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CASE REPORT

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Familial hypokalemic periodic paralysis: a case induced by concurrent hyperthyroidism

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Abstract

Background Familial hypokalemic periodic paralysis (HypoPP) is an uncommon genetic disorder characterized by recurrent episodes of muscle weakness and hypokalemia, typically starting in early adulthood. The existence of hyperthyroidism in the presence of HypoPP is more strongly associated with a diagnosis of thyrotoxic periodic paralysis (TPP), with most cases occurring in Asian males with pathogenic *KCNJ2 or KCNJ18* variants and without a family history of the condition. This case is novel due to the combination of familial HypoPP and hyperthyroidism induced by Graves' disease, a rare occurrence especially in non-Asian populations.

Case presentation A 40-year-old African American man presented with profound muscle weakness after consuming a high-salt meal. He had a significant family history of hyperthyroidism and hypokalemia. On examination, he showed profound weakness in all extremities. Laboratory tests confirmed hypokalemia and hyperthyroidism, and genetic testing identified a pathogenic variant in the CACNA1S gene (c.1583 G > A, p. R528H), with normal SCN4A, KCNJ2 and KCNJ18 sequencing. He was diagnosed with familial HypoPP and hyperthyroidism due to Graves' disease. He was started on PO methimazole 10 mg three times a day and PO acetazolamide 250 mg twice a day. He was advised to follow a low carbohydrate and low salt diet.

Conclusions This case highlights the importance of considering a genetic basis for HypoPP in patients with a family history of the condition, even when hyperthyroidism is present. The combination of familial HypoPP and Graves' disease is rare and emphasizes the need for careful genetic and clinical evaluation in similar cases. Management should focus on correcting hypokalemia, treating hyperthyroidism, and lifestyle modifications to prevent recurrence.

Keywords Hypokalemic periodic paralysis, Graves' disease, CACNA1S, Hypokalemia, Hyperthyroidism

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Background

Periodic paralysis (PP) is a rare channelopathy marked by recurrent episodes of flaccid skeletal muscle paralysis. Hypokalemic periodic paralysis (HypoPP) is categorized into familial or acquired forms [1]. Familial HypoPP is an uncommon genetic channelopathy marked by recurrent episodes of flaccid skeletal muscle paralysis accompanied by hypokalemia [1]. Onset typically occurs in the first to third decade of life [1]. Timely diagnosis and preventive treatment are crucial to mitigate morbidity associated with this condition.

Case presentation

A 40-year-old African American man arrived at the emergency room experiencing profound muscle weakness. He reported an inability to move his upper and lower extremities, sit upright in bed, or achieve a complete range of motion in his head and neck. He endorsed dysphagia and dyspnea and denied nausea, vomiting, chest pain, or urinary symptoms.

Past medical history revealed sporadic muscle tightness occurring 1–3 times per week, alleviated by consuming bananas. Additionally, he reported a prior episode of paralysis associated with hypokalemia at the age of 18. The patient observed a relationship between his muscle symptoms and the consumption of high-salt meals. He was not using any medications, and his family history was noteworthy for hyperthyroidism and episodes of hypokalemia in his brother and mother.

Upon presentation, vital signs were temperature 98.4 °F, blood pressure 127/83 mmHg, heart rate 111 beats/minute, respiratory rate 11 breaths/ minute, and oxygen saturation 96% on room air. He was alert and oriented. Physical examination revealed pronounced weakness in both upper and lower extremities (strength assessed at 0/5) with areflexia.

Laboratory results are shown in Tables 1 and 2. The electrocardiogram demonstrated sinus tachycardia with prolonged QTc interval of 606 ms. Nephrology team was consulted for evaluation and management of his severe hypokalemia. Swift replacement of hypokalemia effectively alleviated his symptoms, albeit leading to transient hyperkalemia that spontaneously resolved. (Table 1).

Genetic testing revealed a heterozygous pathogenic variant in *CACNA1S* [c.1583 G>A (p. R528H)] and normal sequencing of *SCN4A*, *KCNJ2* and *KCNJ18*. The patient received a diagnosis of familial hypokalemic periodic paralysis and concurrent hyperthyroidism due to Graves' disease. Treatment of hyperthyroidism was initiated with oral methimazole 10 mg three times a day. In addition, oral acetazolamide 250 mg twice a day was started, and he was advised to follow a low carbohydrate diet with less than 2000 mg of sodium per day. Genetic testing was offered to patient's family members, who declined the tests.

Table 1 Basic laboratory tests

Blood tests	Reference range & units	Results
Sodium	136–145 mmol/L	139
Potassium	3.5–5.1 mmol/L	< 1.5
Chloride	98–107 mmol/L	105
CO2 Total	22–29 mmol/L	21
Anion Gap	7–18	13
BUN	6–23 mg/dL	18
Creatinine	0.67–1.17 mg/dL	0.91
eGFR	>=60	109
Glucose	70–99 mg/dL	142
Calcium	8.6–10.2 mg/dL	9.3
Calcium Ionized	1.17–1.38 mmol/L	1.32
Magnesium	1.6–2.6 mg/dL	1.9
Phosphorus	2.5–4.5 mg/dL	2.1
Total Protein	6.6–8.7 g/dL	7.2
Albumin	3.5–5.2 g/dL	3.9
Globulin	2.5–4.0 g/dL	3.3
AST	5–40 U/L	64
ALT	5–41 U/L	153
Bilirubin Total	0.2–1.2 mg/dL	0.3
Alk Phos	40–129 U/L	79
Creatine Kinase	39–308 U/L	233
Urine tests		
Random Creatinine		75.02 mg/dL
Random potassium		8 mmol/L

Discussion and conclusions

Triggers for episodes of HypoPP are primarily associated with intense exercise and high carbohydrate intake, and less frequently related to viral infections, stress, cold, salt consumption, and medications (such as glucocorticoids and insulin) [1, 2]. Familial HypoPP is associated with variants in the skeletal muscle sodium channel gene *SCN4A* in 20% of patients or the L-type calcium channel gene *CACNA1S* in 60% of patients [1, 2]. The majority of reported pathogenic variants involve arginine residues in S4 transmembrane segments, with notable hotspots at codons R528 and R1239 [3]. The pathogenic variant observed in this case, c.1583 G>A (p. R528H) in *CACNA1S*, has been documented previously [1, 2]. Mutations associated with this condition trigger a gating pore current and reduce the overall calcium channel current in the cell, but the reduction is too minor to significantly impact the cell's membrane potential. However, when potassium levels drop, the membrane behavior changes significantly, leading to depolarization of the resting membrane potential and unusual muscle membrane depolarization, which would normally only occur at much lower potassium levels. As a result, conditions that cause mild changes in potassium levels, such as elevated insulin levels after consuming carbohydrate-rich meals or thyrotoxicosis (which induces an intracellular shift of potassium due to thyroid hormone's effect on Na+/K+–ATPase), can

Table 2 Thyroid hormone tests

	Reference range & units	Results
TSH	0.270–4.200 mcIU/mL	< 0.006
Free T3	2.1–4.4 pg/mL	13.0
Free T4	0.90–1.70 ng/dL	3.04
Thyroid Stimulation Immunoglobulin (TSI)	<=0.54 IU/L	3.43
Thyroid Peroxidase Ab	0.0–9.0 IU/mL	62.6

trigger episodes of paralysis [4]. Generally, the existence of hyperthyroidism is more strongly associated with a diagnosis of thyrotoxic periodic paralysis (TPP), with most cases occurring in Asian males without a family history of the condition. The role of genetics in TPP has gained increasing attention in recent years. Genetic predisposition plays a crucial role in the susceptibility to TPP. One of the most significant is the presence of certain polymorphisms in genes related to ion channels, particularly those encoding for potassium channels such as *KCNJ2 and KCNJ18* [1, 5]. *KCNJ2 and KCNJ18* encode Kir 2.1 and Kir2.6 respectively, inwardly rectifying potassium channels expressed in skeletal muscle and transcriptionally regulated by thyroid hormone [1]. Therefore, these genetic variants can influence the function of these channels, contributing to the development of TPP. The likelihood of TPP in this case is reduced, given that the patient is not of Asian descent, has a family history of HypoPP, and lacks identifiable variants in *KCNJ2 and KCNJ18*. Nevertheless, Graves' disease and a high-salt diet are factors that likely triggered the HypoPP episode in this patient.

Management of acute paralytic episodes involves maintaining proper control of serum potassium levels, necessitating vigilant monitoring for post-treatment hyperkalemia. Lifestyle and dietary modifications to avoid triggering factors are integral to treatment. Although the precise mechanism is not fully elucidated, carbonic anhydrase inhibitors have demonstrated efficacy in reducing the frequency of familiar HypoPP episodes [6]. There is variability in the response to carbonic anhydrase inhibitors based on genotype; individuals with *CACNA1S* variants tend to exhibit a more favorable response compared to *SCN4A* variants [6]. Additionally, the incorporation of a potassium-sparing diuretic, either in conjunction with carbonic anhydrase inhibitors or as a standalone treatment, may offer advantages for specific patients.

Abbreviations

PP Periodic paralysis
HypoPP Hypokalemic periodic paralysis
TPP Thyrotoxic periodic paralysis

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Author contributions

ZAH wrote the first draft. MH, JS, and EC reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Disclosures

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Competing interests

The authors declare no competing interests.

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