

Sinus arrest in familial hypokalemic periodic paralysis caused by SCN4A mutation: a case report

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Abstract. – BACKGROUND: Primary hypokalemic periodic paralysis (HypoPP), a rare skeletal muscle channelopathy resulting in episodic muscle weakness or paralysis under hypokalemic conditions, is caused by autosomal-dominant genetic mutations. HypoPP limits physical activity, and cardiac arrhythmias during paralytic attacks have been reported. We describe a rare familial HypoPP case complicated by sinus arrest and syncope requiring urgent temporary pacemaker implantation.

CASE REPORT: A 27-year-old Vietnamese man with a family history of periodic paralysis presented with his third attack of muscle weakness triggered by intense football training the previous day. Clinical and laboratory features justified a HypoPP diagnosis.

During intravenous potassium replacement, the patient experienced syncopal sinus arrest requiring urgent temporary pacemaker implantation. The patient gradually improved, responding favorably to oral potassium supplements. Genetic testing revealed an Arg1132Gln mutation in the sodium ion channel (*SCN4A*, chromosome 17: 63947091). At discharge, the patient received expert consultation regarding nonpharmacological preventive strategies, including avoidance of vigorous exercise and carbohydrate-rich diet.

CONCLUSIONS: No evidence has established a relationship between hypokalemia and sinus arrest, and no specific treatment exists for familial HypoPP due to *SCN4A* mutation. Clinician awareness of this rare condition will promote appropriate diagnostic approaches and management strategies for acute paralytic attacks. Treatment should be tailored according to HypoPP phenotypes and genotypes.

Key Words:

Cardiac arrhythmias, Channelopathy, Hypokalemic periodic paralysis, Sinus arrest.

Introduction

Primary hypokalemic periodic paralysis (HypoPP) is a rare skeletal muscle channelopathy with an incidence of 1:100,000 that is generally caused by autosomal-dominant genetic mutations and is more prevalent in men than in women¹. Diagnosis is typically based on clinical presentation and is confirmed by a genetic study². Affected patients present with defects in muscle ion channels that manifest as episodic focal or generalized muscle weakness or paralysis under hypokalemic conditions (serum $K^+ \leq 2.5$ -3.5 mEq/L) caused by the movement of potassium from serum into cells. The first paralytic attack is typically documented between ages 15 and 35 years, and subsequent episodes occur at daily, weekly, or monthly intervals. Attack frequency is highest between ages 15 and 35 years and may decrease with age, tending to become very rare after 40 years of age³. Attacks of muscle weakness may last from hours to days and are often precipitated by stress, viral infection, strenuous exercises, or carbohydrate-rich dietary intake that occurs several hours prior to the attack. Muscle weakness in HypoPP is predominantly detected in the proximal muscle groups of the lower limbs, which may develop into persistent weakness later in life (after the age of 50 years), severely limiting physical activity and sometimes requiring mobility assistance. Case reports have described cardiac complications, including cardiac arrhythmias or electrocardiogram (ECG) abnormalities during hypokalemia-induced muscle paralysis episodes. We report a severe

and rare case of familial HypoPP complicated by sinus arrest and syncope that required urgent temporary pacemaker implantation.

Case Report

A 27-year-old Vietnamese male patient with no comorbidities was admitted to the Department of Emergency, due to the acute onset of painless muscle weakness in his upper and lower extremities after waking up in the morning. The previous day, the patient engaged in intense physical activity, playing football for longer than 60 minutes. The patient did not describe other specific triggers, such as hot or cold exposure, high-carbohydrate meals, alcohol, or stress. The patient described experiencing two previous episodes of muscle weakness and tetraparesis, with the first occurring at the age of 21 years and the second occurring one year later. Both prior episodes occurred after heavy exercise. The patient recovered completely after receiving potassium infusions after both prior episodes. The patient did not take any medications between the ages of 22 and 27 years to prevent another episode of acute muscle weakness and experienced a 5-year attack-free period. The patient did not experience any episodes of dark urine. The two prior muscle weakness episodes were not accompanied by any cardiac symptoms or related arrhythmias.

A review of his family history revealed that his father, male sibling, uncle, and aunt experienced similar muscle weakness episodes accompanied by hypokalemia and were treated with potassi-

um supplements. His father experienced the first attack at the age of 24 years, and both his uncle and his aunt also experienced several episodes throughout their lives.

The physical examination showed a flaccid weakness of the extremities (particularly in the lower extremities). Muscle strength grading was 2/5 in the upper extremities and 3/5 in the lower extremities. Neurologic examination of the cranial nerves, motor skills, sensory perception, reflexes, coordination, and gait was normal.

The initial blood work showed a potassium level of 2.27 mmol/L (normal range 3.4-5.1 mmol/L) at 5:15 AM. All other results were within the normal range, except for creatine phosphokinase (CPK): total calcium level, 2.19 mmol/L; magnesium level, 0.847 mmol/L; serum creatinine level, 0.84 mg/dL; creatine kinase-MB, 22 U/L (normal range <25 U/L); and CPK, 662.93 U/L (normal range <171 U/L). Thyroid function tests and other hormonal assays showed all results within the respective normal ranges (free T4, 17.75 pmol/L; free T3, 4.73 pmol/L; stimulating thyroid hormone, 0.41 mIU/L; cortisol, 978 nmol/L; renin, 13.7 pg/mL; and aldosterone, 10.6 ng/dL). Urinalysis results were as follows: sodium, 121 mmol/L (normal range 160-250 mmol/L), and potassium, 3 mol/L (normal range 26-123 mmol/L). In addition, arterial blood gas analysis on admission revealed a pH 7.395; pCO₂, 35.3 mmHg; pO₂, 100.3 mmHg; HCO₃⁻, 21.2 mmol/L; and lactate, 0.66 mmol/L.

Twelve-lead ECG, taken at the time of presentation, showed sinus rhythm, with a heart rate of 94 bpm and prolonged QT segment (QTc 516 ms; Figure 1). The patient underwent continuous ECG

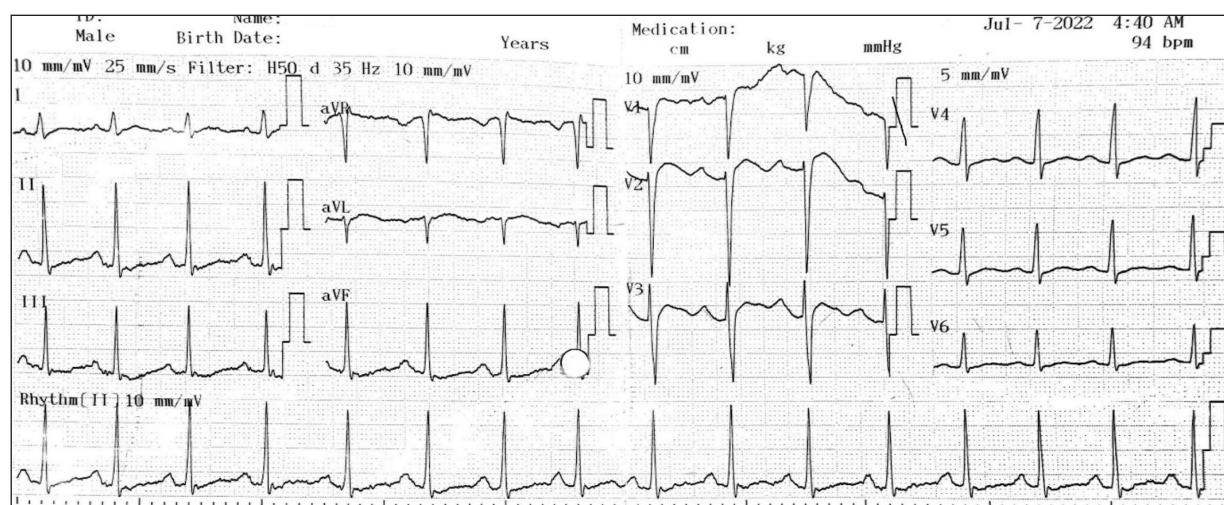


Figure 1. Twelve-lead electrocardiogram showing sinus rhythm and a prolonged QT interval at 516 ms.

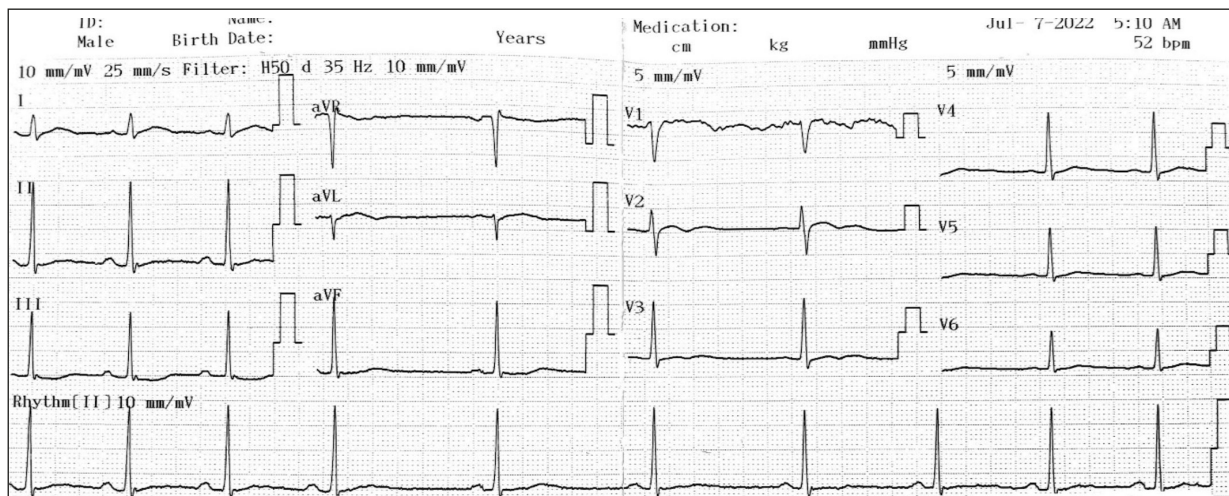


Figure 2. Twelve-lead electrocardiogram showing sinus bradycardia.

monitoring and was initially treated with intravenous (IV) potassium chloride (10 mEq/h, diluted in 0.9% NaCl) delivered through a central venous catheter. Potassium levels were examined at 1-2-hour intervals. Within 30 minutes of treatment initiation, his heart rate began to decrease (Figure 2), and the KCl infusion rate was doubled to 20 mEq/h. After 3 hours, the patient's eyes suddenly rolled back, and the patient experienced syncope. His heart rate dropped to 40 bpm, and ECG monitoring showed an episode of sinus arrest lasting 6 seconds (Figure 3), requiring the immediate implantation of a temporary pacemaker *via* the internal carotid vein. The patient's potassium level plunged to 1.88 mmol/L at 3 hours, with the lowest level of 1.61 mmol/L recorded after 5 hours of IV potassium treatment. After 16 hours of potassium repletion, the patient's potassium level increased to 4.35 mmol/L. The following day, potassium levels were normalized to 4.06 mmol/L, accompanied by complete motility recovery and the resolution of symptoms, including normal serial 12-lead ECG recordings (Figure 4) and 24-hour Holter monitoring. The patient was monitored closely by a cardiologist and an endocrinologist.

The patient was treated with oral magnesium and potassium supplements starting on Day 2 after admission (maintenance dose, 500 mg 3 times each day), and the temporary pacemaker was removed on Day 4. ECG performed on Day 2 showed a normal cardiac structure. Neither electrophysiology study nor electromyogram was performed during the muscle weakness episode because the patient would not consent to these diagnostic procedures.

Genetic testing later revealed a heterozygous mutation in *SCN4A*, resulting in an Arg1132Gln substitution, confirming the diagnosis of familial HypoPP. The patient was discharged on Day 7 and was advised to minimize periodic paralysis triggers, including participation in extreme sports or strenuous exercises, mild exercise at attack onset, and the intake of a high-carbohydrate diet.

Discussion

We report the case of a 27-year-old man with a strong family history of periodic paralysis who presented to the emergency department with his third

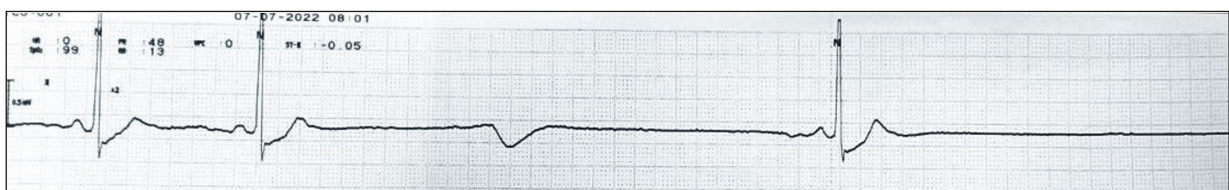


Figure 3. Electrocardiogram monitoring (lead DII) documented the long sinus arrest with syncope that required the implantation of a temporary pacemaker.

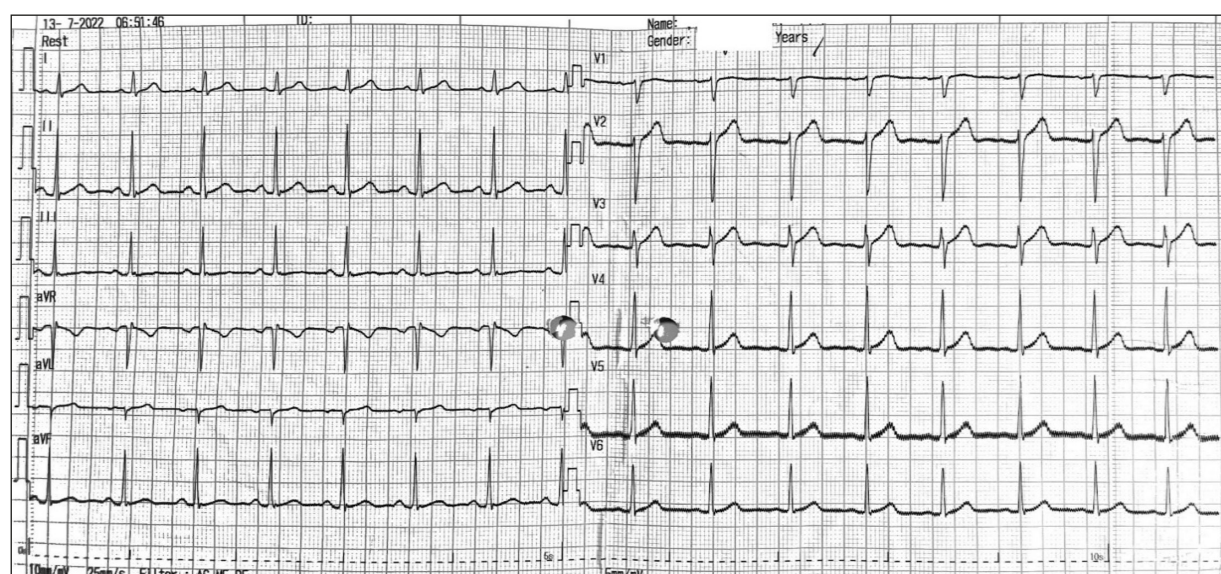


Figure 4. Twelve-lead electrocardiogram after normalization of blood potassium levels, with sinus rhythm and normal QT interval.

paralytic episode, accompanied by hypokalemia. The episode occurred upon waking after engaging in vigorous football training the day prior to admission. A 6-second symptomatic sinus pause that developed during IV potassium administration was managed with the implantation of a temporary pacemaker. Our diagnostic approach for HypoPP was adapted from the diagnostic criteria established by Statland et al² (Table I). After ruling out all alternative hypokalemia causes, including hyperthyroidism, metabolic acidosis, alkalosis, and other causes of secondary hypokalemia, such as distal renal tubular acidosis, the patient's written informed consent was obtained to perform genetic testing to confirm the suspected diagnosis of familial HypoPP.

Genetic testing is recommended as the first diagnostic step for identifying familial HypoPP when moderate to high clinical suspicion indicates the possibility of this diagnosis^{2,4}. HypoPP can develop in response to various genetic mutations in the genes encoding voltage-gated calcium or sodium ion channels, particularly *SCN4A*, *SCN5A*, and *CACNA1S*.

SCN4A encodes the protein NaV 1.4, which forms a sodium ion channel, and *CACNA1S* encodes the protein CaV1.1, which forms a calcium ion channel in the skeletal muscle that transports calcium from the extracellular to intracellular compartments. Mutations in *CACNA1S* are the most common genetic mutations associated with familial HypoPP, identified in 70-80% of patients, whereas mutations in *SCN4A* and *SCN5A* are only observed in 10%-20% of cases. HypoPP caused by mutations in the genes encoding calcium or sodium ion channels present with

similar clinical manifestations. Defects in either channel lead to abnormal resting potential, paradoxical depolarization, and muscle fiber inexcitability due to the altered physiological flux of cations across the muscle cell membrane².

Other periodic paralysis phenotypes include hyperkalemic periodic paralysis (with a prevalence of 1 per 200,000), thyrotoxic periodic paralysis, and Andersen Tawil syndrome (ATS, with a prevalence of 1 per 1,000,000)²; however, HypoPP is

Table I. Supportive diagnostic criteria for HypoPP (adapted from Statland et al²).

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| <ul style="list-style-type: none"> • ≥ 2 attacks of muscle weakness when serum $K^+ < 3.5$ mEq/L |
| <ul style="list-style-type: none"> • 1 attack of muscle weakness and 1 relative with 1 attack when serum $K^+ < 3.5$ mEq/L |
| <ul style="list-style-type: none"> • Any 3 of the following clinical or laboratory features: <ol style="list-style-type: none"> a. Onset between ages 15 and 35 years. b. Attack duration (muscle weakness involving ≥ 1 limb) > 2 hours. c. Positive triggers (high-carbohydrate meal, rest after exercise, stress). d. Improvement with potassium intake. e. Positive family history or genetically confirmed skeletal calcium or sodium channel mutation. f. Positive McManis long exercise test. |
| <ul style="list-style-type: none"> • Exclusion of other hypokalemia causes (renal, adrenal, or thyroid dysfunction; renal tubular acidosis; diuretic or laxative abuse) |
| <ul style="list-style-type: none"> • Absence of myotonia (clinically or latent detected by needle EMG), except eyelids |

HypoPP, hypokalemic periodic paralysis; K^+ , potassium; EMG, electromyogram.

the most common phenotype. These disorders are attributed to different genetic mutations, are triggered by different factors, and present with different clinical manifestations that require specific treatments. ATS is associated with mutations in *KCNJ2*, which encodes the inward-rectifying potassium channel in multiple tissues (identified in 60% of patients diagnosed with ATS). ATS is characterized by periodic paralysis concomitant with dysmorphic features (low-set ears, widely spaced eyes, small mandible, cleft palate, clinodactyly, syndactyly) and typical ECG abnormalities (prolonged QT interval) and is often accompanied by ventricular arrhythmias. ATS episodes can occur under conditions of hyperkalemia, normokalemia, or hypokalemia. Distinguishing between the various disorders is crucial because the treatment and preventive strategies differ substantially depending on the etiology of paralytic episodes. In our patient, an ATS was considered unlikely due to the absence of any physical dysmorphic features.

A positive genetic testing result is necessary to confirm a diagnosis of familial HypoPP. However, genetic mutations cannot be identified in 30% of patients, which requires further examination to exclude the possibility of HypoPP secondary to other conditions (e.g., thyrotoxicosis or blood potassium deficiency or excess identified by provocative testing or electromyography), and differential diagnosis can be made based on the clinical manifestation, serum potassium levels during paralytic episodes, long exercise testing, and the genetic testing results of other family members⁵.

The mean serum potassium level during a muscle paralysis episode in a case series reported by Miller et al⁶ was 2.4 mEq/L, and the serum potassium levels were reported to return to the normal range between episodes. In addition, the occurrence of arrhythmias has previously been reported under normokalemic conditions in some cases of periodic paralysis¹.

Cardiac arrhythmias, including supraventricular tachycardia, isolated premature ventricular contractions, and monomorphic or polymorphic ventricular tachycardia, though uncommon, have been reported as secondary to hypokalemia-induced changes¹. Notably, syncopal sinus arrest or bradycardia, as reported in the present case, is uncommon for cases of HypoPP. Maffè et al³ described a case with similar ECG patterns and syncopal sinus arrest during a paralytic episode requiring the implantation of a temporary pacemaker. However, this patient described by Maffè et al³ had a more severe condition with intense involvement

of the respiratory muscles, requiring orotracheal intubation, whereas our patient retained the function of oropharyngeal and respiratory muscles. In a case series describing 103 members of seven Finnish families with familial HypoPP, Kantola et al⁷ reported seven patients with slow heart rates during severe paralytic episodes but only one case of life-threatening bradycardia. Hypokalemia can only partially explain the development of cardiac arrhythmias, especially in cases of marked bradycardia and sinus arrest. Sinus node automaticity is widely known to depend on the funny current (If) and T-type calcium channels, with minimal dependence on the cardiac sodium channel (INa). Mutations in *SCN5A* (encoding the alpha subunit of INa) are associated with sick sinus syndrome, sinus bradycardia, sinus arrest, and sinoatrial block. Loss-of-function *SCN5A* mutations result in slow recovery from the refractory period, reduced automaticity, and slowed or blocked delivery of impulses generated in the sinus node to the surrounding atrial tissue. The genetic mutation in our case was identified in *SCN4A*, which encodes an NaV 1.4 channel expressed predominantly in skeletal muscle cells; however, evidence suggests that the *SCN4A* alpha subunit is expressed in the normal human heart^{8,9}.

Due to the low prevalence of HypoPP, few recommendations for disease management are supported by evidence in literature, and treatment options remain limited. Current management strategies are based on anecdotal experiences described in case reports or case series. The performance of mild exercise at the onset of acute HypoPP episodes may be beneficial for mild attacks, although oral or IV potassium repletion remains the recommended strategy when hypokalemia is confirmed. Notably, low potassium levels during acute episodes are caused by the movement of potassium from extracellular to intracellular compartments, and excessive potassium repletion during an acute episode may cause post-treatment rebound hyperkalemia when potassium moves back to the extracellular¹⁰. Therefore, potassium supplements should be administered incrementally. Potassium levels and ECG patterns should be regularly monitored during treatment. Acute HypoPP episodes should be treated with 60 to 120 mEq of potassium, and some studies in literature have suggested the delivery of 0.2-0.4 mEq/kg potassium orally every 30 minutes (maximum 200-250 mEq/day) or 40 mEq/L potassium *via* IV (maximum 20 mEq/h, 200 mEq/day). Dextrose-containing IV solutions should not be used to dilute potassium chloride, as

patients could experience an exaggerated insulin response to glucose loads.

Daily potassium supplementation, potassium-sparing diuretics, and carbonic anhydrase inhibitors may be used as preventive therapy when lifestyle changes are not effective. To date, the Food and Drug Administration has only formally approved Keveyis (dichlorphenamide – an oral carbonic anhydrase inhibitor) for treating both primary hypokalemic and hyperkalemic periodic paralysis, with a recommended dosage ranging from 50-200 mg daily in one or two doses¹¹; however, this medication is currently unavailable in Vietnam. Acetazolamide (dose range of 125-1,000 mg daily) is another carbonic anhydrase inhibitor commonly used as empiric off-label treatment for HypoPP in clinical practice. These two carbonic anhydrase inhibitors may cause paresthesia, fatigue, cognitive disturbances, kidney stones, metabolic acidosis, and hypokalemia due to increased potassium excretion. Patients who are started on carbonic anhydrase inhibitor treatment should have their serum potassium levels measured at baseline and periodically throughout the treatment period, and treatment should be discontinued if hypokalemia persists.

Acetazolamide was reported to exacerbate symptoms in some patients with HypoPP associated with mutant sodium channels. In a retrospective review¹² of 74 patients, those with *SCN4A* mutations were less likely to respond to acetazolamide than those with *CACNA1S* mutations (16% vs. 56%). Because genetic testing in our patient was positive for *SCN4A* mutations, we opted against treatment with acetazolamide.

The underlying mechanisms through which carbonic anhydrase inhibitors prevent HypoPP episodes are not completely understood but appear to be independent of carbonic anhydrase inhibition. Carbonic anhydrase inhibitors promote kaliuresis and non-anion gap acidosis, which enhance the opening of calcium-activated potassium channels on skeletal muscle cells and reduce intracellular sodium accumulation, minimizing damage to muscle fiber structure¹³⁻¹⁵.

Potassium-sparing diuretics, such as triamterene (50-150 mg/day), spironolactone (25-100 mg/day), and eplerenone (50-100 mg/day), are potential options, as either monotherapy or as adjuvant therapy with a carbonic anhydrase inhibitor². Eplerenone may be favored over spironolactone because of fewer androgenic side effects. Potassium supplementation should not be used concomitantly with potassium-sparing diuretics unless potassium levels are closely monitored.

Beta-blockers and amiodarone to treat symptomatic arrhythmia should be used with extreme caution because they have been reported to increase the incidence or cause paralytic episodes in patients with HypoPP¹⁶.

Due to the lack of consensus treatment guidelines, several important questions remain unaddressed. Further prospective studies remain necessary to compare the effectiveness of acetazolamide and dichlorphenamide for treating HypoPP. In addition, studies remain necessary to elucidate the mechanism underlying cardiac arrhythmias in HypoPP cases associated with mutations in cardiac sodium or calcium ion channels. Strategies for the improved management of these rare entities remain necessary, particularly when complicated by severe cardiac manifestations.

Conclusions

Limited evidence exists to support a hypothesized relationship between hypokalemia and sinus arrest, and many factors remain unclear, as cases of HypoPP with similar ECG patterns are rare in the literature. Currently, no consensus guidelines have been established regarding treatment for familial HypoPP caused by mutations in *SCN4A*. Clinicians should be aware of this rare entity to adopt an appropriate diagnostic approach and management strategy for the presentation of acute paralytic episodes. Medication should be tailored to each patient based on the corresponding genotypic and phenotypic characteristics of HypoPP.

Ethics Approval

The publication of this case report was approved by the Ethics Committee for Biomedical Research at the University Medical Center HCMC.

Informed Consent

A written consent form was signed by the patient.

Authors' Contributions

T.-D BUI and M.-D. NGUYEN prepared, drafted, and revised the manuscript critically, for important intellectual content. T.-D BUI and H. TRAN contributed substantially to the acquisition, analysis, and interpretation of data. Each author gave final approval to the version of the manuscript submitted for publication and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

There are no conflicts of interest to declare.

Funding

This research received no external funding.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments

We would like to thank our colleagues at the University Medical Center Ho Chi Minh City for their great assistance.

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