Case Report

Phenotypical Variation with Same Genetic Mutation in Familial Hypokalemic Periodic Paralysis

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Hypokalemic periodic paralysis is a genetic neuromuscular disorder characterized by episodes of painless muscle paralysis associated with low serum potassium, exclusively, during the attack. This may be precipitated by heavy exercise, fasting, or high-carbohydrate meals. We report two siblings, presenting at different ages with varying symptomatology—older sibling with episodic weakness in the morning associated with reduced physical exercise and consumption of large carbohydrate meal, whereas younger sibling complained of muscle stiffness following large carbohydrate meal and at the end of physical exercise. Molecular genetic study showed both siblings and their father were positive for calcium channel alpha-1S subunit (CACNA1S) C3716G>A; p.Arg1239His mutation. It is important to check serum potassium in a child presenting with muscle stiffness or weakness after a carbohydrate meal or vigorous exercise. This condition responds with potassium supplement. Often relevant family history and trigger factors with clinical correlation and blood results can lead to its diagnosis.

Keywords: CACNA1S, hypokalemic, paralysis, periodic, phenotypic

INTRODUCTION

Hypokalemic periodic paralysis is a genetic neuromuscular disorder characterized by episodes of painless muscle paralysis for few hours or up to 2 days, associated with low level of blood potassium during the attack, and normal potassium level between the attacks.[1,2] This may be precipitated by heavy exercise, fasting, or high-carbohydrate meals.

CASE HISTORY

We report two cases of siblings who presented at different ages with varying symptomatology.

Case one
A 16-year-old boy presented with episodic weakness in the early hours of morning with difficulty to get out of bed, lasting up to 2h. It was associated with reduced physical exercise, large carbohydrate consumption, and irregular mealtime. There was no associated swallowing difficulty or cardiac symptoms such as palpitation or chest pain. His history included speech delay and early conductive hearing loss. He was born at term, and there were no significant untoward antenatal or postnatal events. His electrocardiogram was normal; creatinine kinase (CK) was 363 IU/L (40–320 IU/L); thyroid function test (TFT) finding was normal; findings for antinuclear antibodies (ANA) and thyroid peroxidase antibodies (TPO) were negative; electromyography (EMG) and nerve conduction study (NCS) findings were supportive of a chronic primary muscle disorder; potassium level was <3.5 mmol/L (3.5–5.3 mmol/L); and clinical examination including neurological examination was unremarkable.

Case two
A 14-year-old boy presented with four episodes of muscle stiffness, wherein he was unable to lift his arm above the shoulder following a large fast-food meal, or a Chinese meal and a bacon sandwich. He had no other health problems. He had been actively taking part in sport, but recently started noticing stiffness of muscles

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How to cite this article: Kumar S, Offiong EE, Sangita S, Hussain N. Phenotypical variation with same genetic mutation in familial hypokalemic periodic paralysis. J Pediatr Neurolsci 2018;13:218-20.
at the end of exercise. His mother had antepartum hemorrhage at 15 weeks of gestation; however, her pregnancy was otherwise uneventful. He was born at 37 weeks of gestation by induced vaginal delivery. CK was 475 IU/L (40–320 IU/L), TFT was normal, and ANA and TPO findings were negative. Potassium level was 2.9 mmol/L (3.5–5.3 mmol/L).

Family tree
These two brothers, and their father, paternal uncle, and paternal grandmother were diagnosed with familial hypokalemic periodic paralysis (FHPP) [Figure 1].

Genetic mutation
Molecular genetic study showed both siblings and their father were positive for calcium channel alpha-1S subunit (CACNA1S) C3716G>A; p.Arg1239His mutation. Both the brothers inherited same family genetic mutation in CACNA1S gene (p.Arg1239His heterozygous mutation) [Figure 2].

DISCUSSION
FHPP is a genetic condition with a prevalence of 1 in 100,000, and it is most commonly inherited in an autosomal-dominant manner, although sporadic and de novo mutations have been reported.[1,2] The majority of cases (almost 70%) are associated with mutation in CACNA1S (muscle calcium channel) gene and 10% of the cases are associated with SCN4A (muscle sodium channel) gene.[1,3]

In our cases, the clinical manifestation and the severity of the condition were variable even within the family members showing similar genotype. It was associated with trigger factors such as large carbohydrate meal. Both the siblings were followed up and reviewed by clinical geneticist. Both of them were advised to take one to two tablets of Sando-K in the beginning of an episode of weakness or stiffness to prevent further worsening. They were subsequently started on acetazolamide following which the number of episodic symptoms of weakness or stiffness reduced significantly. We arrived at the diagnosis for the older sibling by reviewing relevant history and checking potassium level and EMG/NCS findings, and it was confirmed by genetic testing. For the younger sibling, however, an EMG/NCS was not deemed necessary in view of positive family history and genetic confirmation.

There are other causes of periodic paralysis, including thyrotoxicosis and Andersen syndrome. These conditions can mimic FHPP; but in our cases, it was ruled out by negative TPO.[4] Other differential diagnosis includes myasthenia gravis, where weakness typically occurs in the setting of milder degrees of exertion, without periodicity, and often involves bulbar[5] and extraocular muscles,[6] which are rarely affected in FHPP. Respiratory muscle involvement is common in
severe myasthenia gravis. In metabolic myopathies, patients typically complain of exercise intolerance, with myalgia and muscle fatigability, rather than attacks of weakness. Episodic weakness is also seen in secondary hypokalemia due to renal, gastrointestinal, or other causes with clinical or laboratory evidence of the underlying systemic disease; however, hypokalemia persists between attacks.

Current treatment option involves the use of acetazolamide with or without potassium supplements to reduce the significant number of episodes. Genetic counseling is very important. Nonpharmacologic interventions that may be effective for preventing attacks include having a low-carbohydrate diet and refraining from vigorous exercise. Milder attacks can be aborted by low-level exercise. Potassium administration is used during an acute episode; however, one should avoid dextrose-containing intravenous fluids when supplementing potassium in acute attacks. Presence of hypokalemia must be confirmed prior to therapy, as potassium administration can worsen episodes due to hyperkalemic periodic paralysis.

**Conclusion**

It is very important to check serum potassium level in a child presenting with symptoms of muscle stiffness or weakness especially after a large carbohydrate meal or vigorous exercise. This condition responds quickly with potassium supplement and may need intravenous potassium in acute emergency. Often relevant history including family history and trigger factors and clinical correlation with examination and blood results can lead to its diagnosis.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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