Cardiac arrhythmias in primary hypokalemic periodic paralysis: Case report and literature review

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Introduction

Hypokalemic periodic paralysis (HPP) is a rare neuromuscular disorder characterized by episodes of muscle weakness and paralysis accompanied by hypokalemia. Several studies have reported the presence of cardiac arrhythmias, the majority being secondary to hypokalemia-induced changes. However, other studies have described cardiac arrhythmias that cannot be explained by hypokalemia or the diagnosis of HPP. Herein, we describe the case of a pediatric male patient with HPP and recurrent episodes of monomorphic ventricular tachycardia (VT), followed by a systematic literature review on primary HPP and cardiac arrhythmias.

Case report

The patient is a 16-year-old male subject with an unremarkable past medical history, and family history negative for neurologic or cardiac disease. He presented to the emergency department after 48 hours of progressive muscle weakness and urinary retention, occurring after a high-carbohydrate meal. Physical examination was unremarkable. Serum potassium level was 2.7 mmol/L, and electrocardiogram (ECG) showed prominent U waves and prolonged QTc (574 ms). Thyroid function showed normal free T4 (1.1 ng/dL) with slightly elevated TSH (5.4 mIU/L). After oral and intravenous potassium repletion, weakness and urinary retention resolved, along with ECG normalization (QTc 410 ms) (Figure 1). HPP was suspected, and was confirmed with electromyogram documenting 45% decrease in compound muscle action potential amplitude during late-phase post-exercise; HPP genetic panel was negative. He was started on chronic potassium supplementation.

KEY TEACHING POINTS

- Hypokalemic periodic paralysis is a rare neuromuscular channelopathy. Several cases have presented different cardiac electrophysiological manifestations independently of serum potassium levels.
- Different degrees of ventricular arrhythmias have occurred, ranging from isolated ectopy to monomorphic and polymorphic ventricular tachycardia. However, atrial arrhythmias can also occur.
- We highlight the need for a comprehensive cardiac evaluation in patients with primary hypokalemic periodic paralysis.

Prior to his initial evaluation he had experienced 3 previous syncopal episodes; the first happened 3 years before while carrying heavy weights in his house and was preceded by dizziness. This episode was not witnessed. He had 2 other syncopal episodes within 6 months that were not exercise-related. Owing to these, he had a normal echocardiogram and an exercise stress test that showed several premature ventricular contractions, ventricular couplets, and 1 3-beat run of wide QRS tachycardia at approximately 300 beats per minute, during peak exercise and active recovery (Figure 2A). Because of this, he underwent cardiac magnetic resonance imaging, which showed normal cardiac structure and function, and electrophysiology study (EPS), showing no accessory pathways, no inducible ventricular or supraventricular arrhythmias, negative ventricular stimulation test, and no ectopy with high-dose isoproterenol infusion. A loop recorder was implanted at that time.

Arrhythmia-related genetic panel was sent, revealing heterozygous mutations at the Filamin C (*FLNC*) (replacement of arginine with glutamine at codon 1657 (c.4970G>A)) and Ryanodine receptor type-2 (*RYR2*) (replacement of valine with isoleucine at codon 1241 (p.3721G>A)) genes.

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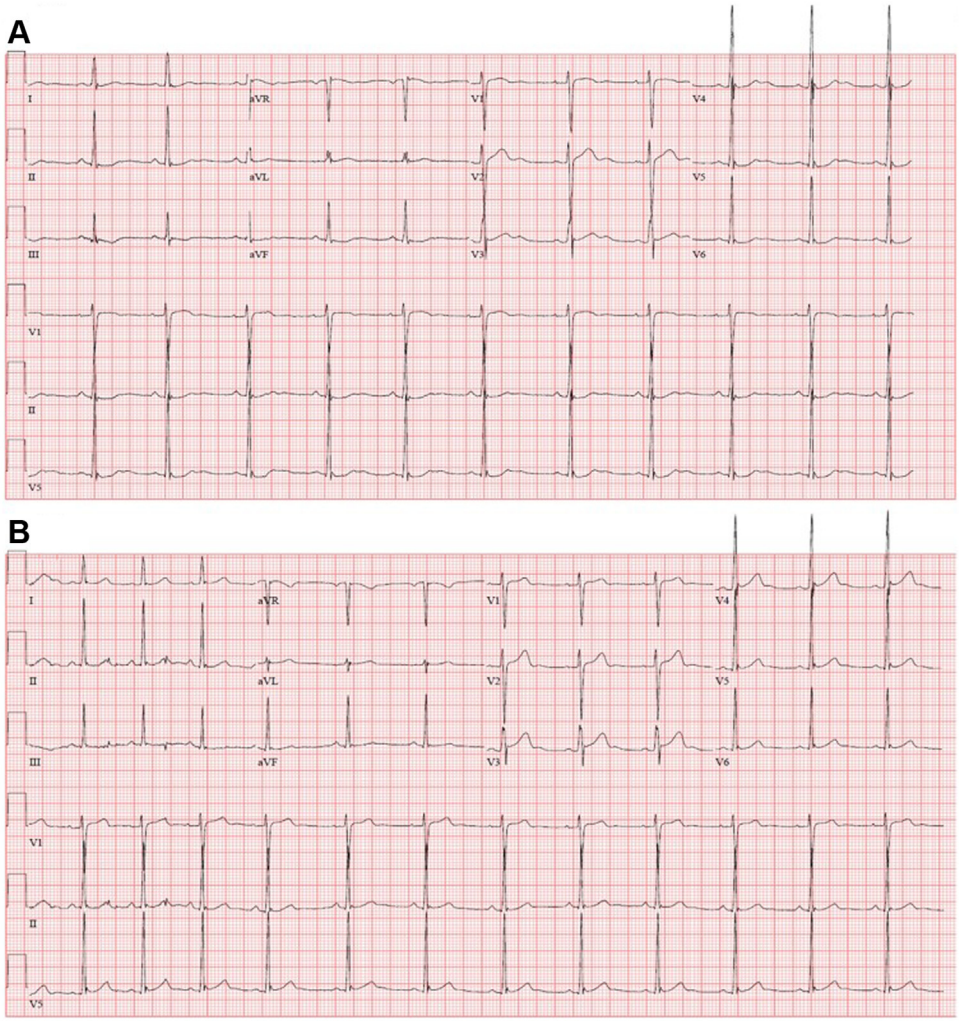

Figure 1 **A:** Electrocardiogram (ECG) obtained during hypokalemia showing normal sinus rhythm and QRS axis, ST-segment depression predominantly in inferolateral leads, U waves, and prolonged QTc interval (574 ms). **B:** Normal ECG during normokalemia (QTc 410 ms).

These had not been previously described in either *FLNC*- or *RYR2*-related diseases, and so were considered variants of uncertain significance.

Over the following 3 months, the patient did not present syncopal episodes, but the implantable device recorded 2 asymptomatic episodes of nonsustained slow wide QRS tachycardia (Figure 2B). Given the presence of ventricular ectopy during exercise stress test and absence of any accessory pathways or inducible supraventricular tachycardia (SVT) during EPS, these tracings were considered as monomorphic VT. These episodes were separated by 2 weeks and occurred at home; thus no K+ levels were available at those exact moments. However, serum K+ levels were 3.9 and 4 mmol/L 10 days before and 15 days after the first and last episode, respectively, with no changes in treatment or neurological symptoms in the interim. All these episodes occurred at rest and he had no ectopy with exercise. After 10 months of follow-up, he continued to manifest intermittent mild weakness but had no further syncopal episodes.

Literature review

Methods

We conducted a search through November 2021 in PubMed for studies on cardiac arrhythmias and/or ECG abnormalities in patients with primary or familial HPP. Studies were included if they described ECG abnormalities or arrhythmias occurring in patients with genotype- and/or phenotype-positive HPP (episodes of focal or generalized skeletal muscle paralysis associated with hypokalemia [serum $K^+ \leq 3.5$ mmol/L]). We excluded those studies reporting classic hypokalemia-induced ECG abnormalities, complications of these, arrhythmias occurring in secondary HPP, and arrhythmias occurring in patients with confirmed Andersen-Tawil syndrome (ATS).

Results

Initial search yielded 687 studies, of which 16 studies reporting 17 cases met inclusion criteria. Including our case, 18 cases were described (Supplemental Table 1).

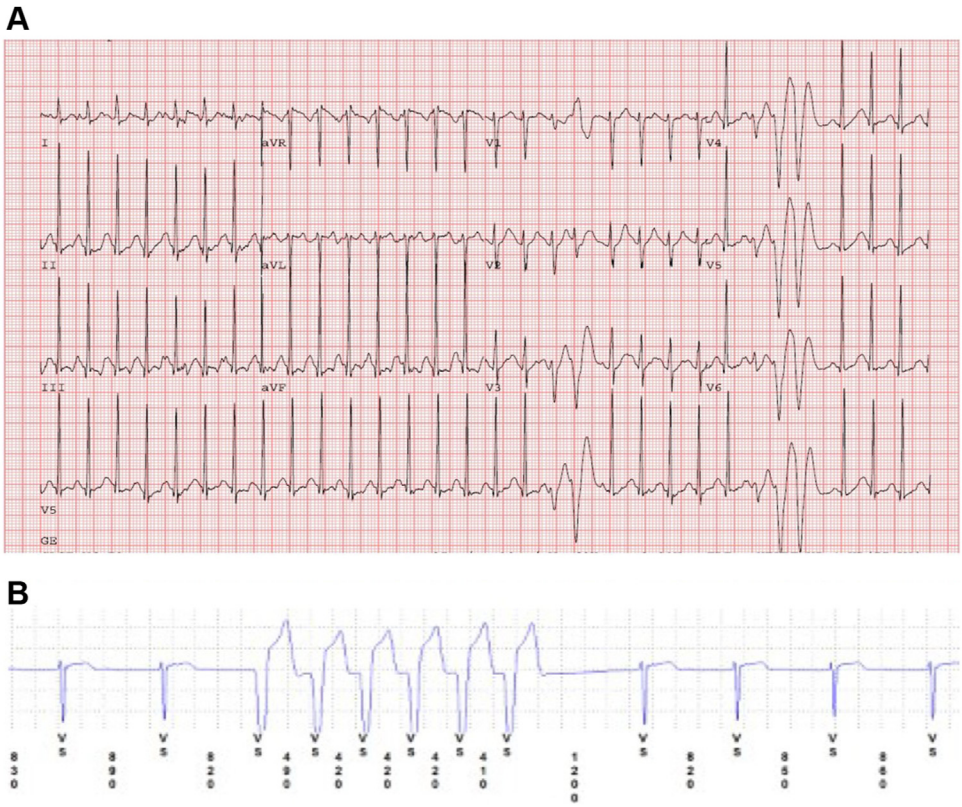

Figure 2 **A:** Electrocardiogram (ECG) obtained at peak exercise (heart rate = 184 beats/min) showing ventricular couplet and 3-beat run of ventricular tachycardia (VT) at 300 beats/min (*arrow*). **B:** Implantable loop recorder transmission showing 6-beat run of monomorphic VT at 140–145 beats/min, over normal sinus rhythm at approximately 70 beats/min.

Demographics

A total of 50% were male; median age at HPP presentation was 14 years (range 5–38 years), while median age at diagnosis of the ECG abnormality or onset of symptoms secondary to arrhythmia was 15 years (range 2–48 years). The most common symptom was syncope in 6 cases (33.3%), followed by palpitations in 4 (22.2%). There was 1 reported arrhythmia-related death (5.6%). Presenting symptoms were clinical manifestations of HPP in 8 cases (44.4%), while symptoms secondary to arrhythmias or diagnosis of ECG abnormality occurred before paralytic events in 4 (22.2%). Initial presentations of arrhythmia and paralytic crisis were simultaneous in 3 cases (16.7%).

It is important to mention that, in the case of our patient, the association of VT and syncope was not documented. Nevertheless, as the only cardiac concern prompting comprehensive cardiac evaluation was the history of syncopal episodes, these were included as this patient's symptoms.

Genetics

Genetic testing for HPP was positive in 2 cases (11.1%); a classic mutation in the *CACNA1S* gene was associated with ventricular ectopy and a strong family history of both arrhythmia and HPP, while *SCN4A* mutation was associated with SVT. Family history was positive for significant premature cardiac disease and/or HPP in 4 cases (22.2%), and for both HPP and arrhythmia in 2 (11.1%). There was history of chronic arrhythmia without HPP and early fatal heart failure in 1 case each.

Characterization of arrhythmia

There were different degrees of ventricular arrhythmias in 12 cases (66.7%), ranging from isolated premature ventricular contractions to monomorphic and polymorphic VT, including bidirectional VT (BiVT). There were 4 episodes (22.2%) of sustained SVT, 1 of them with underlying Wolff-Parkinson-White, and 3 cases (16.7%) with premature atrial complexes.

Reports were further analyzed to determine if arrhythmia or ECG abnormalities occurred in the context of a paralytic crisis and/or hypokalemia. Arrhythmias occurred independently of paralytic crises in 9 patients (50%), were diagnosed during a paralytic episode in 3 cases (16.7%), and occurred both associated with and independent of paralytic crises in 2 cases (11.1%). Relationship between the arrhythmia and paralytic crises was not reported in 4 cases. In relation with serum potassium levels, arrhythmia or ECG abnormalities were associated with hypokalemia and with normal potassium levels in 7 cases (38.9%) each. Potassium levels during the arrhythmia were unavailable or not reported in 4 cases. Interestingly, arrhythmias occurred in the absence of both hypokalemia and paralytic crisis in 5 cases (27.8%).

Assessment of ventricular function

Echocardiographic and/or invasive hemodynamic data were available in 9 cases, showing normal cardiac structure and function in 7 cases (77.8%). There was 1 case with mild right ventricle enlargement in the context of significant atrial and ventricular ectopy, and 1 reduced left ventricle systolic function in a patient with prior myocardial ischemic disease.

Electrophysiological properties

EPS was performed in 6 cases (38.9%); 1 was normal, in 1 there was an accessory pathway, 2 showed dual atrioventricular node physiology, and 2 cases showed inducible VT, both of which had been referred for BiVT.

Discussion

HPP is a genetic neuromuscular disorder characterized by episodes of focal or generalized skeletal muscle paralysis associated with hypokalemia.[1] Attacks typically present during the second decade of life, spontaneously or, most commonly, triggered by carbohydrate-rich meals, alcohol, or rest after strenuous exercise.[1,2] Diagnosis is based on genetic testing showing heterozygous pathogenic mutations in the *CACNA1S* or *SCN4A* genes, present in 70%–80% and in 10% of cases, respectively.[1,2] In cases with negative genetic testing, HPP is diagnosed based on clinical presentation, serum potassium levels during paralytic attacks, and reduction in compound muscle action potential amplitude during or after exercise.[1]

HPP is caused by a skeletal muscle channelopathy. Normally, acetylcholine is released and binds to specific receptors at the neuromuscular junction.[2] Once a threshold is reached, voltage-gated sodium channels, predominantly Nav1.4, are activated.[2] Propagation of action potentials induces a conformational change of the dihydropyridine receptor (DHPR), leading to opening of the type 1 ryanodine receptor (RyR1) anchored in the sarcoplasmic membrane,[2] resulting in increased intracellular calcium, which triggers muscle contraction.[2] *CACNA1S*, located in the chromosome 1q32.1, encodes the Cav1.1 protein, pore-forming α1-subunit of the L-type calcium channel DHPR, while *SCN4A* encodes the pore-forming α-subunit of the skeletal muscle voltage-gated sodium channel Nav1.4.[2] Mutations in these genes alter the conduction for monovalent cations, leading to an alternative conduction pathway known as "current leak," which mainly manifests at resting membrane potentials.[2] Although this would be expected to cause hyperpolarization of the membrane, in the presence of hypokalemia there are decreased outward potassium currents through inward rectifier channels, with a net potassium inward current, leading to paradoxical depolarization and subsequent paralysis.[2]

HPP is rare, with an estimated incidence of 1:100,000.[1] We have reviewed several cases in which HPP occurred with different degrees and types of VT. In this manner, when considering subjects ≤16 years of age, spontaneous VT was observed at a frequency of 1.1 episodes/100,000 children per year,[3] but short runs of VT can occur in 3% of healthy teenagers.[4] It is thus possible that these cases of ventricular ectopy could have been unrelated to HPP. Nevertheless, we cannot dismiss the possibility that ECG abnormalities or arrhythmias and HPP could in fact be related.

Hypokalemia represents a major arrhythmogenic factor, as it can lead to early and late afterdepolarizations, reentrant circuits, and altered activation-repolarization coupling.[5] This could explain, at least in part, the genesis of arrhythmic events in the presence of hypokalemia. However, as exposed before, arrhythmias occurred in normokalemia in at least 7 cases.

Co-expression of altered ion channels in both the skeletal and cardiac muscle could represent a possible mechanism of these arrhythmias in HPP patients. In the case of the *FLNC* gene, mutations are known to cause arrhythmogenic cardiomyopathy and myofibrillar myopathy, which is associated with cardiomyopathy and peripheral neuropathy.[6] Regarding *SCN4A* mutations, although Nav1.4 represents about 1% of the sodium channels in the heart, *SCN4A* mutations have been identified in families with overlapping Brugada syndrome and nondystrophic myotonia.[7] Nevertheless, this concept would be insufficient to explain these findings, as *SCN4A*-related muscle channelopathies are caused by a Nav1.4 gain-of-function mutation, as opposed to the loss of-function mutation of NaV1.5 observed in *SCN5A*-related Brugada syndrome.[7] Furthermore, this model would not apply in the case of arrhythmias in patients with *CACNA1S*-related HPP, as *CACNA1S* expression has been shown to be specific to the skeletal muscle.[8]

Regarding the evaluation and risk stratification of cardiac arrhythmias in HPP patients with normal potassium levels, the authors suggest that, until further research confirms or denies any causal association, these should not differ from those occurring in non-HPP patients without known heart disease. Therefore, in the case of suspected/confirmed ventricular arrhythmias (VAs), these should include baseline ECG, cardiac imaging, ambulatory Holter (eventually followed by implantable loop recorder), and cardiac genetic testing.[9,10] Also, although both were performed in our patient, exercise stress testing and EPS should be individualized and should be considered for a prior history of adrenergic-related symptoms, evaluation of polymorphic VT, assessment of inducibility of sustained VAs, determination of medical/ablative therapy, or assessment of unexplained syncope.

Likewise, the authors consider that these patients could be managed as non-HPP patients with arrhythmias and a structurally normal heart. Thus, asymptomatic HPP patients with isolated ventricular ectopy should not be started on antiarrhythmics or undergo implantable cardioverter-defibrillator placement.[9,10] Furthermore, asymptomatic patients with short runs of slow monomorphic VT that suppress or do not worsen during exercise could participate in competitive sports.[9] On the contrary, EPS with ablation and/or antiarrhythmics might be needed in the case of symptomatic arrhythmia, secondary cardiomyopathy, or other specific

VAs.[9] In this manner, a special consideration should be given to the effect of antiarrhythmics on HPP symptoms. Besides the theoretical effect of different antiarrhythmics on potassium serum levels, beta blockers have been reported to increase the episodes of muscular paralysis in patients with HPP and arrhythmias,[11] verapamil has been shown to positively treat HPP,[12] and amiodarone has been reported to cause HPP through amiodarone-induced thyrotoxicosis.[13] Therefore, we suggest that providers should be extremely cautious at the time of choosing an antiarrhythmic in these patients, and the decision of both proceeding with medical treatment and specific choice of medication should be agreed in an interdisciplinary fashion.

Finally, a special consideration needs to be addressed regarding ATS and the present study. ATS is characterized by the clinical triad of periodic paralysis, dysmorphic features, and typical ECG abnormalities (prolonged QT interval and prominent U waves), generally associated with ventricular arrhythmias.[2,14] The majority of cases are associated with loss-of-function mutations in the *KCNJ2* (50%–60% of cases) or *KCNJ5* (15%) genes, which encode the inward rectifying potassium channels Kir2.1 and Kir3.4, respectively. Kir2.1 is expressed in the skeletal muscle, heart, and brain, and pathogenic mutations lead to altered cell repolarization.[2,14] Owing to the fact that HPP and arrhythmias are encompassed in this entity, patients with ATS were excluded from our review and analysis. However, it is important to emphasize that, first, BiVT represents the hallmark arrhythmia in these patients[14]; and second, although the first description of this disease was published in 1971, it was not until 1994 that this disorder was better characterized as an entity itself.[15] Because of these observations, we cannot disregard the fact that reports of HPP and arrhythmias, especially those reporting BiVT, could have been in fact patients with ATS. Nevertheless, we included these patients in our review, as we cannot rule out that these patients could have been in fact non-ATS HPP patients with cardiac arrhythmias.

Conclusion

HPP is a rare neuromuscular disease that can present with cardiac arrhythmias. Although the presence of a single pathogenic mechanism is unknown, we highlight the need for a comprehensive cardiovascular assessment in patients with HPP.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2022.05.013.

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