CASE REPORT

Familial Hypokalemic Periodic Paralysis

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Port J Pediatr 2022;53:528-31
DOI: https://doi.org/10.25754/pjp.2022.24587

Abstract

Periodic paralysis is a rare neuromuscular disease related to a defect in muscle ion channels and is classified as hypokalemic when occurring in episodes associated with low levels of potassium in the blood. A 12-year-old female adolescent was referred to the emergency department due to the sudden onset of tetraparesis. There were no signs of respiratory distress or difficulty breathing. Neurological examination showed grade II and grade III muscle strength in the lower and upper limbs, respectively. Osteotendinous reflexes were absent, while facial mimic was still present. The mother reported a family history of periodic hypokalemic paralysis affecting several family members. The patient was discharged 20 hours after therapy onset and medicated at home with daily acetazolamide and potassium chloride upon the onset of symptoms. A genetic study was performed in an index case. Periodic familial paralysis is a rare condition, the most common form of which is known as hypokalemia. This case report aimed to emphasize the importance of the patient clinical history and complete physical examination on the diagnosis of periodic familial paralysis.

Keywords: Adolescent; Hypokalemic Periodic Paralysis/diagnosis; Paralysis/geneticsParalysis/therapy

Keypoints

What is known:
- Hypokalemic periodic paralysis causes episodes of extreme muscle weakness typically early in childhood or adolescence.
- Myopathy may develop in affected individuals, resulting in progressive muscle weakness in the proximal muscles of the lower limbs.

What is added:
- Due to their low prevalence in the general population, the experience with treatment has been obtained from the anecdotal reports.
- Better understanding of the genetics of these disorders is important for genetic counselling, improving treatment options, and establishing prognosis.

Introduction

A periodic paralysis is a rare group of neuromuscular diseases related to a defect in the muscle ion channels characterized by sporadic episodes of painless muscle weakness that either occur spontaneously or through the involvement of dietary factors, physical activity, and insulin.[1-4] It is classified as hypokalemic and hyperkalemic when episodes occur in association with low and high blood potassium levels, respectively.[2-4]

Although hypokalemic periodic paralysis is the most common paralysis, it remains a rare entity with an estimated prevalence of 1 in 100 000. Periodic paralysis may either be familial with an autosomal dominant transmission or acquired in patients with thyrotoxicosis. Clinical penetrance is often incomplete, especially in women.[1,2]

Mutation in the gene encoding the dihydropyridine-sensitive calcium channel subunit alpha-1 (*CACNA1S*) in skeletal muscle is the most common genetic abnormality in hypokalemic periodic paralysis which is found in approximately 70% of patients.[3,4] A mutation in the skeletal muscle sodium channel, *SCN4A*, may also be the cause of this disease.[5,6] Families with the latter mutation show more complete clinical penetrance that affect both men and women equally.[5]

As with all periodic paralysis, attacks occur suddenly with general weakness while consciousness is preserved.[2,3]

In hypokalemic periodic paralysis, the episodes begin in late childhood or early adolescence and vary in frequency and duration. Although the episodes usually last several hours, the duration can vary from minutes to days. The episodes can be triggered by rest after

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Received: 12/05/2021 | Accepted: 09/11/2021 | Published online: 01/04/2022 | Published: 01/04/2022

vigorous exercise, stress, or a high carbohydrate meal and are often associated with the increased release of adrenaline or insulin, which causes potassium movement into cells and low blood potassium levels.[1]

Neurological examination during a critical episode of the condition demonstrated weakness, which usually affects lower limbs more than upper limbs. Hyporeflexia or areflexia is typical. Neurological examination between episodes usually shows normal findings.[2-4,6]

The average plasma potassium concentration is 2.4 mEq/L during an episode.[7] Cardiac arrhythmias, such as tachycardia, atrial fibrillation, paroxysmal supraventricular tachycardia, or ventricular fibrillation are rare.[8] During episodes, an electrocardiogram may show findings compatible with hypokalemia, including ST-segment depression, decreased T-wave amplitude, and increased U-wave amplitude.[2,3]

No further diagnostic tests are conducted in case of a family history of hypokalemic periodic paralysis. Otherwise, the diagnosis is suggested by hypokalemia during a typical muscle weakness crisis. However, further testing is required to rule out alternative diagnoses, such as thyrotoxic periodic paralysis and Andersen-Tawil syndrome. A diagnosis can be difficult to make when symptoms are deprecated or after the crisis. In such conditions, other diagnostic options can be used, such as provocative tests, electromyography, and genetic testing, due to the high rate of clinical suspicion.

During an acute phase, the treatment for outpatients involves the administration of oral potassium (0.2-0.4 mEq/Kg/day). In the presence of electrocardiographic alterations, patients need hospitalization and an intravenous infusion of 40 mEq/L in a 5% mannitol solution at a maximum rate of 20 mEq/h (not exceeding 200 mEq/day). The potassium level needs to be checked after treatment.[2-4] Cardiac monitoring is recommended during and after treatment. Recovery may take a few minutes.[6-8] The potassium should not be administered in glucose-containing solutions since patients may suffer from an over-insulin response to carbohydrate loads.[2-4]

As a preventive measure, the patient should be advised to avoid triggers, such as stress, fasting exercise, as well as high-carbohydrate and high-salt meals.[2]

Dichlorphenamide is accepted for hypokalemic periodic paralysis and has been associated with reductions in the attack frequency, severity, and duration of chronic treatment.[2]

Potassium-sparing diuretics are a potential option for the chronic treatment of hypokalemic periodic paralysis.

Case Report

A 12-year-old female adolescent presented to the emergency department due to the sudden onset of tetraparesis. No respiratory distress or other associated signs or symptoms were present, and we could not find any precipitant factor.

There was a family history of recurrent hypokalemic paralysis in the mother, two maternal cousins, and maternal grandfather. The mother was followed in the neurology clinic and medicated with oral potassium and acetazolamide.

On general examination, the patient was alert and

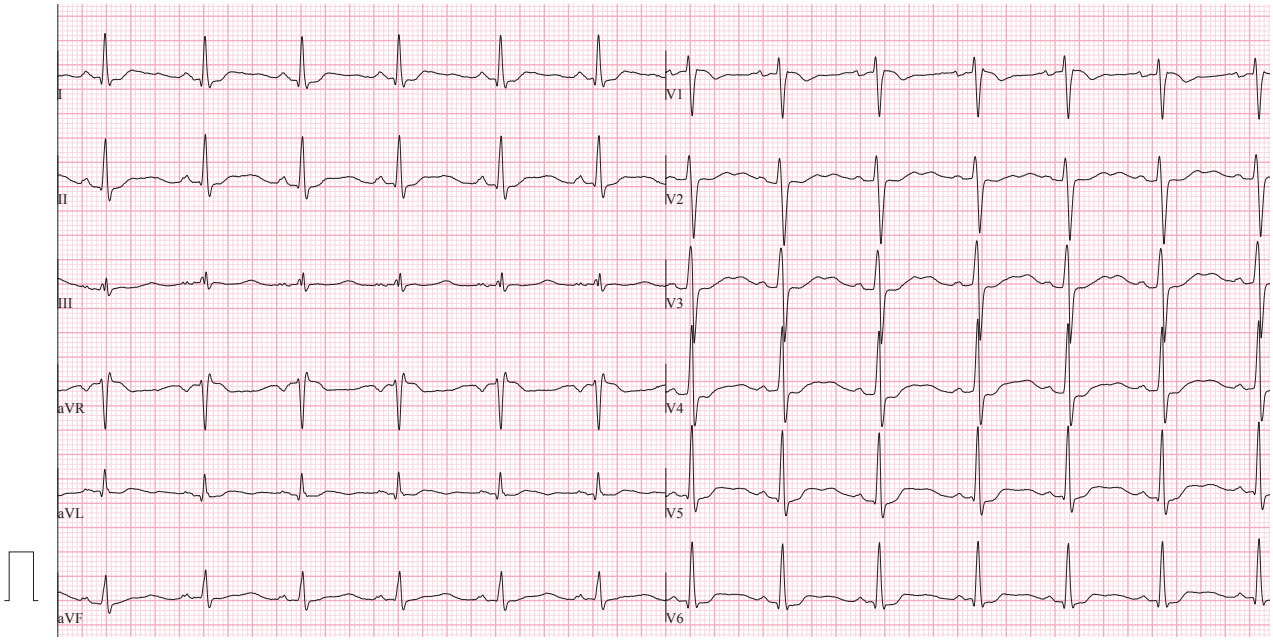

Figure 1. Electrocardiogram on admisson

oriented, without signs of respiratory distress. The blood pressure was 109/56 mmHg with a heart rate of 86 bpm. Cardiac and pulmonary auscultation and abdomen examination were normal. During the neurological evaluation, the patient presented grade II and grade III muscle strength in the lower and upper limbs, respectively. Osteotendinous reflexes were absent.

Venous blood gas analysis showed pH 7.39, bicarbonate (HCO_3^-) 22.4 mEq/L, potassium 1.7 mEq/L, sodium 142 mEq/L, calcium 1.21 mEq/L, chloride 110 mEq/L, glucose 123 mg/dL, and lactates 1.7 mmol/L. The analytical evaluation confirmed hypokalemia of 2.0 mEq/L with normal thyroid function.

Electrocardiogram (Fig. 1) showed a sinus rhythm of 76 bpm with a slightly increased PQ interval, mild ST depression, and prominent U waves. The corrected QT interval was 613 msec.

Potassium reached 2.3 mEq/L in the first three hours and raised to the normal range at 12 hours of treatment. A normal electrocardiogram was noted, followed by the recovery of muscle strength.

Fluid therapy was suspended with potassium normalization (5 mEq/L) and muscle strength recovery.

The patient was discharged 20 hours after the beginning of therapy and was instructed to take acetazolamide (250 mg twice a day) for prevention and potassium chloride upon the occurrence of a severe episode at home.

After this inaugural episode, the patient was followed in the neuropediatric clinic. Since then, she had experienced two new episodes requiring therapy, without the need for resorting to the emergency department. She maintained physical activity and her dietary care involved carbohydrate and salt restriction.

Based on the genetic examination, the pathogenic variant c3716G> Ap (Arg1239His) was heterozygote in the *CACNA1S* gene, confirming the genetic etiology of hypokalemic periodic paralysis.

Discussion

Familial periodic paralysis is a rare condition, the most frequent form of which is known as hypokalemia.[2-4] This condition usually begins in childhood or adolescence, with spontaneous episodes of focal or generalized paralysis that last from minutes to hours and is associated with hypokalemia (< 2.5 mEq/L), while consciousness is preserved.[2,4-6] Severe cases present in early childhood, usually before 16 years old. Weakness may range from a slight transient weakness of an isolated group of muscles to severe generalized weakness.[2,8,9] The severe episodes occur more frequently at night and early in the morning and are often precipitated or aggravated by low potassium consumption or excessive urinary or gastrointestinal losses, high carbohydrate or sodium diet, use of diuretics, corticosteroids, insulin or beta-agonists, infections, emotional stress, vigorous physical exercise, and cold exposure.[2,3,7,8] However, no precipitant factor was observed in our 12 years old patient.

Myopathy may develop in the affected individuals, resulting in progressive muscle weakness in the proximal muscles of the lower limbs. Myopathy can occur without paralytic symptoms.[3]

The diagnosis of periodic paralysis can be confirmed by genetic tests, which is recommended as the first-line diagnostic approach in patients with intermediate to high clinical suspicion. All periodic paralysis has an autosomal dominant transmission. In the absence of an identified genetic mutation in approximately 30% of patients, paralysis subtypes can be distinguished based on clinical presentation and the serum potassium levels during a crisis or episodes.[3,4] However, the differential diagnosis must be performed with normokalemic potassium-sensitive periodic paralysis, hyperkalemic periodic paralysis, thyrotoxic periodic paralysis, and Andersen-Tawil syndrome.

In the hypokalemic form, treatment is based on the acute phase and restoring potassium levels by replacing approximately 40 mEq potassium chloride. Treatment of periodic paralysis episodes includes administration of potassium chloride and prevention of cardiac arrhythmias and respiratory failure. In cases of severe hypokalemia (less than 2.5 mEq/L) or if there is an oral intolerance, the intravenous route should be preferred; however, it should not exceed 10 mEq/hour due to the risk of rebound hyperkalemia. This was the initial option in the case presented, with a slow correction rate. Glucose serum administration was avoided due to the risk of the aggravation of hypokalemia secondary to hyperinsulinism.

The focus in the post-crisis phase should be on the importance of lifestyle changes, avoidance of the possible triggers and inhibitors of carbonic anhydrase, along with the use of acetazolamide.[1,2,4]

The study of therapeutic approaches for rare conditions of periodic paralysis should be conducted during and after attacks and in long-term follow-ups.[8,9]

Approximately 70% of cases result from a mutation in the calcium channel gene *CACNA1S* in type 1 hypokalemic paralysis.[3]

This case report aimed to emphasize the need for a good clinical history and a complete objective examination as proper diagnosis and treatment options.

Author Contribuitions

IR participated in the study conception or design. IR, FS and PS participated in acquisition of data. IR, FS and PS participated in the analysis or interpretation of data. IR participated in the drafting of the manuscript. FS and PS participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

Funding Sources

There were no external funding sources for the realization of this paper.

Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki 2013).

Provenance and peer review

Not commissioned; externally peer reviewed

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Paralisia Periódica Hipocalémica Familiar

Resumo:

A paralisia periódica é uma doença neuromuscular rara, relacionada com um defeito nos canais iónicos musculares. É classificada como hipocalémica quando ocorrem episódios associados a níveis baixos de potássio no sangue. Uma adolescente de 12 anos recorreu ao serviço de urgência por aparecimento súbito de tetraparesia. Não tinha dificuldade respiratória nem sinais de doença respiratória. O exame neurológico revelou força muscular grau II nos membros inferiores e grau III nos membros superiores. Os reflexos osteotendinosos estavam ausentes. A mímica facial estava presente. A mãe referiu história familiar de paralisia hipocalémica periódica, afetando diversos membros. A doente teve alta 20 horas depois do início do tratamento, com indicação de medicação no domicílio com acetazolamida diária e cloreto de potássio em caso de sintomas. O estudo genético foi realizado no caso índice. A paralisia familiar periódica é uma doença rara, sendo mais frequente a forma hipocalémica. O relato deste caso pretende salientar a importância da história clínica e de um exame físico completo no diagnóstico.

Palavras-Chave: Adolescente; Paralisia Periódica Hipopotassémica/diagnóstico; Paralisia Periódica Hipopotassémica/genética; Paralisia Periódica Hipopotassémica/tratamento