Hypokalemic Periodic Paralysis: A Review of Pathophysiology, Clinical Features, and Treatment

Paralisia Periódica Hipocaliemica: Uma Revisão da Fisiopatologia, das Características Clínicas e do Tratamento

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Abstract

Hypokalemic periodic paralysis is a rare genetic skeletal muscle channelopathy characterized by recurrent attacks of tetraparesia associated with hypokalemia. Mutations in skeletal muscle sodium and calcium channels are responsible for the pathophysiology of this condition and each mutation seem to have different implication in both phenotype and response to treatment. Patients with hypokalemic periodic paralysis present with recurrent muscle weakness and hypokalemia, frequently after exercise or carbohydrate rich meals, but are symptom free between attacks. Although potassium administration is the mainstay of acute treatment, carbonic anhydrase inhibitors play a significant role in prophylactic treatment. In this article, we aimed to review the pathophysiology, clinical features, and treatment options of hypokalemic periodic paralysis.

Resumo

A paralisia periódica hipocaliemica é uma canalopatia muscular esquelética genética rara caracterizada por ataques recorrentes de tetraparesia, associados a hipocaliemia. Mutações nos canais de sódio de cálcio do músculo-esquelético são responsáveis pela fisiopatologia desta entidade e cada mutação aparente ter diferentes implicações tanto no fenótipo como na resposta ao tratamento. Os doentes com paralisia periódica hipocaliemica com fraqueza muscular e hipocaliemia recorrentes, frequentemente após exercício ou refeições ricas em hidratos de carbono, mas são assintomáticos entre os ataques. Apesar da administração de potássio ser o pilar do tratamento agudo, os inibidores da anidrase carbónica desempenham um papel significativo no tratamento profilático. Neste artigo, tivemos como objetivo rever a fisiopatologia, as características clínicas e as opções de tratamento da paralisia periódica hipocaliemica.

Keywords: Hypokalemic Periodic Paralysis/diagnosis; Hypokalemic Periodic Paralysis/physiopathology; Hypokalemic Periodic Paralysis/therapy

Palavras-chave: Paralisia Periódica Hipocaliemia/diagnóstica; Paralisia Periódica Hipocaliemia/fisiopatologia; Paralisia Periódica Hipocaliemia/tratamento

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Introduction

Periodic paralysis are a group of skeletal muscle disorders defined by acute attacks of painless flaccid paralysis.[1,2] In hypokalemic periodic paralysis (HPP), acute attacks are associated with hypokalemia however interattack serum levels of potassium are usually within normal range.[1,2] It is commonly a genetic skeletal muscle channelopathy, but secondary etiologies such as thyrotoxicosis, renal tubular acidosis, Gitelman syndrome, barium poisoning, diuretics, and diarrhea have also been described[3].

In Caucasians, the familial autosomal dominant form of HPP seems to be most frequent, as opposed to the sporadic form.[3] In Asians, thyrotoxic periodic paralysis is the most frequent etiology of hypokalemic paralysis.[3] HPP is a rare disease. Most studies report a prevalence of 1/100 000 but one study conducted in England found a prevalence of 0.17/100 000.[4-6] HPP seems to be more frequent in men, mainly due to a lower clinical penetrance among women.[7]

Pathophysiology

Familial hypokalemic periodic paralysis appears to be more frequently related to mutations in two genes: the most frequent one involving the ***CACNA1S*** gene which codes for the α1-subunit of the skeletal muscle calcium channel ($Ca_v1.1$) and the other involving the ***SCN4A*** gene which codes the α-subunit of the voltage-gated sodium channel ($Na_v1.4$), with the former associated with HPP type-1 and the latter with HPP type-2.[3,8] Around 20 mutations affecting both genes have already been described.[9] In fact, differences in both clinical (later onset, myalgias, and worsening with acetazolamide in HPP type-2) and pathological (vacuoles in HPP type-1 and tubular aggregates in HPP type-2) phenotype might be explained by the two different mutation profiles.[8] Interestingly, patients with sodium channel mutations do not seem to progress to permanent muscle weakness.[10]

Some authors hypothesized that in HPP type-2 a cationic leak through the sodium channel ("gating pore current") leads to excessive depolarization.[8] Nevertheless, both mutations appear to compromise the excitation-contraction coupling through voltage sensor dysfunction and impaired channel gating.

Although calcium and sodium channel mutations are recognized as having an etiologic role in HPP, potassium channels, and particularly inwardly rectifying potassium channels (K_{ir}), play an important role in the pathogenesis of this condition, mainly through K_{ir} block by protons and down-regulation of its subunits by low extracellular K^+.[8] Indeed, ***in vitro*** studies suggest carbohydrate triggering of attacks might be due to reduction of K_{ir} and K_{ATP} currents by insulin.[11,12]

Clinical Features and Diagnosis

Familial HPP presents at a younger age than secondary HPP, typically during adolescence.[1,10] Males seem to have higher frequency of attacks than females.[7] Clinical presentation is often mild to severe muscle weakness that can last hours to days and usually happen in the morning or afternoon and resolve within 24 hours.[3,10] Muscle weakness is usually more pronounced proximally and hyporeflexia or areflexia is frequently present. No other accompanying symptom is usually present. Blood work reveals hypokalemia (usually about 2.4 mEq/L).[2] Triggers include high carbohydrate meals and rest after strenuous exercise, which also appear to be more frequent in the familial form than the sporadic ones.[1,13] Additionally, patients with familial HPP recover faster and with less amounts of potassium than patients with secondary hypokalemic paralyses.[3] Carbohydrate rich meal are thought to contribute to inducing attacks due to an insulin dependent reduction in serum potassium levels: carbohydrates stimulate insulin release by pancreatic cells which in turn leads to insertion of GLUT4 (glucose transporter type 4) transporters at the cell membrane and glucose uptake.[14] Consequently, adenosine triphosphatase sodium/potassium pump activity is stimulated leading to uptake of potassium and lowering of its serum levels.[14]

Differential diagnosis of an episode of periodic paralysis includes metabolic myopathies, Guillain-Barré syndrome, acute myelopathy and conditions causing secondary periodic paralysis, such as hyperthyroidism and renal tubular acidosis. As such, laboratory evaluation should include arterial blood gas, creatinine, electrolytes, and TSH measurement.

HPP has a considerable impact in the quality-of-life perception, essentially due to the symptom of muscle weakness, but also on account of fatigue.[15] Interattack period is often asymptomatic but progression to a severe disabling proximal myopathy is frequent.[16]

In all forms of periodic paralysis, an abnormal reduction (≥ 40%) in compound muscle action potential (CMAP) can be found on electrophysiological exercise testing during asymptomatic periods and exercise testing has largely replaced provocative maneuvers.[5,17] In HPP, patients with recent attacks (less than 1 year ago) exhibit marked decrements in CMAP compared with patients who had an attack at least 1 year before and with controls, and so the exercise test appears to have a specificity of 97% for the diagnosis of HPP and a sensitivity of 100% when considering patients with recent attacks.[17] Nevertheless, the mainstay for diagnosis of HPP remains the exclusion of secondary causes and genetic testing. Genetic test reveals a pathogenic mutation in 60%-70% of patients.[2,5]

For patients presenting with muscle weakness associated with hypokalemia, in whom secondary causes have been excluded,

we suggest genetic testing for known mutations of *SCN4A* or *CACNA1S* as the first-line diagnostic test. For patients with a negative genetic test in whom suspicion for a HPP remains high, an electrophysiological exercise testing showing a ≥ 40% reduction CMAP is strongly suggestive of HPP, and appropriate prophylactic treatment should be initiated. Genetic sequencing with the aim of finding a novel mutation could be useful in this setting.

Treatment

During a HPP attack, oral potassium (60 to 120 mEq) is the mainstay of treatment and results in complete recovery in few hours.[10] Slow-release formulations should be avoided; if patient is unable to swallow pills, or if fast release formulations are unavailable, the intravenous solution can be administered orally.[5] Due to the risk of rebound hyperkalemia, intravenous potassium should be reserved for patients presenting with arrhythmia or airway compromise.[5,10] In these cases, a 40 mEq/L solution of potassium chloride in 5% mannitol should be infused at no more than 20 mEq/h; small 5 mEq bolus can be used instead.[5] It is recommended to avoid dextrose or saline solution due to the risk of worsening muscle weakness.[5,18]

The carbonic anhydrase (CA) inhibitors acetazolamide and dichlorphenamide are currently the most effective medications for prevention of attacks in HPP, probably due to their effect in opening the muscular calcium-activated potassium channels (BK), and so, in patients with frequent crisis, maintenance therapy with a carbonic anhydrase inhibitor is the recommended treatment.[8] Acetazolamide (125 to 1000 mg daily) should be used as the first line agent and dichlorphenamide (50 to 200 mg daily) reserved for those who do not respond to acetazolamide.[5,10] The main reason for considering dichlorphenamide as a second-line drug is that, despite being effective in preventing episodic weakness and improving quality of life in HPP, serious side effects are more frequent and include paresthesia, cognitive disorder, and dysgeusia.[19] Unfortunately, it seems that most patients treated with acetazolamide do not improve significantly and dichlorphenamide needs to be employed.[20] Nevertheless, in long-term assessment of the use of dichlorphenamide, it seems the side effects are easily managed.[21] For patients who cannot tolerate carbonic anhydrase inhibitors, aldosterone antagonists may be used (e.g., spironolactone 25 to 00 mg daily).[5,10]

Genetic testing might be useful in determining the ideal treatment for each patient: patients with calcium channel mutations benefit more from the use of acetazolamide than those with a sodium channel mutation.[20,22] Also, patients with SCN4A mutations are more likely to suffer side effects from acetazolamide.[20]

Prophylactic treatment should always include a low carbohydrate diet and eviction of vigorous exercise and may also include oral potassium supplementation since all recommended diuretics cause hypokalemia and oral supplements are not frequently associated with overdosing.[10] No specific therapeutic option currently exists for preventing the progressive myopathy and thus its treatment is similar to the prophylactic treatment described.[23] However, dichlorphenamide seems to be superior to acetazolamide in the treatment of persistent interattack weakness in HPP.[23]

Conclusion

Hypokalemic periodic paralysis is a rare disease that requires prompt recognition and initiation of proper treatment and, accordingly, we recommend potassium measuring in patients presenting with tetraparesia prior to the administration of any fluid therapy. Exclusion of other causes of weakness and secondary etiologies with potential curative treatments is advised. Treatment for acute attacks is based on oral potassium replacement while carefully monitoring for rebound hyperkalemia. Upon discharge, patients should have a referral to a specialist for confirmation of the diagnosis through genetic testing, evaluation of the need for prophylactic treatment with carbonic anhydrase inhibitors, and education on potential trigger avoidance and self-management of the condition.

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