

Confirming Genetic Abnormalities of Hypokalemic Periodic Paralysis Using Next-Generation Sequencing: A Case Report and Literature Review

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Hypokalemic periodic paralysis (hypoPP) is a disorder characterized by episodic, short-lived, and hypo-reflexive skeletal muscle weakness. HypoPP is a rare disease caused by genetic mutations related to expression of sodium or calcium ion channels. Most mutations are associated with autosomal dominant inheritance, but some are found in patients with no relevant family history. A 28-year-old man who visited the emergency room for paralytic attack was assessed in this study. He exhibited motor weakness in four limbs. There was no previous medical history or family history. The initial electrocardiogram showed a flat T wave and QT prolongation. His blood test was delayed, and sudden hypotension and bradycardia were observed. The blood test showed severe hypokalemia. After correcting hypokalemia, his muscle paralysis recovered without any neurological deficits. The patient's thyroid function and long exercise test results were normal. However, because of the history of high carbohydrate diet and exercise, hypoPP was suspected. Hence, next-generation sequencing (NGS) was performed, and a mutation of Arg669His was noted in the *SCN4A* gene. Although hypoPP is a rare disease, it can be suspected in patients with hypokalemic paralysis, and identification of this condition is important for preventing further attacks and improving patient outcomes. Diagnosing hypoPP through targeted NGS is a cost-effective and useful method.

Key Words: Hypokalemic periodic paralysis, Genetic diseases, Arrhythmia

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INTRODUCTION

Hypokalemia is defined as a deficiency of plasma potassium to <3.5 mEq/L. In the body, potassium homeostasis is maintained through various mechanisms. Hypokalemia can cause muscle weakness or paralysis, impairment of respiratory function, cardiac arrhythmias, and constipation¹⁾.

Hypokalemic paralysis can be caused by secondary rea-

sons to existing diseases, such as thyrotoxicosis, distal renal tubular acidosis, Gitelman syndrome, primary hyperaldosteronism, use of drugs such as diuretics or licorice, or some hereditary diseases. Patients with this condition exhibit episodic muscle weakness and hypokalemia during muscle paralysis without loss of consciousness or sensory deficits²⁾.

In the Asian population, thyrotoxic periodic paralysis (TPP) is a common cause of hypokalemic periodic paralysis (hypoPP)³⁾. HypoPP also can be caused by a rare genetic disorder

der, referred to as familial hypoPP. Although the frequency of familial hypoPP is not known, the incidence of 1 per 100,000 people has been reported⁴⁾. Familial hypoPP is an autosomal dominant inheritance with mutations in the expression of the sodium voltage-gated channel alpha subunit 4 (SCN4A) gene or calcium ion channels (CACNA1S; Calcium voltage-gated channel subunit alpha1 S). In some cases, it has been identified as idiopathic or sporadic hypoPP in some cases without family history⁵⁾.

We report a case of HypoPP diagnosed using next-generation sequencing in a patient without a relevant family history who experienced a paralysis attack and electrocardiographic changes as the first clinical manifestations.

CASE REPORT

A 28-year-old man was admitted to the emergency room with complaints of a quadriplegia attack that had occurred 3 hours prior to the visit. There was no facial or respiratory muscle weakness or autonomic symptoms. The patient reported mild muscle pain after exercising the day before the visit and consumption of a lot of bread for dinner. Paralysis of the upper and lower limbs appeared bilaterally and started in distal areas such as hands and feet and progressed to the proximal area. The patient reported no paresthesia or hypoesthesia.

He had no respiratory or swallowing difficulties, he denied facial muscle weakness, and conversation was possible. He did not report any medications or herbal supplements, and there was no history of thyroid disease. The patient reported no underlying disease and no history of arrhythmia, chest pain, or dyspnea. In addition, the patient mentioned that he had experienced intermittent episodes of weakness in the lower extremities after exercising since his early twenties, although the symptoms were temporary and improved with time. There was no similar episode or specific disease history in the patient's family (Fig. 1).

On physical examination, the patient's blood pressure was 134/78 and the heart rate was 84 beats/min. His body mass index was 19.96, indicating normal weight. No jugular venous distension, goiter, or lymphadenopathy was observed. On auscultation, a regular heartbeat was noted, and there was no murmur. There were no specific findings on chest

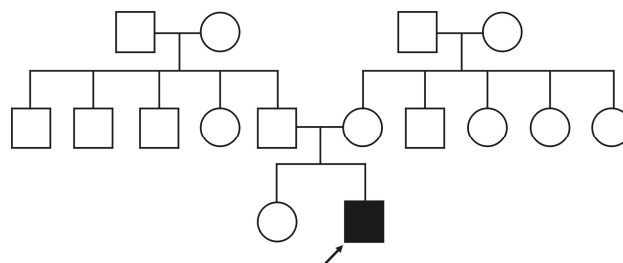


Fig. 1. Pedigree based on family history.

and abdominal examinations. There were no deformities or edema of the extremities, and the distal pulses were present and bilaterally equal.

Neurological examination revealed motor grade 1 and flaccid paralysis of all extremities. There were no specific findings in the sensory test. His blood sugar test indicated hypoglycemia or hyperglycemia.

Initial electrocardiogram (ECG) revealed a heart rate of 78, a flat T wave, and QT prolongation (QT/QTc 542/621 ms) (Fig. 2A). The results of the blood test conducted at the visit were available after 1 hour and 30 minutes and showed potassium at 1.50 mmol/L (3.5-5.0 mmol/L), while arterial blood gas analysis indicated metabolic acidosis. Although intravenous potassium infusion was started immediately, his blood pressure temporarily decreased to 80/50 and his ECG showed bradycardia, ST depression, and a U wave (Fig. 2B). The patient complained of chest discomfort and dyspnea. At that time, the result for cardiac enzyme was in the normal range, and the serum potassium level was 1.35 mmol/L (3.5-5.0 mmol/L). The potassium injection rate was increased accordingly, and oxygen was supplied. After 20 minutes, his blood pressure reached 110/60 and the pulse rate recovered to 67/min, but chest discomfort continued. Intravenous potassium infusion was continued, and the patient was admitted to the intensive care unit for closer observation. In the follow-up ECG after 12 hours, he had a normal sinus rhythm, and the QRS prolongation resolved (Fig. 2C). The muscle paralysis gradually improved starting from 4 h after his initial hospital visit. In follow-up ECG, a normal sinus rhythm was noted. After 24 h, the muscle weakness completely resolved, and the serum potassium level increased to 3.4 mmol/L.

A test was performed to evaluate the cause of hypokalemia. The patient's urine sodium and potassium as well as serum

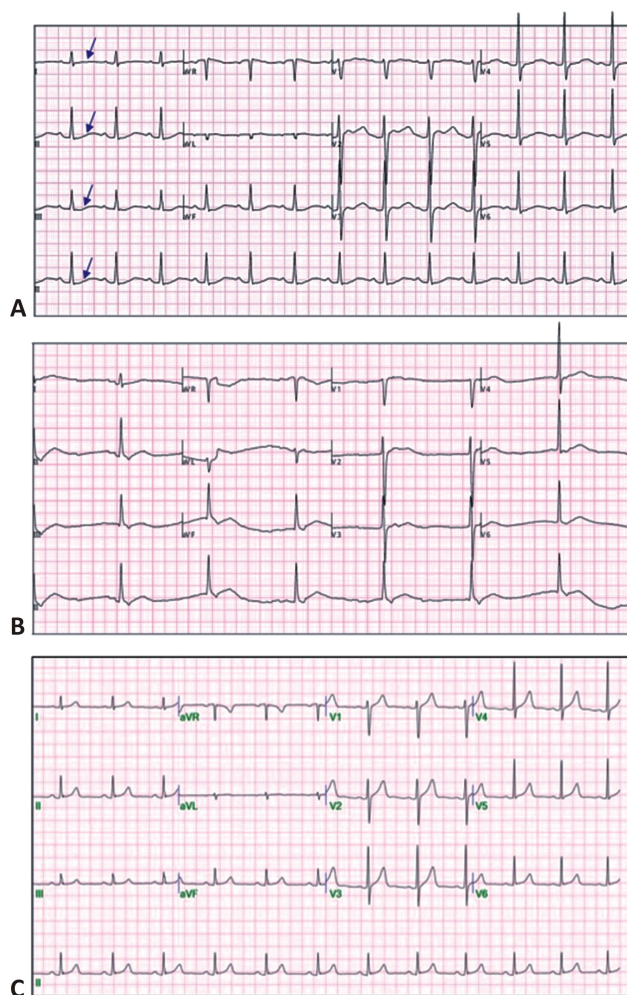


Fig. 2. Initial electrocardiogram findings showed QT prolongation and a flat T wave (blue arrows) (A). Follow-up electrocardiogram showing bradycardia and a flat T wave (B). In the follow-up ECG after 12 hours, electrocardiogram showed normal sinus rhythm, and the QRS duration was in the normal range (C).

aldosterone and renin levels were measured to eliminate adrenal involvement, and the values were normal. Thyroid function test results were in the normal range. After normalization of potassium level, his potassium remained in the normal range without infusion, and he recovered without any neurological deficits. There were no specific findings in the subsequent blood tests.

A long exercise test was performed to differentiate between inherited neuromuscular disease, but no findings were indicative of hypoPP. However, the patient had previously experienced an episode of mild muscle weakness, and he reported at this visit that his symptoms had occurred after

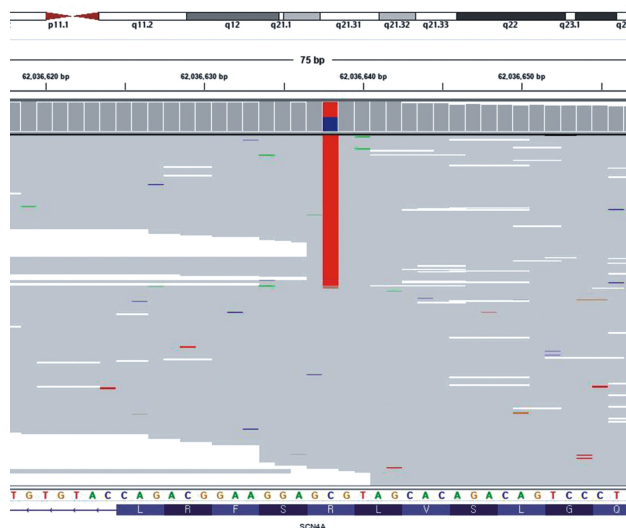


Fig. 3. Results of NGS (SCN4A p.Arg669His).

a break from exercising and with a high carbohydrate diet; therefore, hypoPP associated with genetic disease was suspected, and next-generation sequencing (NGS) with a related gene panel for neuromuscular genetic disease was performed. An Arg669His mutation of SCN4A was noted in the NGS results, and the condition was diagnosed as hypoPP (Fig. 3).

The patient was educated about aggravation factors that could help prevent symptoms, and potassium tablets were provided for use when muscle weakness occurred. The patient is undergoing regular follow-up and has been in a stable state without any paralysis attacks for more than 6 months.

DISCUSSION

Hypokalemic paralysis is caused by existing diseases such as thyrotoxicosis, distal renal tubular acidosis, Gitelman syndrome, primary hyperaldosteronism, drugs such as diuretics or licorice, and hereditary diseases.

HypoPP is a rare genetic disease caused by a mutation in the SCN4A or CACNA1S gene. It is recognized primarily as an autosomal dominant genetic disease but is found in patients without a relevant family history, such as the patient in this case report^{2,5}. An SCN4A mutation was found in this patient. A previous report focused on a case of confirmed SCN4A gene mutation through NGS. Moreover, both

Table 1. Clinical features of hypoPP patients with SCN4A mutation

	Case		Reference		
			Kim et al. ¹²⁾	Miller et al. ¹³⁾	
Protein alteration	Arg669His	Arg669His (n=1)	Arg672Gly (n=3)	Arg672Cys (n=1)	- (n=7)
Country	South Korea	South Korea	America	South Korea	America
Age at onset, yr.	28	17	6.7±1.2	12	16±5
Duration of attacks, hr.	3	1	5.3±0.6	10	1.0±0.6
Frequency of attacks/mo.	First attack	3-4	Daily	2-3	7±0.6 (4-14)
Family history	No	Yes	Yes	No	-
Response to acetazolamide	Beneficial	No effect	Deleterious (4 case)	No effect	Deleterious (4 case)

abbreviations: yr, years; hr, hours; mo, months.

the hypoPP pattern and the phenotype of normokalemic periodic paralysis were observed⁶⁾. Table 1 summarizes the characteristics of patients who have previously been identified with the SCN4A mutation. In this case, the onset age was older, and the attack frequency was lower, and most of the patients had a family history of symptoms or disease. Moreover, use of acetazolamide for other cases mostly was ineffective, and worsening of symptoms was reported. However, in the presented patient, acetazolamide was used, and no paralysis attacks were observed. Thus, the possibility of electrolyte imbalance was not considered in this case, although QT prolongation and a flat T wave were observed on initial electrocardiogram.

Patients have been reported to exhibit episodic muscle weakness and hypokalemia during muscle paralysis without loss of consciousness or sensory deficit²⁾. The weakness most commonly involves the lower limbs rather than upper limbs and proximal muscles more frequently than distal muscles. Facial and respiratory muscles typically are spared⁷⁾.

Paralytic attacks can be triggered by resting after strenuous exercising, a high carbohydrate diet, mental stress, prolonged fasting, acute febrile illness, and often appear several hours after exposure to the aggravation factor(s). These factors increase the release of insulin or epinephrine and promote movement of potassium into the cells, resulting in low levels of potassium in the blood. As a result, education is necessary to avoid such exacerbations to prevent acute severe symptoms in hypoPP patients.

If hypokalemia is correctly diagnosed and corrected, the symptoms can be addressed, and reversible recovery can be achieved. However, if the diagnosis is delayed or incor-

rect, it is possible that patients can experience fatal situations such as arrhythmia or cardiac arrest, although this is rare^{8,9)}.

Therefore, it is important to consider the patient's history and work through adequate differential diagnoses to identify and correct possible causes of symptoms as soon as possible. In this case, although QT prolongation and a flat T wave were observed on initial electrocardiogram, the possibility of electrolyte imbalance was not considered. Because normal saline was injected at a faster rate than potassium infusion, hypokalemia worsened instantaneously, and the ECG changes and symptoms worsened. The patient experienced a paralysis attack for the first time at this visit, but it was confirmed that he had previously experienced intermittent weakness in his lower extremities.

If a definite cause for a secondary disease in patients with hypoPP is not identified, even patients without family history should be considered for this condition. In this case, NGS can be a useful tool for diagnosing hypoPP. NGS is a second-generation DNA sequencing method that replaces the traditional Sanger sequencing method. With this approach, targeted sequencing allows a high-sensitivity and high-specificity testing method because the technique uses primers for desired genes by sequencing only specific genes¹⁰⁾.

Prior to development of NGS, hypoPP was diagnosed with a molecular diagnosis based on Sanger sequencing of hot spots or exon-by-exon screening for specific genes. However, this method is not optimal because it is time consuming¹⁰⁾. In total, 500-bp nucleotide bases can be analyzed for 3 h at a time with Sanger sequencing. For NGS, 1-Gb nucleotide bases can be analyzed in 3-5 days, which would require

25,000 days to analyze using the Sanger sequencing. Additionally, Sanger sequencing costs \$2 million, whereas NGS only costs \$4,000. Thus, NGS is advantageous in terms of cost and time¹¹. As previously reported, introduction of NGS for diagnosing hypokalemic muscle weakness is more cost-effective than previous methods, and this approach increases identification of hypoPP in patients with muscle weakness, thereby preventing additional attacks and further issues.

In conclusion, this study evaluated the cause of hypokalemia in a patient who visited the hospital due to an acute paralysis attack. Because patients often are admitted to the emergency room due to acute paralysis, if a patient is identified in early stages, a neurological examination should be performed to determine if the issues are caused by electrolyte imbalance. The possibility of electrolyte disturbance should be considered if QT prolongation and T wave changes are observed on the ECG. Thus, although it is a rare disease, hypoPP can be suspected in these patients. In addition, targeted NGS is a cost-effective and useful method for diagnosing hypoPP.

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