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CASE REPORT

Thyrotoxic periodic paralysis: a case study and review of the literature

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ABSTRACT

Acute hypokalemic paralysis is a rare cause of acute weakness. Morbidity and mortality associated with unrecognized disease can occur and include respiratory failure and possibly death. Common causes of hypokalemic paralysis include thyrotoxic periodic paralysis (TPP) which is a disorder most frequently seen in Asian males. TPP is characterized by sudden onset of hypokalemia and paralysis that primarily affects the lower extremities. Treatment of TPP includes replacing potassium rapidly, using nonselective beta-blockade and correcting the underlying hyperthyroidism as soon as possible. TPP is curable once euthyroid state is achieved. It is vital for physicians to be able to differentiate TPP from familial hypokalemic periodic paralysis, a more common cause of periodic paralysis in Caucasians and western countries. We describe a 19-year-old Caucasian man who presented with acute onset lower extremity paralysis secondary to acute hypokalemia and was found to have new onset Graves' disease.

Abbreviations: TPP: Thyrotoxic periodic paralysis

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1. Introduction

Hyperthyroidism is associated with a number of muscular disorders, including thyrotoxic myopathies, myasthenia gravis, exophthalmic ophthalmoplegia, and periodic paralysis [1]. As it is the most frequent etiology of hyperthyroidism [2], Graves' disease is the most common disorder in the majority of patients with TPP. Despite the higher incidence of hyperthyroidism in females, more than 95% of TPP occurs in males [3]. Early recognition of TPP is crucial to provide appropriate treatment and to avoid the risk of rebound hyperkalemia that may occur if high-dose potassium replacement is given. This literature review article highlights the importance of early diagnosis of acute muscle weakness and appropriate timely management in decreasing morbidity, mortality, and health care expenditure.

2. Case report

A 19-year-old healthy Caucasian man (AB), with no past medical history, presented to the emergency department with acute onset generalized muscle weakness, more pronounced in his lower extremities. AB described going to bed in his normal state of health. Upon awakening the following morning, he started experiencing severe weakness with inability to sit up in bed; requiring full assistance for activities of daily living. AB reported two episodes of similar presentation at the age of 12 years and most recently three months prior to this presentation. Muscle weakness during previous presentations was described as mild, transient, and self-limited, resolving in a matter of days. Also noted at time of presentation was a history of 40 lbs weight loss over two months in spite of increased appetite. AB denied palpitations, heat intolerance, dysphagia, dysphonia, dyspnea, and change in bowel movements. The remaining review of systems was negative. AB has never smoked and denied use of diuretics, laxatives, alcohol, or recreational drugs. Patient denied use of any prescribed or non-prescribed medications. There was no known history of radiation or thyroid toxin exposure. Family history was negative for periodic paralysis or thyroid disorders.

Physical examination revealed a cachectic male who appeared his stated age, with blood pressure: 100/54 mmHg, pulse: 110 beats per minute, temperature: 98.7°F, respiratory rate: 16 breaths per minute, and oxygen saturation: 97% on room air. He was alert, oriented, and in no acute distress. Head exam was significant for temporal muscle wasting bilaterally, lid lag, orbital lag, and mild exophthalmos. Neck exam showed diffuse symmetric enlargement of thyroid gland with firm consistency and lack of bruit. Cardiopulmonary and abdominal examinations were unremarkable. Neurologic exam was positive for brisk and symmetric patellar reflexes and fine

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tremors in bilateral hands with extension. Strength was 4/5 in all muscle groups of bilateral lower extremities. The remaining neurological examination was unremarkable.

Initial serum potassium on presentation to the emergency department was 1.9 mEq/L (3.5–5.1 mEq/L), with normal acid-base status that was confirmed on repeat testing. Previous serum potassium less than a month prior to this presentation was 4.9 mEq/L. Serum phosphorus: 3 mg/dL (2.5–4.5 mg/dL), magnesium: 1.7 mg/dL (1.6–2.3 mg/dL). Electrocardiogram showed sinus tachycardia with a ventricular rate of 108 beats per minute.

An initial clinical diagnosis of periodic hypokalemic paralysis was made. Treatment began with 20 mEq of intravenous potassium chloride (KCl) as well as 40 mEq of oral potassium in the emergency department and was then started on a normal saline infusion with 10 mEq/L of potassium. His serum potassium was checked four hours later and was 3.4 mEq/L. Re-examination at four hours was significant for complete resolution of lower extremity weakness with no change in the rest of his physical examination.

Serial measurements of his serum potassium level while in the hospital showed rapid improvement of his potassium with level of 4 mEq/L on hospital day 2. Initial thyroid-stimulating hormone level (TSH) returned at <0.02 mU/L (0.47–4.68 mIU/L), free thyroxine (T_4) level: 5.5 ng/dL (0.8–2.2 ng/dL), and total triiodothyronine (TT3): 539 ng/dL (80–206 ng/dL).

Thyrotoxicosis was diagnosed, and the patient was given propranolol 10 mg PO three times a day (TID) as well as methimazole 10 mg PO TID. The patient's thyroid-stimulating immunoglobulin level was elevated at 382% (<140%) and thyroid peroxidase antibody was 4 IU/mL (<9 IU/mL). Ultrasonography of the soft tissue of the neck showed mildly prominent thyroid gland with marked increased vascularity. The patient was discharged home with the diagnosis of TPP secondary to new onset Graves' disease. At six week post-discharge follow-up, AB's weight had returned to normal and there had been no more episodes of muscle weakness or paralysis. His physical exam was remarkable for improved exophthalmos, lid lag, and orbital lag, and mild symmetric thyroid gland enlargement with absence of bruit. Repeat thyroid function tests at that time were as follows: TSH:<0.02 mU/L, free T4: 1.8 ng/dL, and TT3: 209 ng/dL.

3. Discussion

TPP is defined as episodes of muscle weakness in patients who have high levels of circulating thyroid hormone. TPP is most commonly seen in Asian men in the third to fifth decade of life [4]. Paralytic attacks in TPP usually begin after symptoms of hyperthyroidism have developed. The frequency of attacks is variable and duration of episodes ranges from hours to several days [5]. Weakness is more common in the lower as opposed to upper extremities and proximal muscles more than distal, with hip and shoulder involvement both reported in literature. TPP may present with symmetric or asymmetric weakness, and mild myalgias have been described in some cases. Bowel and bladder function are typically not affected during episodes. Ocular muscle involvement has also been described; however whether this is a result of hyperthyroidism itself or a symptom of TPP remains unclear [6]. Rare symptoms include speech impairment, dyspnea, dysphagia, and visual changes. Other signs during an attack or episode include decreased or lack of reflexes, arrhythmia, and low serum potassium level. Patients regain muscle strength between episodes initially, but there is a chance for development of persistent muscle weakness over time with repeated attacks. Triggers include, but are not limited to, resting after extreme exercise, meals high in sodium content, meals high in carbohydrate content, and time of day, with increased frequency of episodes occurring in the early morning [7,8].

The etiology of TPP is related to skeletal muscle ion channel defects [9]. A disruption of any one of several ion channels may result in muscle weakness and paralysis. Intracellular shifts of potassium are responsible for muscle weakness during the episodes. In patients with TPP, it has been found that there is increased activity of Na^+/K^+-ATPase pumps in the skeletal muscle cell membranes. Thyrotoxic patients with periodic paralysis have been found to have higher Na^+/K^+-ATPase pump activity compared to those without paralytic attacks. Catecholamine release enhances Na^+/K^+-ATPase activity in skeletal muscles, explaining the higher frequency in early mornings as well as post-exercise [8].

Hyperinsulinemia has been suggested as an important factor for developing hypokalemic paralysis in patients with TPP. In a study by Supamai Soon Thornpun et al., it was found that subjects with a history of TPP were more obese and had lower sensitivity to insulin than those with a history of simple thyrotoxicosis [10]. Foods high in carbohydrates stimulate release of insulin, explaining the higher frequency seen post-prandial [8].

The strong predilection for TPP to occur in males suggests that androgens may contribute to pathogenesis of TPP. Yu Yao et al. showed that episodes of paralysis in Chinese men with TPP were associated with elevated serum testosterone [11]. Men also have higher muscle-to-body mass ratio as the result of testosterone-mediated hypertrophy of myoblasts and thus total amount of Na^+/K^+-ATPase is higher in

men compared to women which also make the male gender more susceptible to TPP episodes [8]. Androgens have been reported to increase the expression and activity of the Na^+/K^+-ATPase and therefore correlate with TPP episodes [12,13]. Androgen has shown to increase activity of sodium-potassium channels. It also enhances binding of the ß-adrenergic receptors in animal models. There have been some case reports in which patients experiencing TPP episodes were found to have adrenal adenomas and high levels of dehydroepiandrosterone and 17-hydroxyprogesterone [12]. The severity of muscle weakness in these patients cannot be explained by the severity of hyperthyroidism and there may be a role of other hormones including androgens in the occurrence of paralysis attacks [12].

The mechanism of action of exercise-induced TPP is also not completely understood. It is known that during exercise there is release of potassium from the intracellular space to the extracellular space while during rest there is shift of potassium towards the intracellular space. This mechanism, in addition to the effect of catecholamines, are likely largely responsible for paralytic attacks during the recovery phase of exercise.

More information is coming to light in regards to the genetics involved in TPP. Gene mutations in potassium channel Kir2.6 have been found to play a role in TPP. Kir2.6 is primarily expressed in skeletal muscle and is transcriptionally regulated by thyroid hormone [14]. Kir2.6 is a type of inwardly rectifying potassium channels (Kir channels) which is expressed in skeletal muscles and has a vital role in stability of membrane potential. Mutation of the gene encoding this channel has been found in TPP patients and is associated with increased prevalence of paralytic episodes in those patients. Thyroid hormones upregulate transcription of this gene. Impaired cell membrane depolarization as a result of reduced outward K current in these patients causes muscle weakness. One study revealed the prevalence of Kir2.6 mutation among Caucasians and Brazilians with TPP of about 33%, and was statistically significant [14].

The diagnosis of TPP is made based on clinical presentation and exclusion of disorders associated with low potassium. High serum T3 and T4, low serum TSH levels, and thyroid uptake scan showing symmetric diffuse uptake are part of the diagnostic evaluation. Abnormal electrocardiogram (ECG) and electromyogram (EMG) findings consistent with hypokalemia can aid in diagnosis when accompanied with biochemical evidence of hypokalemia. A muscle biopsy may sometimes be warranted. Biopsy of skeletal muscles in a number of patients with TPP has shown different muscle structural changes. These changes include, but are not limited to, sarcolemmal nuclear proliferation, vacuolation, atrophy of muscle fibers, fatty infiltration, and mitochondrial changes. These structural distortions interfere with muscle contraction leading to paralysis [15,16].

Treatment of acute TPP is quickly reducing thyroid hormone levels in addition to potassium supplementation. During management, it should be kept in mind that there is a risk of rebound hyperkalemia due to release of K and phosphate from the cells in recovery phase. Treatment of hypokalemia with intravenous K results in a more rapid response compared to oral supplementation. There is no confirmed role for prophylactic use of potassium between attacks [8]. Nonspecific beta-blockers, however, have been shown to reduce the frequency and severity of attacks. Treating hyperthyroidism will prevent attacks and may even reverse muscle weakness [7,8]. Non-selective β-blockers could terminate neuromuscular symptoms rapidly while reducing an intracellular shift of potassium and phosphate. In a study by Shih-Hua Lin et al., administration of oral propranolol, 3 mg/kg, resulted in correction of serum potassium and phosphate in two hours and complete amelioration of paralysis without causing rebound hyperkalemia or hyperphosphatemia [17]. Propranolol at a dose of 40 mg, four times a day, has been successfully used in about two thirds of carbohydrate-induced TPP cases to prevent the attacks [8]. Due to the specific role of the β2 receptor in mediating the catecholamine-induced increase in Na^+/K^+-ATPase activity in skeletal muscle, metoprolol and other selective β-
blockers do not protect patients from paralytic attacks [18].

Patients should be screened for concomitant use of medications that can cause hypokalemia like glucocorticoids, which inhibit insulin secretion from the β-cells of the pancreas in addition to affecting metabolism of carbohydrate. By effects on insulin sensitivity, glucocorticoids can induce TPP attacks. There have been reported cases of prednisone use prior to TPP attack in patients diagnosed with hyperthyroidism [19]. A literature review revealed at least two cases of TPP induced by methylprednisolone and two cases caused by a single dose of prednisone [18,20]. If clinically able, medications such as glucocorticoids should be discontinued during the treatment of TPP.

TPP should be differentiated from hypokalemic periodic paralysis (familial periodic paralysis) which presents in a clinically identical manner but has a number of important differences, and is not related to thyroid hormone levels.

FPP is an autosomal dominant disorder that affects both sexes equally, is more common in Caucasians relative to TPP, and usually manifests within the first two decades of life. In contrast, TPP

would usually present in the third to fifth decade of life [4,5], is sporadic in its pattern of onset (i.e., no family history of paralysis) and is always a consequence of thyrotoxicosis.

4. Conclusion

Thyrotoxic period paralysis can be the initial presentation of thyrotoxicosis. This condition is very rare in Caucasian populations. TPP is commonly misdiagnosed in western countries because of its similarities to familial periodic paralysis. Diagnosis of TPP is often delayed and confused with more common causes of hypokalemia and lower-extremity paralysis, likely because of the subtle presentation of thyrotoxicosis, in addition to lack of awareness about this disorder. Increased awareness among physicians about this disorder will result in early diagnosis, appropriate treatment, and the prevention of rebound hyperkalemia.

Disclosure statement

No potential conflict of interest was reported by the authors.

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