Chapter

Thyrotoxic Hypokalemic Periodic Paralysis

Mustafa Cesur and Irmak Sayın Alan

Abstract

Thyrotoxic hypokalemic periodic paralysis (THPP) is a rare but life-threatening complication of hyperthyroidism characterized by recurrent episodes of muscle weakness due to intracellular potassium shifting in the presence of high levels of thyroid hormone. Attacks can be triggered by many factors. Its differential diagnosis from the other common causes of hypokalemic paralysis is necessary to maintain targeted therapy. Outcome was right away positive under potassium replacement therapy. Hyperthyroidism should be treated to prevent attacks.

Keywords: hypokalemia, periodic paralysis, thyrotoxicosis

1. Introduction

Hypokalemia can be defined as a serum potassium level under 3.5 mEq/L. The symptoms of severe hypokalemia are nonspecific and mainly are related to muscular or cardiac functions and its effects on nerves. In severe and life-threatening hypokalemia (serum potassium of less than 2.5 mEq/L) generalized weakness and dangerous ventricular tachyarrhythmias may occur. Heart muscle can be affected by arrhythmias and may lead to heart failure [1, 2]. Acute decrease of serum potassium may be more arrhythmogenic than chronic hypokalemia [3].

Acute hypokalemic paralysis is a clinical syndrome presenting with low serum potassium levels and acute systemic weakness. The muscular weakness ranges from minor weakness to complete flaccid paralysis. This clinical syndrome is extremely rare. Fortunately, it is a treatable condition. Thyrotoxic hypokalemic periodic paralysis (THPP) is one of the reason of acute hypokalemic paralysis [4]. Approximately 32% of acute hypokalemic paralysis has found to be related to thyrotoxicosis [5].

The association between thyrotoxicosis and periodic paralysis was first described by Rosenfeld in 1902. THPP is a rare condition, which occurs in 2% of patients with thyrotoxicosis. THPP is mainly sporadic, but may be associated with certain HLA haplotypes [6]. There is no exact knowledge about genetic disposition of THPP. Genetic analysis identified heterozygous variants in candidate genes. But no single pathogenetic mutation has been identified. Several single-nucleotide polymorphisms in these genes have been associated with THPP. Determination of the complete genetic architecture in the future studies will be helpful to understand the pathophysiology of THPP [7, 8].

Triggering factors	
• Awakening in the middle of sleep	• Alcohol
• High carbohydrate intake	• Cold exposure
• High salt intake	• Drugs (diuretics, estrogen, laxatives, steroids and amphotericin B, etc.)
• Epinephrine	• Insulin
• Menstrual cycle	• Upper respiratory tract infections
• Radioactive iodine treatment	• Trauma
• Rest after strenuous exercise	• Surgery
• Emotional stress	
• Abuse of thyroid hormone	

Table 1.
Triggering factors of Thyrotoxic hypokalemic paralytic episodes.

THPP is generally associated with intermittent episodes of muscle weakness and occasionally with severe paralysis. Paralytic attacks are mostly precipitated by strenuous exercise, high glucose intake, or hyperinsulinemia. THPP is a widespread complication of hyperthyroidism in males (85%) of Asian origin with a frequency of almost 2% [4, 9]. The case of THPP in the females is a rare occurrence. The reason for this is mysterious but proposes that androgens have a role in the pathogenesis of THPP. Cases with symptoms are generally between 20 and 40 years of age [10, 11]. Rarely it can be seen in children and adolescents [12] or elderly [13].

The best part of etiological agents for thyrotoxicosis may be related with THPP. The major agent was reported to be Graves' disease [12, 13]. Silent thyroiditis and subacute thyroiditis are the rest etiologies [4]. THPP related with Coronavirus disease 2019 (Covid-19) infection reported in some data. Higher incidence of hyperthyroidism was reported in patients with Covid-19 infection, probably related to immune response to the infection. Thyroid function was shown to be improved when the infection was resolved [14, 15].

Various circumstances, including TSH-secreting pituitary adenoma [16], using high doses of thyroxine [17, 18], and iodine-related thyrotoxicosis with inattentive use of iodine or with drugs containing iodine (e.g., iodinate contrast agents or amiodarone) [19–21] have also been involved.

One of the Turkish cases occurred as the first manifestation of interferon-alpha-induced Graves' disease [22] while another occurred after radioactive iodine therapy, which led to the consideration of radiation thyroiditis [23]. There are many triggering factors [4, 24, 25]. The triggering factors of thyrotoxic hypokalemic paralytic episodes are given in **Table 1**.

2. The pathophysiology of THPP

The pathophysiology of THPP is poorly understood. In THPP, flaccid paralysis occurs with comparatively minor alterings in the serum potassium level. Hypokalemia is the characteristic evidence with elevated thyroid hormones. It is generated with a quick shift in K from the extracellular space to the intracellular department, particularly into the muscles. Increased adrenergic responses and elevated circulating levels of insulin

and thyroid hormones raise Na^+/K^+-ATPase activity. Additionally, thyroid hormones rise the sensitivity of beta-receptors, so catecholamine-mediated cellular K uptake is raised [26, 27]. These suggestions may explain why insulin and epinephrine stimulate paralytic attacks. Carbohydrate-rich meals increase insulin release, and stress-related factors (e.g., emotional stress, cold, trauma, and infection) increase epinephrine delivery. Exercise also delivers K from the skeletal muscles, while rest encourages flow of K, so paralytic attacks may be seen during rest after strenuous exercise [28].

The robust preference for THPP to occur in males brings forward that androgens may take part to pathogenesis of THPP. Androgens have been reported to enhance the expression and activity of the Na^+/K^+-ATPase and hence related with TPP attacks [29]. Potassium channel Kir2.6 gene mutations have been established to take a role in THPP. Kir2.6 is mainly expressed in skeletal muscle and is transcriptionally arranged by thyroid hormone. Mutation of the gene coding this channel has been established in THPP cases and is related with high prevalence of paralytic attacks in those patients [30].

3. Differential diagnosis

In an acute attack, THPP must be distinguished from other causes of acute hypokalemic paralysis. Hypokalemic paralysis symbolizes a heterogeneous category of disorders, which cause an ultimate mutual pathway existing as acute weakness and hypokalemia. Hypokalemic paralysis can be divided into two main groups. The first group contains the patients with hypokalemic periodic paralysis, which is related to an acute exchange of potassium into the cells (**Figure 1**). The second group contains the patients presenting with hypokalemic paralysis, which is related to potassium

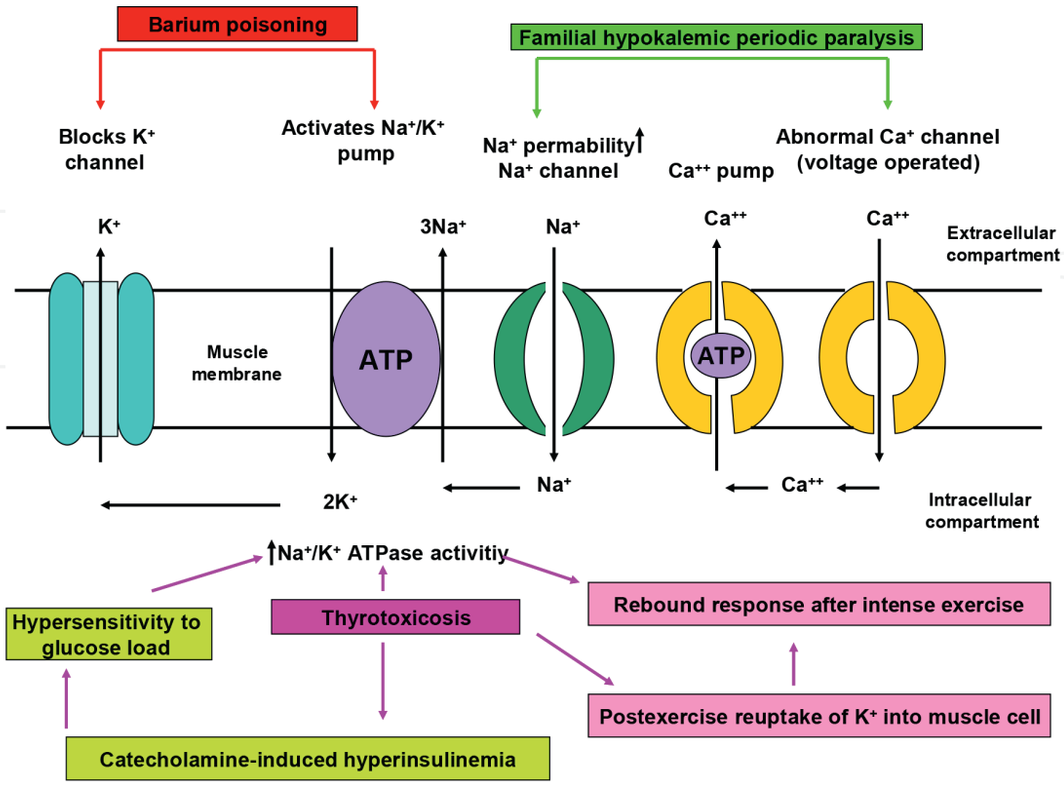

Figure 1.
Pathogenesis of hypokalaemic paralysis in transcellular distribution of potassium without depletion.

Transcellular distribution of potassium (no depletion)	Actual potassium depletion	
	Renal loss	Extra-renal loss
• Familial periodic paralysis	• Distal RTA	• Celiac disease
• Thyrotoxic periodic paralysis	• Sjögren's syndrome	• Tropical sprue
• Barium poisoning	• Medullary sponge kidney	• Severe diarrhea
	• Chronic toluene exposure	• Short bowel syndrome
	• Fanconi's syndrome	
	• Primary aldosteronism	

Table 2.
Differential diagnosis of hypokalemic paralysis.

depletion. Diagnosis among paralytic attacks is hard as the patient may have normal force and potassium levels. Electromyography shows unusualness in a few patients but is frequently normal, particularly among episodes when no clinically detectable weakness is present. Hypokalemic paralysis happens in different situations, and the diagnosis may require a broad research for the underlying etiology since the treatment changes according to the reason [31].

The diagnosis of THPP is made based on clinical presentation and exclusion of disorders associated with low potassium (**Table 2**).

4. Clinical features

THPP attacks mostly occur in the late night or early morning and last from a few hours up to several days. Prodromal symptoms such as aches, cramps, and stiffness can be seen [32]. Generally, the proximal muscles are more seriously affected than the distal muscles. The acute episode at first involves the lower limbs, followed by girdle muscles and thereafter upper limb. Atypical findings such as asymmetric paralysis are uncommon. Presentations alter widely from mild, transient, self-limited motor dysfunction to total flaccid paralysis, with recovery occurring first in those muscles affected last. Bladder, bowel, and sensory functions are generally not affected and mental skills are never damaged [10]. Paralysis of respiratory, bulbar, and ocular muscles has been rarely reported in severe attacks of THPP. Respiratory muscle involvement, even though rare, generally can be fatal [33]. Deep tendon reflexes are prominently reduced or absent. Moriyama et al. reported that sudden deafness in a man with THPP, circulatory failure, and electrolyte instability in the right inner ear was accepted to have caused the deafness [34]. Patients completely recover between the attacks [26].

5. Laboratory features

Hypokalemia is the main laboratory finding in THPP. However, normokalemic THPP cases have also been reported [35, 36]. Normokalemia may lead to overlooked diagnosis [36]. The level of hypokalemia is important [31]. Serum potassium level may be one of the markers of survey of the disease for its reasoning of fatal and life-threatening ventricular arrhythmias [37, 38]. Hypomagnesemia and

hypophosphatemia have been reported to be common in THPP. These laboratory results may aid differentiate THPP from familial hypokalemic periodic paralysis [39]. Elevated serum T3 and T4, low serum TSH levels, and thyroid uptake scan showing symmetric diffuse uptake are component of the diagnostic assessment. Patients with elevated T3 and normal T4 levels have been reported, particularly in patients who have Graves' disease or an adenoma who usually have T3 thyrotoxicosis [40]. Serum creatine phosphokinase (CPK) was found to be high [39, 41]. Rhabdomyolysis may be seen in severe THPP [42]. In addition to hypokalemia [43] and hypophosphataemia [44], hyperthyroidism alone may cause rhabdomyolysis [45]. ECG alterations in THPP vary from nondiagnostic to those demonstrating typical features of hypokalemia [46]. ECG alterations related with hypokalemia and/or other ECG abnormalities may be seen. ECG findings may help in early diagnosis of THPP [47, 48]. Sinus tachycardia, ventricular tachycardia, ventricular fibrillation, high QRS voltage, first-degree AV block, atrial flutter, and atrial fibrillation are significant signs proposing THPP in patients who present with paralysis and hypokalemia [48–50]. An artificial-intelligence-assisted-ECG system trustworthy recognizes hypokalemia in patients with paralysis, and combining with routine blood tests makes precious judgment assistance for the early diagnosis of THPP [51].

6. Management

Patients with acute paralysis must be hospitalized in a monitored condition for cardiac arrhythmias. Acute management of THPP contains potassium chloride replacement, cautious observation, and close monitoring of serum potassium levels. Potassium replacement can be done in two ways: oral or intravenous. A recommended protocol is 30 mEq of oral potassium every 2 hours until recovery begins, with a maximum dose of 90 mEq in 24 hours. Intravenous supplementation is the major choice if the patient shows signs of cardiac dysrhythmia, respiratory distress or is unable to take oral medications. The dosage of potassium varies between patients and can be standardized according to renal clearance and cardiovascular condition. Potassium replacement should not exceed 90 mEq/24 h because of the possibility of rebound hyperkalemia. Rebound hyperkalemia appears to be an important trouble in THPP, taking place in approximately 40–59% of treated attacks [4, 10, 52, 53]. In contrast to familial periodic paralysis, regular oral potassium supplementation is ineffective for prevention of the attacks in THPP [53]. Imminent monitoring of serum potassium levels throughout the acute attack is necessary. Continual cardiac monitoring is suggested for all patients throughout medical management and observation. A cardiology consultation should be provided for serious arrhythmias/ECG changes. Correction of hypomagnesemia, if present, is additionally suggested.

The best way to prevent and to permanently treat the periodic paralysis is to treat the thyrotoxicosis permanently. THPP does not disappear completely unless patients become euthyroid. Thus, the management of hyperthyroidism is the mainstay of therapy. Permanent treatment is so important and could be done by antithyroid drugs, radioiodine therapy, or surgery [27]. During treatment of hyperthyroidism, precipitating factors should be avoided. While antithyroid drugs may be used to induce remission, the performance of this therapy is changeable and relapses are frequent. By the end of the acute attack, radioiodine therapy or thyroid surgery is preferable to permanently end the thyrotoxicosis. For high recurrence rates of long-term treatment with antithyroid drugs, early permanent therapy, especially with radioactive iodine, is

recommended because surgical stress may further induce paralysis. However, surgical therapy with close monitoring can be performed if necessary [4]. Chemical ablation has mainly shown benefit in elderly individuals, pregnant, cardiac and pediatric patients [54]. Non-selective beta-blockers (e.g., propranolol) have been shown to significantly improve thyrotoxic symptoms and maintain relief of paralytic attacks by blocking catecholamines' effect on ion channels [55]. Selective β-blockers do not act on skeletal muscle, which makes them less beneficial in the treatment of THPP [27]. In spite of likely benefits, beta-blockers (principally non-selective agents) are known to have a mild deleterious effect other metabolic parameters [56].

The effects of glucocorticoids in the management of hyperthyroidism have been evaluated in many different studies. Even though glucocorticoids have been used to treat hyperthyroidism, they may further cause harmful effects, including the development of THPP.

Glucocorticoids may induce hypokalemia by increasing the Na^+/K^+-ATPase level in skeletal muscle and also by creating hyperinsulinemia. In addition, glucocorticoids can also release muscle weakness by stimulating myopathy and renal potassium waste owing to its mineralocorticoid effects [11]. Consequently, glucocorticoids can trigger these attacks. This is an infrequent complication of thyrotoxicosis. But for physicians, it is important to be aware of the risk of provoking thyrotoxic paralysis when using high-dose glucocorticoids in the thyrotoxic phase [57]. Lastly, acetazolamide may worsen the attacks in THPP and should be avoided [52].

In conclusion, THPP is rare but life-threatening complication of thyrotoxicosis. It needs early diagnosis and immediate treatment of hypokalemia, then permanent therapy of thyrotoxicosis.

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