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Thyrotoxic Periodic Paralysis – Clinical Diagnosis and Management

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1. Introduction

1.1. Definition

Periodic paralysis comprises a group of neuromuscular diseases in which the patients present with paroxysmal muscle weakness of the limbs. [1] The most common causes are *thyrotoxic hypokalemic periodic paralysis* (TPP) and familial hypokalemic periodic paralysis (FPP). [1]

Thyrotoxic periodic paralysis (TPP) is a medical emergency characterized by an acute and reversible attack of muscle weakness associated with the *hypokalemia*. [1, 2] TPP is the most common form of acquired flaccid paralysis in adults with *hyperthyroidism* and can occur in patients of any ethnicity, [3, 4] although it is more frequent in Asian populations. [5] TPP is the newest form of endocrine channelopathy included in the large group of periodic paralysis and should be included in the differential diagnosis of acute muscle weakness in patients seeking emergency care.

2. Epidemiology

The association of loss of limb muscle strength and Graves' disease was first published by Rosenfeld in the German literature at the beginning of the last century. [6] In English, the first report was made by Dunlap and Kepler in 1931, describing four patients. [7] In 1968, the first case of TPP diagnosed in Brazil was described by Pereira *et al.* [8]

TPP is more frequently described in Asian descendants, [5] but it can occur in patients of other ancestries. [3, 4] This aspect is particularly important because TPP should not be excluded in the differential diagnosis of paralysis based only on the patient's ethnicity. Although thyro-

toxicosis has a higher incidence in women, the paralysis affects predominantly men, with a male:female ratio of approximately 30:1. [2]

TPP symptoms occur in young adults, in contrast to FPP, in which the paralysis crises begin at an earlier age, usually before puberty. [1] TPP is more common between the third and fifth decades of life, which coincides with the peak incidence of thyrotoxicosis [9]. In a study performed with 35 Brazilian patients, the age at diagnosis ranged from 19 to 51 years, [2] similar to the international literature. [9, 10] Unlike the familial form, TPP appears as a sporadic disease. [11] However, rare cases of TPP with a family history of paralysis and thyrotoxicosis have been reported. [12, 13]

3. Etiology and genetic susceptibility

The paralysis crises occur only in the presence of the thyrotoxic state, regardless of its etiology. Several causes of thyrotoxicosis with paralysis have been reported, including Graves' disease (GD), toxic adenoma, toxic multinodular goiter, amiodarone-induced thyrotoxicosis, TSH-producing pituitary tumor, lymphocytic thyroiditis, and factitious thyrotoxicosis. [2] In most of the cases, TPP is associated with the hyperthyroidism in GD, [9, 14] and the paralysis crisis may be an atypical form of initial presentation of the disease. In our studies, there are also a report of TPP in a patient who used formulations containing levothyroxine to lose weight. [2]

The methodological approach to determining the genetic susceptibility to TPP is difficult. This is due in part to the absence of a familial pattern of inheritance that allows linkage analysis by polymorphic allele markers, as almost all of the cases described in the literature are sporadic. Second, the number of cases is relatively small, making an association study to identify genetic susceptibility difficult. Thus, the first genes to be studied were the ones most commonly related to FPP (*CACN1A5* and *SCN4A*) [15], a clinical condition physiopathologically similar to the TPP. However, the investigation of these genes revealed that patients with TPP were negative for these mutations [17, 18]. Several other genes were subsequently studied, and although there were reports of patients bearing the *KCNE3* mutation [18, 19], these patients were later proven to have only a polymorphic variant. [20]

More recently, after the study of Plaster *et al.* [21] on a familial paralysis form associated with facial dysmorphism and arrhythmias called Andersen-Twail Syndrome, a new group of candidate genes arose. Thus, the *KCNJ12* gene (potassium channel Kir2.2) was included in the screening for TPP mutations. Kir2.2 became the candidate of greatest interest because of its expression in the skeletal muscle and the presence of the consensus elements (*cis*), the Thyroid Response Elements (TRE), in its regulatory region. Although no mutation has been found in this group of genes in TPP, during the study of the *KCNJ12* gene, a novel paralog gene was discovered and called *KCNJ18* (Kir2.6). [22] Four different mutations were identified, including two missense (T354M & K366R) and two nonsense (R399X & Q407X) mutations that combined are present in 33% of patients with TPP. [22] These mutations result in a defect in muscle repolarization. The high K⁺ levels in the muscular system keep the cell in a partially *depolarized*

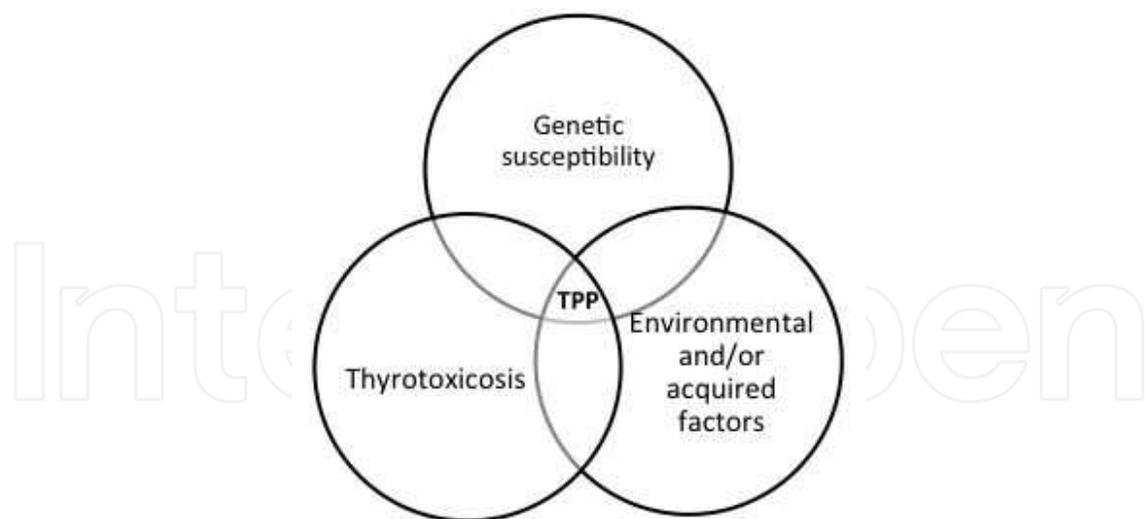


Figure 1. Theoretical model of multifactorial interaction in TPP. Modified from Ref. [1]

state, and the membrane becomes unable to trigger a new muscle excitation-contraction coupling, resulting in flaccid paralysis. [22]

4. Physiopathology

The physiopathology of TPP remains incompletely understood. Evidence suggests that TPP results from a combination of three factors: genetic, environmental, and thyrotoxicosis [1]. From this association, we hypothesized that the interaction of these factors would alter the channel dynamics of the cell membrane at the neuromuscular junction, triggering the *paralysis crises* only in patients genetically susceptible. [2] There are reports of a patient with history of TPP who suffered a paralysis crisis after taking excessive doses of thyroid hormone, [23, 24] which supports this hypothesis. [25]

In Figure 1, we described a theoretical model of multifactorial interactions in TPP. The genetic factors could include a defect in one of the ion channels involved in excitation-contraction coupling (Ca^{2+} , Na^+ , and K^+) or a defect in one of the channel's regulatory subunits (β , δ , or SUR, for example). Alterations in one of these genes would be responsible for the generation of non-functional ion channels, which would define the TPP as an endocrine channelopathy. [26, 27]

The environmental factors include the excessive consumption of carbohydrate-rich foods, alcohol, or resting after intense exercise. Thyrotoxicosis would be the limiting factor and essential for the paralysis crisis. [1] In addition, several other studies have demonstrated that the activity of the Na^+/K^+ -ATPase pump is increased in thyrotoxicosis and is more exacerbated in patients with TPP. [28, 29] The hypokalemia observed in these cases is due to the increased K^+ influx into a cell secondary to the increase in the activity of the Na^+/K^+ -ATPase pump and by the hyperinsulinemic response to carbohydrate intake in patients susceptible to TPP. [25,

30] Androgens also can increase the activity of the Na^+/K^+ -ATPase pump, which explains the higher incidence of the disease in young males. [30]

According to the mechanism illustrated in the Figure 2, we believe that during the TPP crisis, the mutated Kir2.6 potassium channel retains potassium in the sarcolemma, causing hypokalemia and flaccid paralysis.

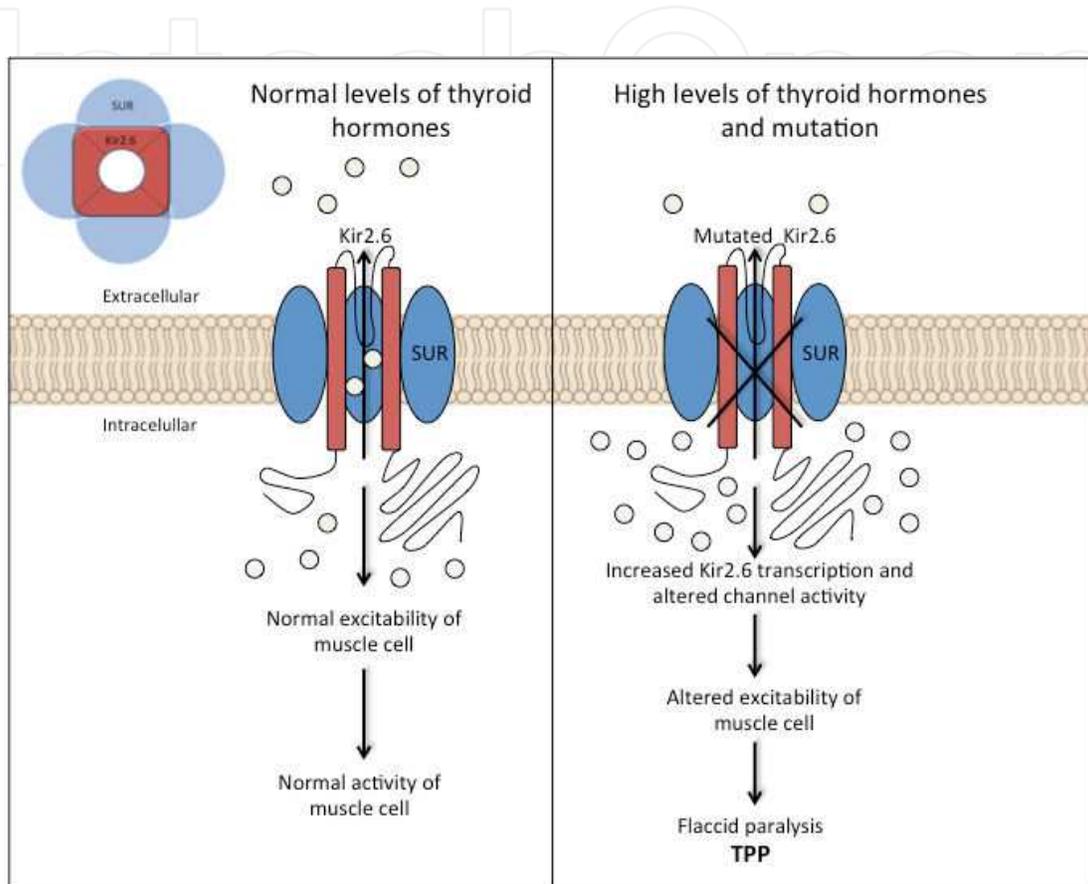


Figure 2. Physiological regulation of Kir2.6 by thyroid hormone and when mutated.

5. Clinical presentation

Illustrative case report of TPP:

A 32-year-old mulatto male patient was brought to the emergency room at 5:00 am by relatives in a wheelchair. He reported being healthy until six months prior to presentation when episodes of muscle weakness in his lower limbs began to develop and kept him from getting out of bed and walking. He also complained of weakness of lower intensity in upper limbs. He denied pain or loss of sensation. All episodes spontaneously resolved without motor sequelae. During physical examination, a decreased in strength, especially in the lower limbs, and hypoactive deep tendon reflexes were noted. In addition, the patient also exhibited diffuse goiter, ocular proptosis, and thyrotoxicosis symptoms (tachycardia, excessive sweating,

tremor of the extremities, and 10 kg weight loss). Eating several slices of pizza and soda in a restaurant was identified by the patient as the triggering factor for the crisis the following the next day.

The laboratory tests at the time of the crisis demonstrated hypokalemia ($K=1.9$ mEq/L; Normal Range: 3.5 to 5.1 mEq/L). The ECG demonstrated the presence of “U” waves and decreased amplitude of the T wave, and oral and intravenous potassium replacement was initiated. The paralysis crisis was resolved after the medication, and the patient was referred to the clinic for the etiologic diagnosis. During the investigation, Graves’ disease was diagnosed with TSH <0.05 mUI/L (Normal range: 0.5-4.5 mUI/L), free T4 >6.0 ng/dL (Normal range: 0.6-1.5 ng/dL), and total T3=535 ng/dL (Normal range: 30-200 ng/dL). The ultrasound revealed diffuse enlargement of the thyroid gland and increased vascularization detected by Doppler. [1, 31] I scintigraphy revealed an uptake of 21% over 2 hours (normal range from 1 to 8%) and 50% over 24 hours (normal range from 3 to 23%). Methimazole and propranolol treatments were initiated followed by the definitive hyperthyroidism therapy with radioactive iodine.

The case above illustrates the importance of a proper diagnosis to determine the specific treatment. Many patients already exhibit signs of hyperthyroidism due to Graves’ disease (goiter and exophthalmia) or thyrotoxicosis symptoms at the time of the paralysis crisis, but often the thyroid alteration is not recognized at the time and may be confused with hysteria or neuro-anxiety. Often, patients are erroneously classified as psychiatric and consequently treated with benzodiazepines.

The paralysis crises are transient and remit spontaneously, and their frequency, duration and intensity vary. [1] Because of this variability in the clinical presentation, the delayed diagnosis is not uncommon. Many patients report multiple visits to the emergency department with a sudden onset of muscle weakness of the limbs before the diagnosis.

Muscle weakness typically affects the proximal muscles of the lower limbs and is usually symmetric. [31] Some patients may present with tetraparesis or tetraplegia, which can be confused with Guillain-Barre syndrome, transverse myelitis, myasthenia gravis, or an acute spinal cord compression. However, in TPP, there is no urinary incontinence or intestinal dysfunction, nor is there a history of infection or trauma. [32] Although rare, there are reports of respiratory muscle paralysis that requires mechanical ventilation. [1, 33] It is important to distinguish TPP from other neuromuscular disorders that also presents with proximal muscle weakness inherent to thyrotoxic myopathy. In these other disease, the patients exhibit muscle atrophy and increased tendon reflexes, and the symptoms are proportional to the severity of the thyrotoxic state. [34]

TPP may be preceded by prodromal symptoms such as muscle pain, cramps, and/or stiffness of muscles of the affected limbs. [32] Frequently, the patients report that crises occur when they get up during the night or early in the morning after a day of intensive exercise and/or consumption of a large amount of food.

Sensitivity is preserved in the physical-neurological examination. However, as shown in Figure 3, the tendon reflexes are decreased or absent in the majority of the patients, [32] in contrast to the expected hyperreflexia in a thyrotoxic patient without paralysis. The duration

of the crisis is variable, lasting up to 72 hours. [31] In a recently published study, the average duration of most cases was two to six hours. [2]

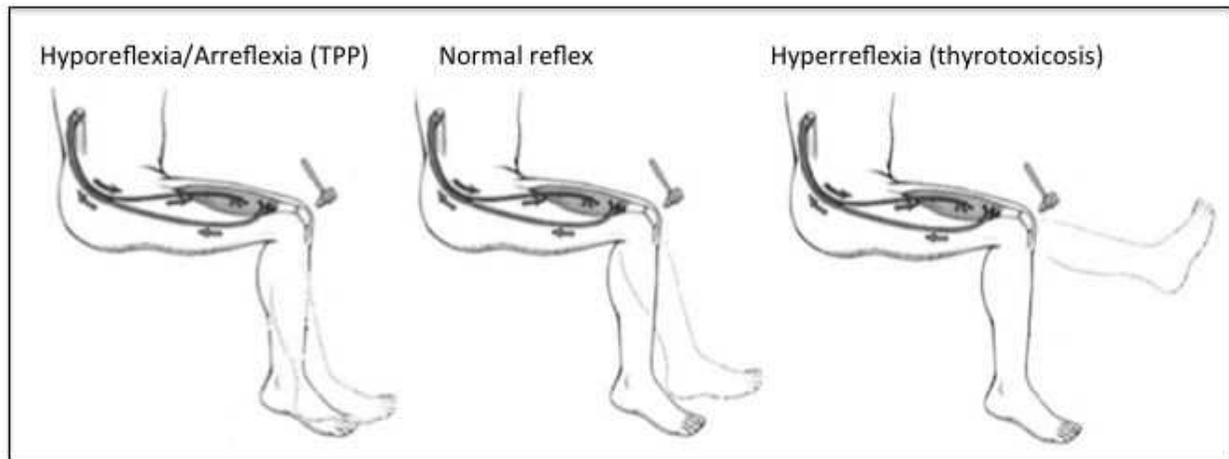


Figure 3. Patellar tendon reflex in patients with TPP, normal individuals, and individuals with thyrotoxicosis.

6. Laboratory and differential diagnosis

The confirmation of thyrotoxicosis, i.e., TSH suppressed in the presence of high levels of thyroid hormones (total and free T3 and T4), is essential for the definitive diagnosis of TPP. Hypokalemia is the primary laboratory alteration at the time of crisis. [9, 35] There are some reports of normokalemia, [36, 37] but we believe that these reports are due to errors during data collection, i.e., data collection in a late stage of the crisis after the serum concentrations of potassium have already recovered, [9] or due to improper storage of the samples, predisposing them to hemolysis. [2]

Hypokalemia results from the influx of ion into the intracellular compartment and does not indicate total depletion of the body potassium. [28] Calcium levels are normal, and creatine phosphokinase (CPK) might be elevated. [2] Some patients exhibit hypophosphatemia and *hypomagnesemia*, [9] both without need for replacement.

Other complementary exams, such as ultrasound, thyroid scintigraphy, and antibody measurements (anti-thyroglobulin, anti-peroxidase, and anti-TSH receptors (TRAb), may be necessary to define the etiology of hyperthyroidism. During the paralysis crisis, some patients exhibit a myopathic pattern on electromyography, which disappears in the remission period. [38] Muscle biopsy demonstrates nonspecific histological findings, and the study of the cerebrospinal fluid does not add any information to the diagnosis, both being dispensable during the investigation of TPP. [2]

We present a table 1 summarizing the major clues for differential diagnosis of acquired muscular disorders in young adults, including clinical and analytical features.

	Thyrotoxic hypokalemic periodic paralysis (TPP)	Familial hypokalemic periodic paralysis (FPP)	Guillain-Barré syndrome	Proximal myopathy
Thyrotoxicosis	Yes (symptoms can be very subtle)	No	No	Yes (duration rather than severity of the thyrotoxic state is proportional to muscle weakness)
Age of onset (years)	20-45 (95%)	Before 16 (80%)	All	All
Frequency	Rare	Rare	Rare	Common (67% of thyrotoxic patients)
Male to female ratio	30:1	3:1	1.5:1	More common among men
Muscle paralysis	Yes (sporadic recurrent acute paralysis)	Yes (sporadic recurrent acute paralysis)	Yes (weakness and paralysis with ascending progression)	No
Ethnicity most frequently affected	East Asian	White	Any	Any
Family history of paralysis	No	Yes	No	No
Precipitating factors	Heavy carbohydrate and/or salt meal, alcohol, exercise, stress	Heavy carbohydrate and/or salt meal, alcohol, exercise, dehydration	Usually preceded by an infection	No
Dysautonomia	No	No	Yes	No
Deep tendon reflexes	Usually absent or depressed	Usually absent or depressed	Absent or depressed	Normal and often hyperactive
Severe respiratory muscle weakness	Very rare	Rare	10-30% of patients	Very rare (in the acute thyrotoxic myopathy only)
Facial muscles weakness	No	No	Common ($\geq 50\%$)	Very rare
Duration of muscle symptoms	30 min-6h	≥ 24 h	Progressive over days to 4 weeks	Throughout thyrotoxic state
Potassium level during the muscle symptoms (mmol/L)	1.5-3.0	2.8-3.5	Normal	Normal

	Thyrotoxic hypokalemic periodic paralysis (TPP)	Familial hypokalemic periodic paralysis (FPP)	Guillain-Barré syndrome	Proximal myopathy
Cerebral spinal fluid	Normal	Normal	Albuminocytologic dissociation	Normal
Nerve conduction analysis	Not specific, not necessary	Not specific	Useful and helpful for diagnosis	Not specific, not necessary
Clinical course	Remission when euthyroidism is reached	Chronic myopathy	Recovery; residual deficit in up to 20%; death in some patients	Weakness of proximal muscles that remits when euthyroidism is reached
Genetic inheritance	Mutation in KCNJ18 gene in up to 33% of patients	Mutation in CACN1A5 gene (80%) and SCN4A gene (15%)	None	None

(Adapted with permission from reference [2])

Table 1. Clues for differential diagnosis of acquired muscular disorders in young adults

7. Treatment and follow-up

The administration of oral and/or intravenous (IV) potassium is recommended during the paralysis crisis to accelerate the recovery and prevent a possible cardiac arrhythmia. [2] The oral use of potassium should be preferred, [39] but if a faster recovery is necessary, potassium may be slowly IV infused, usually over 2 hours. The main concern about potassium replacement is rebound hyperkalemia [40] because the potassium abnormality is not due to total potassium depletion but intracellular ion trapping. Therefore, monitoring the serum K levels during the treatment and suspending the infusion at the first sign of the muscular force recovery is recommended. [2]

Non-selective beta blockers, especially oral propranolol (80-240 mg/day), [2] may be useful in TPP treatment, especially when awaiting the FT4 and TSH results, by limiting the time of the crisis without inducing rebound hyperkalemia. [41, 42] These drugs block the adrenergic stimulation of the Na⁺/K⁺-ATPase pump activity, resulting in lower K influx to skeletal muscle.

Early treatment for the underlying cause of thyrotoxicosis is the most important procedure in patients with TPP. When euthyroidism is reached, the paralysis crises remits definitively. [34] Triggering factors such as high intake of carbohydrates, alcohol, and intense physical exercise should be avoided until the resolution of the *thyroid* disease. [43] In cases of thyrotoxicosis caused by excessive intake of thyroid hormones, the drug is suspended. In hyperthyroidism

associated with Graves' disease, toxic multinodular goiter, or toxic adenoma, the definitive treatment with radioactive iodine or thyroidectomy should be established immediately. Anti-thyroid drugs (methimazole or propylthiouracil) should be prescribed as adjuvant while the patient waits for the definitive therapy.

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