Myopathy as the first symptom of hypokalemic periodic paralysis – case report of a girl from a Polish family with CACNA1S (R1239G) mutation

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Abstract

Purpose: Presenting the case of unusual onset hypokalemic periodic paralysis (HypoPP) where myopathy had developed two years before paralysis occurred.

Material and methods: A Polish three-generation family with HypoPP and mutation in CACNA1S (R1239G) has been investigated. Clinical presentation with unusual onset of the disease, biopsy results and genetic research in one family member were described.

Conclusion: HypoPP is a rare disease it needs to be taken into consideration not only in cases of paroxysmal weakness but also when there is myopathy of unknown origin.

Key words: HypoPP, myopathy, CACNA1S.

Introduction

Hypokalemic periodic paralysis (HypoPP) is a rare inherited disorder with the overall incidence in the general population of about 0.4-1 cases per 100 000 [1]. HypoPP is a channelopathy caused by mutations in calcium or sodium channels [2]. The disease usually starts in the first or second decade of life and paroxysmal muscle weakness, usually induced by strenuous effort or carbohydrate-rich meal, is the most common symptom. Typically, myopathy develops several months or years after the onset of muscle weakness episodes and the background of its development is uncertain. Frequent alterations in intracellular and extracellular ionic concentrations could be responsible for muscle injury, yet the correlation between the frequency of weakness attacks and myopathy development has not been observed. Interestingly, in one member of a Polish family with HypoPP myopathy symptoms had been detected two years before the onset of muscle weakness attacks. The article includes clinical case presentation and the results of genetic investigation of the patient and of her family members.

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Received 09.03.2007 Accepted 29.04.2007

Material and methods

A 10 year old girl was hospitalized in Department of Developmental Neurology in Poznań University of Medicine Sciences because of Achilles tendons' shortening which had been first observed during a periodic school check-up two years earlier. The girl had not experienced any walking related problems earlier and her parents did not notice tendon shortening. The girl was admitted to hospital with suspicion of cerebral palsy. She was born from a second pregnancy – the pregnancy course during the first and second trimester was normal, yet during the third trimester her mother had suture put on under general anaesthesia because of uterine cervix insufficiency. The girl was born in 40th week of gestation with body weight of 2 750 g and scored 10 in Apgar scale. Her subsequent development was normal – the onset of sitting and walking occurred at usual time and intellectual development was also normal. Family history was meaningful for the occurrence of HypoPP (*Fig. 1*).

Until hospitalization no muscle weakness had occurred, but the reduction of Achilles tendons, finger gait, bilateral absence of plantar reflex, leg cramps – especially in the right leg – and reduction of diameter of right calf were all found on neurological examination. Because of earlier suspicion of cerebral palsy cranial and vertebral NMR scans were performed which revealed no abnormalities, and neither did EMG. Genetic examination was carried out and the presence of mutation of α1 calcium channel R1239G was confirmed.

Figure 1. **The patient's family genealogical tree. The reported patient is marked "K" (full black circle in the lowermost line)**

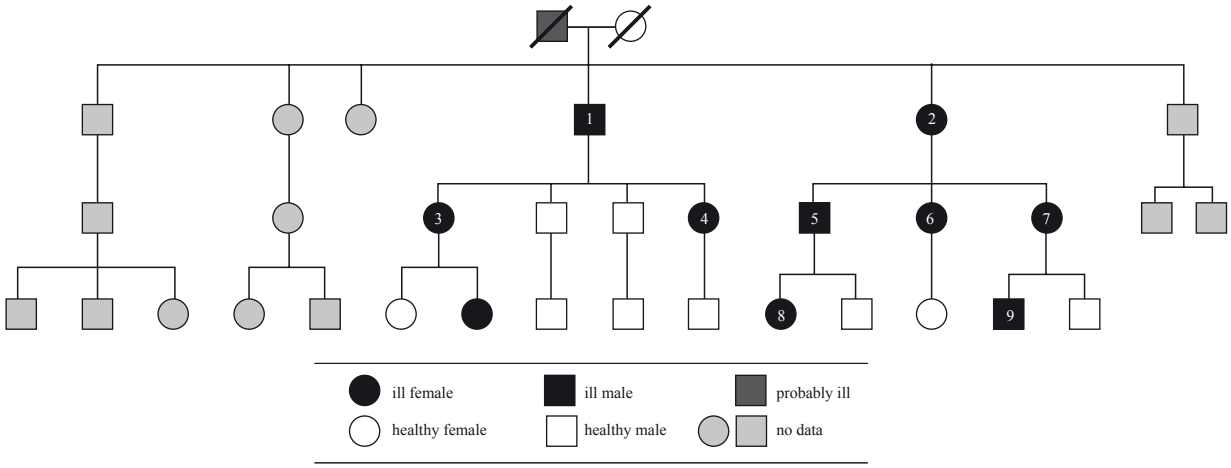

Table 1. **The history of the attacks and beginning of the disease in the patient's family**

Patients	Age Sex	Age at onset	Frequency of paralysis	Other symptoms
1	70 male	About 14	1-2 times per year	One generalised attack with arrested breathing. Attacks after intake of carbohydrate rich meals or alcohol.
2	63 female	11	Very often, mainly at night or early in the morning	The patient cannot walk.
3	40 female	11	Especially in the week before menstruation	Now the attacks occur mainly after stress or strenuous physical exercise. Attacks were very frequent when she was a teenager and occurred mainly at night.
4	34 female	12	1-3 times per month	Attacks occur mainly after stress or strenuous physical exercise. Some attacks induced problems with breathing, mainly when she was teenager and occurred mainly in the morning.
5	35 male	9	Very often, everyday	During attacks he experiences generalised weakness and has problems with sitting. Attacks occur mainly afternoon and early morning.
6	32 female	9	Almost every day	Worse attacks before menstruation, mainly at night; some days she cannot get up in the morning.
7	30 female	7	Almost every day	Worse attacks before menstruation, mainly at night; some days she cannot get up in the morning.
8	15 female	3	Rare attacks	First symptoms she described as feeling of "heavy" legs; especially during summer months and after exercises.
9	12 male	11	1-2 times per month	Weakness in the whole body, mainly afternoon and early morning.
K	10 female	10	Very often, almost every day	Myopathy developed before muscle weakness attacks.

A few weeks after the genetic diagnosis the attacks of paroxysmal weakness occurred and the remaining family members underwent neurological and genetic examination. In this family the disease usually started between 3 and 14 years of age and muscle weakness occurs mainly after big efforts, carbohydrate-rich meals, alcohol, before menstruation and during exposure to stress. Total or partial paralysis has been observed in each family member and the episodes occurred mainly at night or early in the morning. The incidence of episodes occurrence ranged from 1-2 times per year to daily. The lowest incidence of occurrence could be noted in Patient 1 but in this case the incidence had been higher in the past. The most severe attack was noticed in Patient 1 after intravenous administration of glucose when paralysis of respiratory muscles developed (*Tab. 1*).

Microscopic examination was performed for Patient 7 which revealed HypoPP characteristic vacuolar myopathy and irregular tubular aggregates.

Discussion

HypoPP is a rare autosomal dominant disorder with the estimated occurrence of about 0.4-1/100 000 in the general population. The disorder is caused by mutations in calcium (CACNA1S) or sodium (SCN4A) channels; the mutations comprise intramembrane subunit and thus impair muscle cells excitability. The type 2 of HypoPP is caused by mutation in sodium channel (R669H, R672G, R672C or R672S) [3]. The most popular type 1 of HypoPP is caused by calcium channel mutations (70%) on 1q31-31 chromosome. The mutation impairs α1 subunit of Ca channels [4]. R1239H, R528H and R1239G (rarest) mutations have been described [5]. So far R1239G mutation has been found in two families. The basic symptoms of HypoPP are paroxysmal, total or partial weakness of skeletal muscles. Severity, incidence and duration of weakness differ between individuals depending on the type of affected channels and on the type of genetic defects in the same channel. Besides, phenotypic manifestations of the same genetic defect and in the same ion channel can differ between members of the same family as was the case in our study. Disease onset occurs in the first or second decade of life, most often between 15 and 35 years of age. Weakness can be provoked by carbohydrate-rich meals, sodium-rich meals, stress, alcohol, insulin intake and, particularly, the rest that follows strenuous physical effort from the preceding day [6,7]. Usually the attacks occur at night time and early in the morning. Increased incidence of the attacks during menstruation has been noticed. Weakness is most pronounced in the most recently exercised muscles. Involvement of respiratory muscles and arrhythmias are rare [8]. Onset, frequency and character of weakness observed in the family we have investigated is similar to earlier descriptions. Myopathy that occurs independently of frequency and severity of attacks can sometimes be observed [9] and it usually develops in advanced stage of the disease. The causes of the myopathy are not clear, though a probable cause could involve alterations in ionic concentrations, especially in intra- and extracellular Na and K concentrations. The case we report on confirms that myopathy can occur irrespective of the weakness attacks and changes in muscle cells can progress in the absence of persisting weakness. On the other hand, myopathy can develop before onset of periodical paralysis and not produce any symptoms at that stage. Although HypoPP is a rare disease it should be included in differential diagnosis not only if there is paroxysmal weakness but in all cases of myopathy of unknown origin.

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