under control. The use of nonselective β -blockers is important during early treatment with antithyroid drugs or after radioactive iodine when a euthyroid status is not yet achieved. Regular potassium supplementation as prophylaxis against further paralysis when the patient has a normal serum potassium level is ineffective. Acetazolamide and T_4 , which have been reported to reduce the frequency of paralytic attacks in FHPP and

other forms of hypokalemic periodic paralysis, may worsen the attacks in TPP (68, 69) and should be avoided.

Conclusion

TPP is a rare condition in non-Asians, and the diagnosis at initial presentation is often delayed because of the subtlety of the clinical features of thyrotoxicosis and the similarities of the paralysis with other more common conditions. With population mobility and admixture, TPP is becoming more common in Western countries. Early diagnosis prevents serious cardiopulmonary complications. TPP is a curable disorder that resolves when a euthyroid status is achieved.

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