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CASE REPORT – OPEN ACCESS

Familial Hypokalemic Periodic Paralysis with Mutation in a Voltage-Gated Calcium Channel

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ABSTRACT

Background: Familial hypokalemic periodic paralysis (FHPP) is an autosomal dominant disease presented by the presence of painless weakness attacks accompanied by a low level of serum potassium. Mutations in genes encoding ion channels Calcium voltage-gated channel subunit alpha 1S, SCN4, and KCNJ2 have been recognized in this disorder.

Case Report: A 15-year-old male patient was admitted to our hospital with a complaint of muscle weakness, which started about 4 years ago, recurring almost twice a week. Especially when he ate carb-rich meals or stayed after a long time in the cold, he described a feeling of numbness and weakness. FHPP was diagnosed due to CACNA1S gene mutation from the family in which six members are affected in three generations.

Conclusion: FHPP, which is an uncommon cause in cases presenting with sudden muscle weakness, is an important neuromuscular emergency, which should be kept in mind and may cause mortal results when not treated.

Keywords: CACNA1S, familial periodic paralysis, hypokalemia, hypokalemic periodic paralysis, muscle weakness

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INTRODUCTION

Familial hypokalemic periodic paralysis (FHPP) is an autosomal dominant heterogeneous disease. Symptoms frequently begin in the first or second decade. Paralytic attacks with associated hypokalemia are characterized by painless skeletal muscle weakness that occur at irregular intervals. Weakness is more pronounced in proximal muscle groups than distal, deep tendon reflexes may be normal or decreased. The disease can result in death due to respiratory paralysis or arrhythmia (1, 2).

Mutations in genes encoding three ion channels have been recognized in FHPP. These are Calcium voltage-gated channel subunit alpha 1S, Sodium channel α subunit (SCN4A), and Potassium voltage-gated channel subfamily J member 2 (KCNJ2). There are few studies on the frequency of these genetic mutations and it varies according to countries (1–4). We report the case of a teenage boy with FHPP due to CACNA1S gene mutation from a Turkish family in which six members are affected in three generations.

CASE REPORT

A 15-year-old male patient was admitted to our hospital with a complaint of muscle weakness, which started about 4 years ago, recurring almost twice a week. Especially when he ate carb-rich meals or stayed after a long time in the cold, he described a feeling of numbness and weakness that started more prominently in his upper limb and started within minutes of his entire body and passed by himself. There was no consanguinity between parents, but it was learned that there were periodic paralytic attacks that healed spontaneously in his father, grandmother, aunt, and two cousins (Fig. 1).

There were no medications, he used regularly. However, in a similar paralytic attack, his aunt had a low potassium level in his tests and he was recommended to take oral potassium by the doctor. For this reason, it was learned that patient, his father and cousins used oral potassium when their complaints developed without consulting a doctor, and then their complaints decreased by up to 4 h. However, there was no individual in the family diagnosed genetically.

Our patient had no complaints at the time of admission and his serum electrolytes were normal. Two h after feeding with a meal rich in carbohydrates, numbness and weakness in the arms started. The upper limb motor power was 4/5, while the lower limb motor power was 5/5. Deep tendon reflexes were hypoactive. Another system examination was normal. Blood gas was taken from the patient and it was demonstrated that pH 7.341, pCO_2 54.2 mm Hg, and potassium 3.0 mmol/L. Thyroid function tests were normal. The electrocardio-

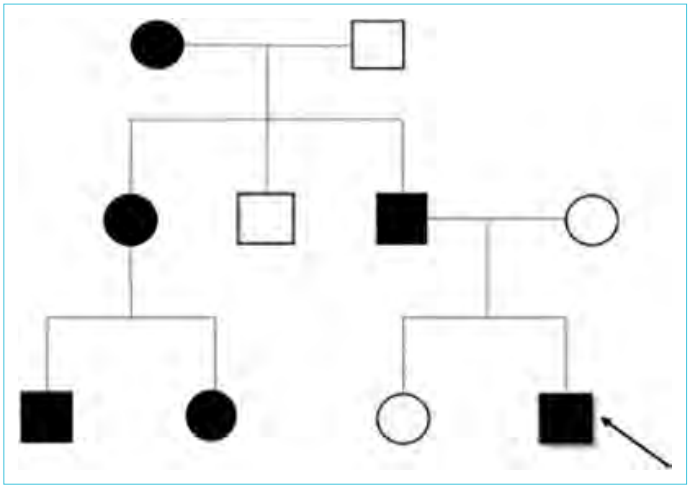

Figure 1. The patient's pedigree

gram was normal. After the patient was given oral potassium in a controlled dose, his complaints disappeared after a short time. Genetic analysis was performed considering FHPP and revealed a previously reported heterozygous c.1583G>A (p.Arg528His) mutation in *CACNA1S*(NM_000069.3). It was recommended to a diet low in sodium and carbonhydrate and rich in potassium and oral potassium replacement during attacks.

DISCUSSION

FHPP is a disease with a prevalence of about 1/100,000 (2). The patients are completely normal between attacks. Neuromuscular disorder characterized by painless muscle weakness and serum K <3.5 mEq/L during attacks. Often, there is a triggering factor that attacks with a carbohydrate-rich meal, exposure to cold, immobility for a long time, fever, stress, and some medications. The duration of paralytic attacks varies from one to 72 h, with an average of 24 h. The recovery period is shortened with potassium replacement (5). In our case, it was described that the first attack appeared at the age of 11 and that the attacks were provoked by carb-rich meals or after prolonged cold exposure. It was learned that the first attacks lasted more than 24 h, and when he used oral potassium in his subsequent attacks, he healed in a shorter time.

FHPP is related to mutations in the calcium channel gene CACNA1S and the sodium channel gene SCN4A. The clinical findings are the same for patients with FHPP caused by calcium or sodium channel mutations. These channel defects lead to an abnormal leakage current, which is active at the resting potential and generates susceptibility to paradoxical depolarization of the fiber and inexcitability in the setting of low extracellular potassium. The alpha 1-subunit of the skeletal muscle L-type voltage-dependent calcium channel is encoded by the CACNA1S gene. It is situated in the membrane of the transverse tubular system. The two most common mutations outcome in one amino acid changes of a histidine for an arginine in the S4 part of domain II (Arg528His) or in the S4 part of domain IV (Arg1239His) in the alpha-subunit of the calcium channel (6). This causes to membrane depolarization, inactivation of sodium channels, and paralysis. Penetrance is about 90% in males and lower in females (6). Another cause of familial periodic paralysis is Andersen-Tawil syndrome, which develops as a result of potassium channel defect due to KCNJ2 mutation. Andersen-Tawil syndrome is related to a highly variable phenotype of periodic paralysis, cardiac arrhythmia, and dysmorphic features. Paralytic attacks might be associated with high, low, or normal serum potassium levels in this syndrome (2).

There are several studies related to the type of genetic mutation in FHPP from different countries. CACNA1S mutations are between 60 and 70% in hypokalemic periodic paralysis patients in USA and European patients. The most common mutations affect in the CACNA1S gene are R528H, R1239H, and R1239G (2–4). In contrast, SCN4A mutations are the most common genetic cause of FHPP in China. There are few case reports related to FHPP in our country. Different SCN4A mutations were reported independent two Turkish families (7, 8) Sakallıoğlu et al. (9) reported a Turkish FHPP patient due to R1239H mutation in CACNA1S gene. In our patient, FHPP due to CACNA1S gene R528H mutation was determined. A total of six family members were affected from the disease. Large case series are needed to determine the frequency of genetic mutations for FHPP in our country.

The differential diagnosis in a patient with hypokalemic paralysis is important. Because different therapies are required for each type. Primary periodic paralyses are genetic neuromuscular disorders related to mutations in the skeletal muscle. Secondary causes of hypokalemic paralysis contain renal causes (renal tubular acidosis, Gitelman syndrome, and primary hyperaldosteronism), thyrotoxicosis, diarrhea, barium intoxication, and drug use (laxatives, diuretics, corticosteroids, and thyroid hormone tablets) (2, 10).

CONCLUSION

FHPP, which is a rare cause in cases presenting with sudden muscle weakness, is an important neuromuscular emergency, which should be kept in mind and may cause mortal results when not treated. Family history should definitely be questioned in cases that present with the complaint of weakness.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflict of interest to declare.

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