Thyrotoxic Channelopathies

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Abstract

Thyrotoxic periodic paralysis (TPP), a disorder most commonly seen in Asian men, is characterized by abrupt onset of hypokalemia and paralysis. The condition primarily affects the lower extremities and is secondary to thyrotoxicosis. Early recognition of TPP is vital to initiating appropriate treatment and to avoiding the risk of rebound hyperkalemia that may occur if high-dose potassium replacement is given.

Here we present a case of 31 year old male with thyrotoxic periodic paralysis with diagnostic and therapeutic approach.

Introduction

Thyrotoxic periodic paralysis (TPP) is most common in Asian populations, with an incidence of approximately 2% in patients with thyrotoxicosis of any cause. TPP is characterized by acute onset of severe hypokalemia and profound proximal muscle weakness in patients with thyrotoxicosis. TPP is commonly misdiagnosed in western countries because of its similarities to familial periodic paralysis. Familial periodic paralysis is an autosomal dominant disorder caused by a defect in the gene coding for L-type calcium channel 1-subunit (CACNA1S) on chromosome 1q31–32. The neuromuscular presentations of both are identical, and to enhance diagnosis of TPP, physicians need to look for subtle features of hyperthyroidism in the presence of hypokalemic periodic paralysis. Early diagnosis not only aids in definitive management with nonselective beta-blockers and correction of hyperthyroidism, but also prevents the risk of rebound hyperkalemia due to excessive potassium supplementation.

Case Report

A 31 year old South Indian man with a history of recurrent muscle weakness and hypokalemia presented in our Emergency department with generalized muscle weakness, more pronounced in his lower extremities. The patient’s symptoms started in the early morning, and he was unable to walk to the bathroom. He had had similar episodes before and took potassium supplements sporadically. His initial episode of hypokalemia and paralysis had occurred 6 years earlier. He denied use of diuretics, laxatives, alcohol, or recreational drugs. He reported intermittent palpitations and diarrhea and had no family history of periodic paralysis.

On physical examination, he had a mildly enlarged thyroid with firm consistency, irregularly irregular heart rate (Figure 1) and decreased muscle strength and tendon reflexes in both lower extremities. He had no exophthalmos or sensory or cranial nerve deficits.

In the Emergency department, his initial potassium level was 2.4 mEq/L with normal acid-base status. His phosphorous level was 2.6mg/dL (reference range 2.7-4.5 mg/dL) and serum magnesium level was 1.9 mg/dL (reference range 1.7-2.6 mg/dL) on admission. His CPK enzyme levels were 85 U/L (reference range 51 – 294 U/L). Urine potassium per 24 hours was 2.3 mmol/day (reference range 2.5-125 mmol/day). Electrocardiogram showed atrial fibrillation with a ventricular rate of 130 beats per minute. Initial diagnosis of hypokalemic periodic paralysis was made. Patient was commenced on intravenous potassium 10mEq/hr. Oral potassium supplementation was also given. His symptoms improved the next day with the complete recovery of muscle power in the lower extremities.

On the following day, thyroid function test showed serum TSH of 0.005 µIU/ml (reference range 0.50-6.8 µIU/ml) and a free T4 level of 3.34 ng/dl (reference range 0.89-1.76 ng/dl). Patient was further evaluated for cause of thyrotoxicosis and was found to have high titres of TRab (TSH Receptor Anti-body). Tc 99m scan of the thyroid showed homogenous uptake in both the lobes, suggestive of Graves Disease (Figures 2 and 3). He was commenced on Carbimazole 10 mg twice a day and Propranolol 40mg twice daily. Patient’s serial serum potassium levels continued to remain normal without

Fig. 1: ECG at the time of presentation in casualty

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Received: 06.03.2016; Revised: 24.09.2016; Accepted: 30.09.2016
oral potassium supplements during his stay in hospital and he was sent home with the diagnosis of TPP secondary to Graves Disease. Patient is on regular follow up on OPD basis and there is no further episode of hypokalemia and or quadripareseis. Last Thyroid profile report is as follows – TSH of 1.067 µIU/ml and fT4 – 1.08 ng/dl.

Discussion

Even though it is commonly seen in Graves’ disease, TPP is not related to the etiology, severity, and duration of thyrotoxicosis. Family history of periodic paralysis is usually absent.

The pathogenesis of thyrotoxic periodic paralysis has long been thought related to increased Na+–K+ ATPase activity in skeletal muscle, liver, and kidney to induce an influx of potassium into the intracellular space. Among the various Na/K-ATPase subunits, the α1-, α2-, β1-, β2-, and β4-subunits are expressed in skeletal muscles. 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. 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.

The events that lead to paralysis with hypokalemia and hypophosphatemia in patients with TPP are complex. They include hyperthyroidism and/or hyperadrenergic activity and hyperinsulinemia. This mechanism alone, however, associated paradoxical depolarization of the resting membrane potential. Recent findings that loss of function mutations of the skeletal muscle-specific inward rectifying K+ (Kir) channel, Kir2.6, associate with thyrotoxic periodic paralysis provide new insights into how reduced outward K⁺ efflux in skeletal muscle, from either channel mutations or inhibition by hormones (adrenaline or insulin), can lead to a vicious cycle of hypokalemia and paradoxical depolarization.

Thyroid hormones can increase Na/K-ATPase activity in skeletal muscle, liver, and kidney to induce an influx of potassium into the intracellular space. Among the various Na/K-ATPase subunits, the α1-, α2-, β1-, β2-, and β4-subunits are expressed in skeletal muscles. 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. 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.

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In conclusion, 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 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.

References