Clinical Review

Periodic Paralysis Syndromes: A T3 Thyrotoxicosis Case and Review of Literature

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Abstract

Description

Periodic paralysis is a group of muscle diseases that are related to transmembrane ion channels. Dysfunction of these channels causes an increase in sodium-potassium (Na-K) adenosine triphosphatase (ATPase) activity that pushes potassium into the cells that result in serum hypokalemia that manifests as muscle weakness. Beta-adrenergic stimulation and insulin sensitivity might also play a role.

Periodic paralysis is divided into hereditary and acquired forms. Thyrotoxic periodic paralysis is an acquired form of periodic paralysis that manifests as muscle weakness, hypokalemia, and hyperthyroidism. The onset of the symptoms is mainly over the age of 20 and can be triggered by intense physical activity, stress, and excessive carbohydrate intake.

This review presents the different types of this disease (hypokalemic, hyperkalemic, thyrotoxic, and Andersen-Tawil syndrome) while presenting a unique case of T3 thyrotoxicosis causing periodic paralysis.

Keywords

hypokalemic periodic paralysis; thyroxine/adverse effects; substance-related disorder; hypokalemic periodic paralysis, diagnosis; paralysis; thyrotoxicosis; Andersen Syndrome

Introduction

Periodic paralysis (PP) is a family of muscle diseases relating to the dysfunction of transmembrane ion channels, which results in painless muscle weakness. It has an autosomal dominant pattern of inheritance and is associated with either hypokalemia (hypokalemic PP and Andersen-Tawil syndrome) or hyperkalemia (hyperkalemic PP). In contrast, thyrotoxic periodic paralysis (TPP) is an acquired form of PP that presents with hypokalemia and hyperthyroidism.[1, 2] If symptoms of muscle weakness and hypokalemia resolve with potassium repletion, then hypokalemic PP or TPP should be considered, even if the patient does not have any family history of PP. This presentation will discuss different types of PP and includes a rare case of TPP.

Case

A 49-year-old male with previous episodes of muscle weakness presented with bilateral lower extremities weakness. The patient experienced soreness in lower extremities for 5 days, which changed to weakness and difficulty ambulating the night before admission. On the day of admission, the patient had difficulty getting out of bed and called an ambulance. He denied diarrhea, nausea, vomiting, bowel or urinary incontinence, history of muscular or neurological disorders, cancer, use of diuretics or statins, recent travel or trauma.

The patient was hospitalized 20 years ago for a similar episode. At the time, muscle weakness improved after the repletion of low potassium levels. He also had other milder episodes after that and relates those to electrolyte imbalance.

He expressed that his diet is irregular with minimal water intake and ample consumption of caffeine and carbonated beverages. He works a physically demanding job in a hot kitchen that makes him sweat profusely.

Physical examination showed normal muscle strength of upper extremities and 2/5 muscle strength of the lower extremities. The potassium level was 2.8 mmol/L, while magnesium was 2.5 mg/dL. Erythrocyte sedimentation rate, C-reactive protein, vitamin B12, folic acid, methylmalonic acid, treponema, adrenocorticotropic hormone, antinuclear antibody, urinalysis, urine toxicology and blood culture were all normal. Urine electrolytes showed sodium of 151 mmol/L, potassium of 95 mmol/L, and chlorine of 230 mmol/L. Thyroid stimulating hormone (TSH) was low at < 0.01 uIU/mL, normal free T4 at 1.17 ng/dL, and he had a mildly elevated T3 at 197 ng/dL. Thyroid function test from the previous hospitalization in 2000 showed a low TSH of < 0.03 uIU/mL, free T4 of 2.50 ng/dL, high total T3 of 379.8 ng/dL and positive thyroglobulin antibody. (He was never treated for the thyroid disease before.) EKG was normal and computed tomography of the brain, as well as magnetic resonance imaging of the cervical, thoracic and lumbar spine was negative

After admission, he received 20 mEq of intravenous potassium and 1 dose of magnesium. As soon as the potassium was finished, the patient's symptoms significantly improved to the point where he was able to ambulate independently to go to the bathroom. The patient was discharged home, started on propylthiouracil and instructed to follow up in outpatient.

In this case, it is suspected that the patient had TPP. First, the patient had muscle weakness with hypokalemia that improved with potassium supplementation. He had a similar episode when he was 30. He had a high intake of carbohydrates through carbonated beverages, as well as working at a physically demanding job, which caused significant perspiration. His hyperthyroid state was never treated over the past 20 years and at our admission was more consistent with T3 thyrotoxicosis.

Clinical Features

Hypokalemic PP

Hypokalemic PP usually begins in late childhood or teenage years with the frequency of attacks ranging from weeks to months. Each episode may last several hours to days. The precipitating factors for hypokalemic PP are the same as TPP. Hypokalemia is seen during the attack with normal potassium levels between the attacks.[3] If hypokalemia persists between attacks, then it may be due to the secondary causes of hypokalemia such as renal potassium loss. EKG findings may show changes that are associated with hypokalemia such as an increase in the amplitude of U waves, a decrease in the amplitude of the T wave, and depression of the ST segment.[4]

The long term consequence of hypokalemic PP is myopathy that may begin after the age of 50. The severity of the myopathy varies with ion channel mutation. Sodium channel abnormalities are associated with less severe myopathy but more severe myalgia and attacks beginning at a younger age.[5]

Hyperkalemic PP

Hyperkalemic PP starts early in life with symptoms that are less severe, more frequent, and somewhat shorter in duration than hypokalemic PP, although it can be hard to differentiate between hypokalemic and hyperkalemic PP just based on these clinical manifestations. It is usually a generalized flaccidness but can happen with focal muscle deficit such as extremity fatigue as well. Triggers are more or less the same except for fasting and potassium-rich nutrients. On physical examination, delayed muscle relaxation will be noticed after a contraction. The disease gets less severe with aging, but the muscle weakness can get progressively worse and affect bodily functions.

TPP

The majority of patients with TPP have the onset of attacks between 20-39 years of age. However, TPP can also present in younger patients.[6] The attack of TPP is commonly seen at nights or early mornings with a higher incidence reported during summertime. During the attack, the symptoms may last for several

hours to days. TPP episodes can be triggered by excessive physical activity, stress, and high carbohydrate intake, such as carbonated beverages. TPP also can be precipitated by cold exposure, infection, alcohol intake, corticosteroid use, bronchodilator use and menstrual cycles.[7]

The characteristic of TPP is hypokalemia with generalized muscle weakness; although, it affects proximal muscles more, with lower extremities more than the upper extremities.[8,9] Symptoms can progress to flaccid quadriplegia.[10] Myalgia can be seen in less than half of the patients. Reflexes can be normal or abnormal. In severe cases, patients may experience bulbar and respiratory weakness requiring ventilator support. Occasionally, the patient may be asymptomatic, have only symptoms of hyperthyroidism, or have subclinical hyperthyroidism. Urinary retention of sodium, potassium and phosphate can be seen together with oliguria and constipation.[11]

Andersen-Tawil syndrome

Andersen-Tawil syndrome is more likely if a patient has a triad of periodic paralysis, ventricular arrhythmia and dysmorphic features (short stature, clinodactyly, hypertelorism, and micrognathia). Prolonged QT interval is present in EKG. Potassium might be low, normal or even high.

Epidemiology

Hypokalemic PP is the most common presentation of PP with an incidence of 1 in 100,000 people. It is more common in males than in females. Hyperkalemic PP is twice as rare as hypokalemic PP but with the same number of men and women being diagnosed.[12]

Though hyperthyroidism is more common in females, Asian males have higher chances of being diagnosed with TPP.[10, 13] TPP is associated with any causes of hyperthyroidism with the most common being Graves' disease. T3-thyrotoxicosis-causing PP is exceedingly rare, and there are only 3 cases reported before the case presented above.[14-16]

Andersen-Tawil syndrome is 10 times rarer than hypokalemic PP.[1]

Genetics

Unlike hypokalemic PP, which is mostly hereditary, TPP can present without any family history. One study observed that 1/3 of the patients with hypokalemic PP had a positive family history versus only 1/10 of patients with TPP. [11] At times the disease is present and no mutation can be identified, as reported in some Asian countries.[11] These results indicate that hypokalemic PP can also be presented in a sporadic form and the mutation may be dependent on different ethnic backgrounds or associated with environmental factors.

Pathophysiology

Hypokalemic PP

In patients with hypokalemic PP, there is a defect of the alpha-1 subunit of the dihydropyridine-sensitive calcium channels and sodium-channel protein type 4 subunit (SCN4A) encoded sodium channels in skeletal muscle. Although the exact mechanism of how calcium channels play a role in potassium regulation in muscle cells is unknown, one of the observations suggests that the calcium channel may act as a voltage sensor for excitation-contraction coupling in skeletal muscle.[17] In contrast, sodium channels create a gating pore current that allows depolarization during the hypokalemic PP attack.[1, 17]

Hyperkalemic PP

In patients with hyperkalemic PP, a gene that produces SCN4A (a subunit of voltage-gated sodium channels) changes and sodium channels remain open and leak longer than usual. That results in desensitization, muscle weakness and paralysis, together with the release of potassium into serum and elevation of serum potassium levels. This is an autosomal dominant disorder.[18-20]

TPP

It has been shown that thyroid hormone (TH), both T3 and T4, increases sensitivity to beta-adrenergic stimulation that results in increased activity of Na-K ATPase in the skeletal muscle membrane.[21] Patients with TPP have higher Na-K ATPase activity and that results in an influx of potassium into the cells and diminished levels in the serum. It has been shown that thyroid hormone-responsive elements

(TREs) are located upstream of the genes that transcribe Na-K ATPase subunits.[22] TH can increase the number of subunits through gene transcription and protein translation. Finally, both adrenergic response and increased insulin release from high carbohydrate diets can increase Na-K ATPase activity, which results in an influx of potassium into the cell.[22]

Studies have suggested that TPP may be associated with potassium ion channels defect, such as a mutation in the gene encoding Kir2.6. This gene is regulated by TH. Finally, since TPP is more common in males, it has been suggested that testosterone plays a role in periodic paralysis by increasing the activity of Na-K ATPase, as shown in animal studies.[23-25] Despite all postulations of the pathogenesis of TPP, however, the exact mechanism is unknown.[25]

Andersen-Tawil syndrome

The mutation is mostly on the Kir2.1-encoding gene.[1]

Laboratory Manifestations

TPP presents with hypokalemia with a mean serum potassium level of 2.1 Meq/l and a hyperthyroid state with low TSH and high T4. High T3 with normal T4 is extremely rare, as in this case. Hypophosphatemia and hypomagnesemia are present.[26] Creatinine kinase (CK) may be present with rhabdomyolysis in severe cases, which explains the mild myalgia. CK may also be within the normal range.[2]

Other lab values such as arterial blood gas, urinary potassium-creatinine ratio, transtubular potassium gradient and phosphate level can indicate secondary causes of hypokalemia, such as renal tubular acidosis or diabetic ketoacidosis.[27] By performing such labs, one can correctly diagnose whether the symptoms are caused by hypokalemic PP, TPP or secondary causes of hypokalemia.

EKG may show changes that are associated with hypokalemia, such as ST depression, sinus tachycardia, U waves, abnormal PR intervals, higher QRS voltage, and first-degree atrioventricular (AV) block.[28]

Treatment

The treatment for both hypokalemic PP and TPP is the administration of potassium, which facilitates symptom recovery. Intravenous administration is more effective than oral supplementation. It is recommended that the administration of potassium in the first 24 hours does not exceed 90 mEq due to possible rebound hyperkalemia.[29]

EKG monitoring is recommended during the potassium repletion. In patients who do not respond to potassium treatment, intravenous propranolol has shown to resolve muscle weakness and hypokalemia of TPP since it is associated with the beta-2 adrenergic activity.[7, 30] For TPP, abnormal thyroid function should be addressed with appropriate medical management. For Graves' disease, radioactive iodine or surgery prevent relapses as compared to anti-thyroid medication treatment alone.[2]

Admission to the hospital is required if intravenous supplementation is needed or based on clinical judgment for severe cases with significant hypokalemia. At times, the diagnosis is not certain, and admission is warranted for diagnostic workup.

Prevention

All patients should avoid precipitants such as high carbohydrate intake, intense physical activity, excessive perspiration and stress. For prophylactic purposes, potassium supplementation may be beneficial in hypokalemic PP but not in TPP, presumably because of the continuous thyroid hormone effect on cells.[22]

Medication for hypokalemic PP prevention includes carbonic anhydrase inhibitors, acetazolamide or potassium-sparing diuretics such as spironolactone or triamterene that increase the potassium level.[8, 31]

To prevent the recurrence of TPP, patients might need long term beta-blocker treatment. Non-selective beta-blockers such as propranolol are preferred over selective beta-blockers because of the epinephrine-mediated beta-2 receptor activation that causes hypokalemia.

Differential Diagnosis

Differential diagnosis is very broad. Due

Table 1. Different types of Periodic paralysis.[1] Reproduced with permission from: Gutmann L, Conwit R. Hypokalemic periodic paralysis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on January 9, 2020.) Copyright © 2019 UpToDate, Inc. For more information visit www.uptodate.com.

	Hypokalemic periodic paralysis	Thyrotoxic periodic paralysis	Hyperkalemic periodic paralysis	Andersen-Tawil syndrome
Age at onset	First or second decade	>20 years	First decade	First or second decade
Attack frequency	Infrequent (a few times a year)	Infrequent	Frequent (up to several a day)	Monthly
Attack duration	Hours to days	Hours to days	Minutes to hours	Days
Precipitants	Exercise Carbohydrate load Stress	Exercise Carbohydrate load Stress	Exercise Fasting Stress K-rich food	Rest after exercise
Potassium level during attack	Low	Low	Normal or elevated	Low, normal, or elevated
Associated features	Later-onset myopathy	Symptoms of thyrotoxicosis Low TSH with high T4 or high T3	Myotonia on examination and/or EMG Later onset myopathy	Dysmorphic features Ventricular arrhythmias Long QT Interval
Etiology	Autosomal dominant inherited defect in calcum or sodium ion channel on muscle membrane	Thyrotoxicosis Possible inherited predisposition	Autosomal dominant inherited defect sodium ion channel on muscle membrane	Autosomal dominant inherited defect of inward rectifying potassium channel
Penetrance	Nonpenetrance common, especially in women		High	Nonpenetrance and incomplete penetrance common
Epidemiology	Clincal expression in men more frequent than women	Highest incidence in Asians and in men more than women	Sexes equally affected	Marked intrafamilial phenotypic variation
Preventive treatment	Carbonic anhydrase inhibitors K-sparing diuretics	Euthyroid state Propanolol	Carbonic anhydrase inhibitors Thiazide diuretics Inhaled beta-agonists as needed	Carbonic anydrase inhibitors

TSH: thyroid stimulating hormone; T4: thyroid hormone (thyroxine); T3: thyroid hormone (triiodothyronine); EMG: electromyography.

to muscle weakness, it is important to consider other etiologies, such as myelopathy, myasthenia gravis, Guillain-Barre syndrome or botulism. [32]

Symptoms of myelopathy include loss of motor and sensory function, bowel or urinary incontinence, paresthesia, weakness and numbness, as well as difficulty with coordination. Muscle weakness in myasthenia gravis is more prominent when the muscle is used repetitively and the symptom improves with rest. In Guillain-Barre syndrome, the patient experiences muscle weakness and paresthesia starts from lower extremities and progresses to the upper extremities. In foodborne botulism, a patient will have symptoms of diplopia, droopiness of the eyelids, facial muscle weakness, dysphagia, slurred speech and muscle weakness.

Though hypokalemia and muscle weakness suggest hypokalemic PP, it is never a certain diagnosis. TPP can be assessed with the measurement of thyroid function tests, while other causes of hypokalemia are abundant and will need to be ruled out. Potassium intake might be inadequate, or there might be increased gastrointestinal (nausea and vomiting) or urinary loss (diuretics, non-absorbable anions, loss of gastric acid, polyuria, low magnesium, renal tubular acidosis). Increased potassium entry into the cell, such as with insulin use, hypothermia, elevated beta-adrenergic activity, barium intoxication and antipsychotic drugs can happen as well and cause hypokalemia.[33]

Conflicts of Interest

The authors declare they have no conflicts of interest.

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