Original Communication

Downbeat positioning nystagmus is a common clinical feature despite variable phenotypes in an FHM1 family

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Abstract

Clinical examination and mutational analysis were carried out in three patients of a Japanese familial hemiplegic migraine (FHM) pedigree. Each affected member demonstrated a broad clinical spectrum that included hemiplegic migraine with progressive cerebellar ataxia, migraine without aura, and episodic ataxia. Despite this variability, all members exhibited marked downbeat positioning nystagmus, and magnetic resonance images (MRI) all showed cerebellar atrophy predominantly of the cerebellar vermis. All affected members had a T666M missense mutation in the protein encoded by the *CACNA1A* gene (calcium channel, voltage-dependent, P/Q type, alpha 1A subunit). Although clinical features associated with the T666M *CACNA1A* mutation are highly variable, downbeat positioning nystagmus may be an important clinical feature of this disease.

Introduction

Mutations in the brain-specific P/Q type Ca^{2+} channel alpha1 subunit gene, *CACNA1A*, have been identified in three clinically distinct disorders, spinocerebellar ataxia type 6 (SCA6 MIM # 183086), episodic ataxia type 2 (EA2; MIM #108500), and familial hemiplegic migraine type 1 (FHM1; MIM #141500) [13],[21]. Point mutations are mostly responsible for its two allelic disorders, FHMI and EA2, while SCA6 is associated with small expansions of a CAG repeat at the 3' end of the gene.

Patients with the SCA6 also frequently experience episodes of vertigo and oscillopsia, and develop downbeat positioning nystagmus (DPN) [8],[12],[19],[21]. EA2 is characterized by episodes of cerebellar ataxia usually associated with migraine symptoms, interictal nystagmus, mild residual and in some cases a progressive cerebellar incoordination. Familial hemiplegic migraine (FHM) is characterized by episodes of recurrent hemiplegia during the aura phase of a migraine headache. The episodes may last for days and are associated with symptoms of sensory, language, or visual disturbances and variable degrees of somnolence, confusion, or coma. Molecular genetic studies have demonstrated the existence of three types of FHM: FHM1 with a mutation in *CACNA1A*, FHM2 (MIM #602481) with a mutation in the gene encoding the alpha-2 subunit of the sodium/potassium pump (*ATP1A2*), and FHM3 (MIM #609634) with a mutation in the gene encoding the alpha subunit of the sodium channel (*SCN1A*) [3], [4],[13].

Although gaze-evoked nystagmus is known to be frequent in FHM1 [6], DPN in patients with FHM1 has not gained much attention and the precise incidence has not yet been investigated. In the present study, we report a Japanese family with a T666M missense mutation in the protein encoded by *CACNA1A*. The affected members demonstrated a strikingly broad clinical spectrum that included hemiplegic migraine with

progressive cerebellar ataxia, migraine without aura, and episodic ataxia. Despite this variability, all members exhibited marked DPN.

Patients and Methods

The pedigree of our present family is shown in Figure 1.

Patient 1

A 46-year-old man, the proband of the family, had vertigo and oscillopsia that were more pronounced with changes in head posture, since about age 20. At the age of 36, he developed episodes of sudden onset hemiplegia with sensory disturbances on the left of his body followed by headache. The attacks occurred without warning or precipitating factors, and improved within 24 hours. The episodes occurred two to five times annually. At the age of 43, he developed a staggering walk. Neurological examination revealed moderate gaze-evoked nystagmus, severe DPN, dysmetria of both legs and ataxia of gait. Brain MRI demonstrated cerebellar atrophy, most marked in the vermis. The patient was diagnosed as having hemiplegic migraine. Treatment with acetazolamide (500 mg, two times daily) abolished the headaches, but did not improve the cerebellar ataxia or DPN.

Patient 2

A 78-year-old woman, the mother of the proband (Patient 1), was requested by telephone to visit our institution. She claimed that she had had no episodes of headache, vertigo or hemiplegia but experienced episodes of staggering gait and slurred speech about once annually since about 63 years of age; she did not seek medical attention as it was sufficient for her to lie down a day to relieve the episode. Neurological examination

disclosed mild gaze-evoked nystagmus, severe DPN, bilateral mild cerebellar ataxia in the heel-knee tapping test, and unstable tandem gait. Brain MRI revealed atrophy in the cerebellar vermis, milder than that in Patient 1. She complained of vertigo associated with DPN. She responded to an inquiry that she had continued to have episodic vertigo since she was young.

Patient 3

A 52-year-old man, a brother of Patient 1, was requested by telephone to visit our institution. He was not currently symptomatic, but admitted to migraine several times annually since his 20's. Neurological examination revealed mild gaze-evoked nystagmus, severe DPN, mildest bilateral cerebellar ataxia on the heel-knee tapping test, and unstable tandem gait. Brain MRI demonstrated atrophy of the cerebellar vermis, milder than that in Patient 1. He claimed to have vertigo accompanying the DPN, and in response to a questionnaire, that he had continued to have such a sensation since his teens.

The father of proband did not have any neurological deficits or migrainous episodes. We were unable to obtain information concerning the existence of hemiplegic migraine, cerebellar ataxia, or vertigo in the other relatives including parents and siblings of patient 2.

Methods of Genetic Analysis

All procedures of the study were approved by the Hokkaido University Ethics Committee and informed consent was obtained from all patients. Genomic DNA was prepared from peripheral blood monocytes of the patients according to standard

procedures. PCR primers used in this study were described by Ophoff [13]. DNA amplification was performed by PCR. All PCR products were purified using the QIA quick PCR Purification Kit (QIAGEN), and were directly sequenced using BigDye® Terminators v1.1 Cycle Sequencing Kit on an ABI 310 Genomic Analyzer (ABI). Expanded CAG triplet repeats in *CACNA1A* causing SCA6 were analyzed as described previously [18].

Results

The clinical features of our patients are summarized in Table 1. According to the International Classification of Headache Disorders, 2nd edition [9], patient 1 was, aside from a lack of Item-D (At least one first- or second-degree relative has had similar attacks), compatible with the diagnostic criteria of FHM. Patient 2 did not have a definite history of migraine, but the clinical picture, aside from a high age at onset, was consistent with episodic ataxia except [11]. Patient 3 had definite episodes of migraine without aura. These clinical features are suspected to result from a mutation in the *CACNA1A* gene, and PCR sequencing demonstrated that all three affected were heterozygous for the missense mutation T666M. We also investigated the expansion of CAG repeats within *CACNA1A* in the family, and all members were demonstrated to carry normal lengths of CAG repeats (data not shown).

Discussion

Although the T666M mutation is the most frequently identified mutation in *CACNA1A* among FHMs [6], [15], [17], the clinical phenotype of patients with the T666M mutation has been shown to be strikingly variable [1], [5], [15], [17]. Furthermore, many families

with mutations in *CACNA1A*, including T666M, have also been reported to suffer from progressive cerebellar ataxia [5], [6]. The family described here also showed a diverse range of clinical features, with variable degrees of cerebellar ataxia. In addition, there are no reports of patients with the T666M mutation being diagnosed with episodic ataxia [11]. These phenotypic variabilities may present difficulties in diagnosing FHM according to the criteria of the International Classification of Headache Disorders (2^{nd} edition) [9], which emphasizes the presence of FHM patients in the first or second generation of the proband patient. In the family described here, for example, it is difficult to diagnose patient 1 as having FHM by the proposed diagnostic criteria. Such familial cases have been reported previously [1], [15]. Accordingly, we suggest that the diagnostic criteria of FHM be revised in such a manner as to describe patients with cerebellar ataxia and/or various types of migraine including hemiplegic migraine in the first or second generation of the relevant family.

Interestingly, the affected members of this family had phenotypic variabilities in general, but shared DPN and vertigo that that had continued from young ages. There was no difference in the severity of DPN among our patients (data not shown). Although little information is available in the literature, this finding suggests an additional feature of FHM that may be relevant to the mutation in the *CACNA1A* gene. It is remarkable that DPN is also common in patients with the mutation responsible for SCA6 [19]. Some patients with EA2 have been also reported to have DPN [11]. We now report DPN in kindred with FHM1. This has not been reported previously, but is likely to represent a common effect of *CACNA1A* mutations. This needs to be confirmed in further FHM1 families. At present, the role of the cerebellum in developing DPN is not clearly established. Growing evidence suggests that an imbalance in the vertical vestibulo-ocular

reflex (vVOR) generates DPN [7],[20]. Purkinje cells, that are selectively involved in SCA6, are connected directly with the vestibular nucleus [20]. Previous investigations showed that Purkinje cells located mainly in the cerebellar flocculus and vermis played an important role in vVOR cancellation [2],[7],[20]. These regions are known to be severely affected in SCA6 [10]. Furthermore, VOR gain in SCA6 was shown to be within normal limits [14]. Thus, DPN in SCA6 was considered to be due to a dysfunction of vVOR cancellation.

A larger number of patients with FHM1 must be studied histopathologically to elucidate whether the DPN is due to a neural mechanism similar to that in SCA6. DPN is likely to be the earliest clinical manifestations of FHM1, which may provide important clinical signs. In addition, although DPN is recognized in patients with miscellaneous cerebellar disorders [2], it may be useful for diagnosing FHM1. Acetazolamide is already known to depress the paroxysmal symptoms of FHM1 [16],[17]. Among many patients with migraine, there may be patients similar to our patient 3. It is estimated that acetazolamide is more effective in such patients than is triptan. If DPN is confirmed in further cases of FHM1, it would be a useful criteria or symptom for rapidly diagnosing the disease. To define the frequency of this clinical feature, patients suspected of having FHM1 and all patients with *CACNA1A* mutations should be examined for the presence of positional DPN.

Acknowledgements

This work was supported in part by a Grant-in-Aid for the *Research Committee for Ataxic Diseases* of the Research on Measures for Intractable Diseases from the Ministry of Health, Welfare and Labor, Japan, by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan, by a Grant from the Kanae Foundation and by a Grant from the Uehara Foundation.

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Legends

Table 1. Clinical features of our patients

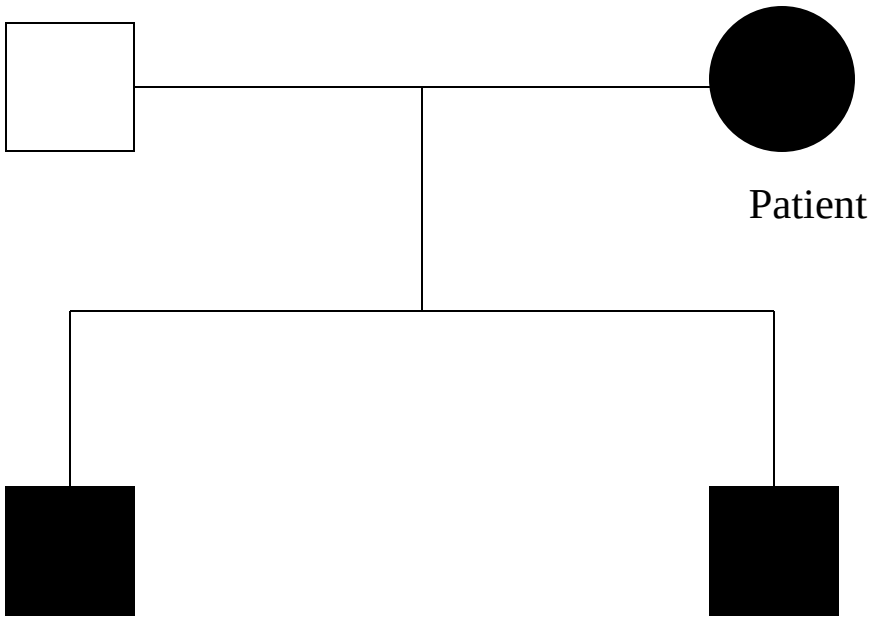
Figure 1. Pedigree of present family

□, man; ○, woman; / ; deceased. Solid symbols show affected subjects.

Table 1 Clinical features of our patients

	Patient 1	Patient 2	Patient 3
Present age (yrs)	46	78	52
Age at onset (yrs) of main clinical manifestation	36	63	20's
Age at onset (yrs) of vertigo and oscillopsia	20's	girlhood	teen's
Gaze nystagmus	moderate	mild	mild
Downbeat positioning nystagmus	severe	severe	severe
Cerebellar ataxia	moderate	mild	very slight
Headache attack	+	-	+
Cerebellar atrophy	moderate	moderate	mild
Main clinical manifestation	hemiplegic migraine	episodic ataxia	migraine without aura

Figure 1


Patient 2; episodic ataxia
Patient 3; migraine without aura
Patient 1; hemiplegic migraine