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Case Report

Successful treatment of normokalemic periodic paralysis with hydrochlorothiazide

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Abstract

Background: Periodic paralysis (PP) is an autosomal dominant muscle disorder characterized by periodic muscle weakness attacks associated with serum potassium level variations. It is classified into hypokalemic (hypoKPP), hyperkalemic (hyperKPP), and normokalemic (normoKPP) forms based on the ictal serum potassium level. HyperKPP and normoKPP are caused by mutations of the same gene *SCN4A*, the gene encoding the skeletal muscle voltage-gated sodium channel. Prophylactic treatment with thiazide diuretics is highly effective in preventing attacks in hyperKPP. However, the efficacy and safety of such diuretics in normoKPP remain unclear.

Case: We describe a familial case of normoKPP wherein the affected individuals showed periodic muscle weakness attacks, with an early childhood onset, and a lack of serum potassium level variation during the paralytic attacks. Sequencing analysis of *SCN4A* gene revealed a heterozygous missense mutation (c. 2111C > T, p. Thr704Met) in all symptomatic family members. Oral administration of hydrochlorothiazide, a thiazide diuretic, markedly improved the paralytic attack frequency and duration in the affected individuals without adverse effects.

Conclusion: Our case demonstrates the efficacy of hydrochlorothiazide in the prophylactic treatment of normoKPP caused by the *SCN4A* mutation of p.Thr704Met, the most frequent mutation of hyperKPP.

Keywords: Normokalemic periodic paralysis; *SCN4A*; Hydrochlorothiazide; Treatment; Sodium channel

1. Introduction

Skeletal muscle sodium channelopathies are rare autosomal dominant diseases characterized by episodic abnormalities of muscle membrane excitability [1]. Gain-of-function mutations in *SCN4A* encoding the α-subunit of the skeletal muscle voltage-gated sodium channel cause myotonia and periodic paralysis (PP), while the loss-of-function mutations cause congenital myopathy [2]. PP is characterized by recurrent episodes of muscle weakness associated with serum potassium level variations. Some patients with PP have normal serum potassium levels during weakness attacks. PP was initially classified into hypokalemic (hypoKPP), hyperkalemic (hyperKPP), and normokalemic (normoKPP) forms based on the ictal serum potassium level. *SCN4A* mutations give rise to both hyperKPP and hypoKPP. However, the mutations that cause hyperKPP and hypoKPP are distinct [3]. NormoKPP families harbored the same *SCN4A* mutations as those

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in hyperKPP families [4]. Thus, normoKPP is now considered a variant form of hyperKPP.

Diuretics are effective in treating PP; however, the mechanism of action is unclear. The prophylactic therapy with potassium-sparing diuretics in hypoKPP, thiazide diuretics in hyperKPP, and carbonic anhydrase inhibitors in both disorders is recommended. However, the efficacy and safety of these diuretics in normoKPP remain unclear.

Herein, we report a familial case of normoKPP caused by *SCN4A* mutation of p.Thr704Met wherein the affected individuals were successfully treated with hydrochlorothiazide without adverse effects. Our case suggests that hydrochlorothiazide may be effective in preventing the episodic weakness in normoKPP with mutation of p.Thr704Met.

2. Case report

An 11-year-old girl presented to our emergency room with flaccid paralysis of the lower extremities, which had begun 1 h earlier. She could not walk or sit up in bed. Interview with her parents revealed that she had experienced periodic muscle weakness attacks over the past 8 years. During the early stage, her paralytic attacks occurred once or twice a week, lasting for a few minutes. However, the recent attacks occurred more frequently, i.e., three or four times a week, lasting for 2 or 3 h. The muscle weakness mainly occurred in her lower extremities. The attacks often began after awakening in the morning and didn't be triggered by potassium rich foods, cold temperatures, or fatigue. Interview with the family members further revealed that similar attacks were also experienced by her mother, brother, and sister (Fig. 1).

Neurological examinations showed a symmetrical decrease in muscle strength of her lower extremities, but not sensory impairments. There was no grip or percussion myotonia. Deep tendon reflexes were absent in the lower extremities. The patient showed normal serum potassium levels even during attacks. Brain magnetic resonance imaging (MRI) showed no abnormality. Two hours after being hospitalized, her clinical manifestations naturally returned to normal.

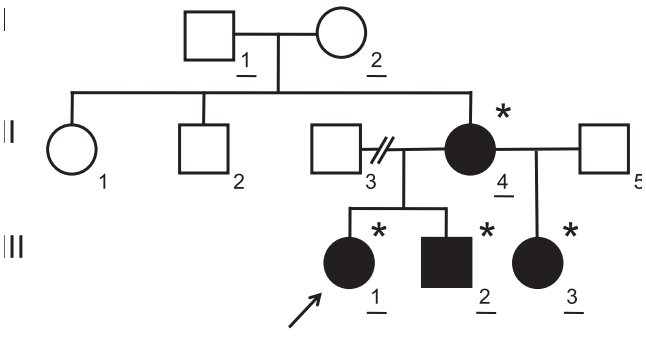

Fig. 1. The pedigree of this family. Affection status for periodic paralysis is as noted. Filled squares and circles indicate affected male and female individuals, respectively; open symbols, unaffected. Underlined pedigree numbers denote individuals whose DNA was available and who were analyzed in the present study. Asterisks denote *SCN4A* mutation carriers. The proband is indicated by an arrow.

Mutation screening was performed by sequence analysis of the entire coding region of the *SCN4A* gene in all symptomatic family members (II-4 and III-1, 2, and 3) and asymptomatic maternal grandparents (I-1 and 2). All participants provided their written informed consent, and the study was conducted in compliance with the Institutional Review Board of Asahikawa Medical University. We identified a *SCN4A* missense mutation (c.2111C > T, p.Thr704Met) in all affected members, but not in the unaffected maternal grandparents.

The patient was started on a prophylactic treatment with hydrochlorothiazide (25 mg daily). The initial dosage of hydrochlorothiazide was gradually increased up to 50 mg daily, based on the clinical response. The paralytic attack frequency and duration remarkably decreased after the medication administration (Fig. 2a). Her serum sodium and potassium levels remained normal. Her mother and brother also showed normal serum potassium levels during attacks. They were treated with hydrochlorothiazide and showed a marked improvement in paralytic attacks (Fig. 2b and c). Her sister underwent a follow-up examination without any medications because of the low frequency of attacks.

3. Discussion

A familial case was reported with normoKPP. The diagnosis was made on the basis of the following clinical features: periodic muscle weakness attacks in the lower extremities and lack of serum potassium level variations during the attacks. Their clinical features were similar to those reported in hyperKPP except for ictal serum potassium levels. All affected individuals carried the p.Thr704Met mutation in *SCN4A*. Testing of the maternal grandparents confirmed that the mutation occurred *de novo* in the mother of the proband. Thus, the *SCN4A* mutation segregated with the PP phenotype in this family.

The mutation p.Thr704Met identified in this family accounts for the majority of patients with hyperKPP [5]. However, in a large series of patients with the p.Thr704Met mutation, increased serum potassium levels during attacks were observed in only 50% of cases [6]. The reason why this mutation also cause normoKPP remains to be fully elucidated. This mutation occurs at the transmembrane segment of the sodium channel and impairs the slow inactivation process, which prevents the muscle from recovering after contraction and

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