

Pseudomigraine With Lymphocytic Pleocytosis: A Calcium Channelopathy? Clinical Description of 10 Cases and Genetic Analysis of the Familial Hemiplegic Migraine Gene *CACNA1A*

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Objective.—To report the clinical findings of 10 patients diagnosed with pseudomigraine with lymphocytic pleocytosis and the results of mutational analysis of the *CACNA1A* gene in 8 of these patients.

Background.—Pseudomigraine with lymphocytic pleocytosis, also referred to as headache with neurologic deficits and cerebrospinal fluid lymphocytosis (HaNDL), is characterized by episodic transient neurologic dysfunction associated with moderate to severe headache and cerebrospinal fluid lymphocytic pleocytosis. Episodes are recurrent and the condition is self-limiting. The etiology of this sporadic condition remains unknown, but the episodic nature and its ability to be triggered by angiography is somewhat reminiscent of the phenotypic features of familial hemiplegic migraine, a condition caused by mutations in the *CACNA1A* gene.

Design/Methods.—Utilizing retrospective chart review, we describe the clinical features of pseudomigraine with lymphocytic pleocytosis in 10 patients. Whole blood was taken from 8 patients (2 were lost to follow-up) and used for DNA testing. The *CACNA1A* gene was screened for mutations using heteroduplex analysis and direct DNA sequencing.

Results.—Clinical features of pseudomigraine with lymphocytic pleocytosis included transient episodes of weakness, sensory and visual symptoms, aphasia, and confusion lasting minutes up to 4 hours. Sensory symptoms, typically affecting the face and arm, were the most common presentation. Localization of symptoms did not conform to vascular territories. Headache was typically throbbing and most often bilateral. Genetic analysis did not identify any mutations in the *CACNA1A* gene.

Conclusions.—Similarities between familial hemiplegic migraine and pseudomigraine with lymphocytic pleocytosis include recurrent headache with reversible neurologic deficit, cerebrospinal fluid lymphocytic pleocytosis, and triggers such as angiography. Even so, heteroduplex analysis and DNA sequencing failed to identify any sporadic mutations or shared polymorphisms in the exons or the intron/exon boundaries of the *CACNA1A* gene. These results do not support a role of the *CACNA1A* gene in the etiology of pseudomigraine with lymphocytic pleocytosis.

Key words: headache, pseudomigraine with lymphocytic pleocytosis (PMP), headache with neurologic deficits and cerebrospinal fluid lymphocytosis (HaNDL), *CACNA1A* gene

Abbreviations: PMP pseudomigraine with lymphocytic pleocytosis, FHM familial hemiplegic migraine
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Pseudomigraine with lymphocytic pleocytosis (PMP), also referred to as headache with neurologic deficits and CSF lymphocytosis (HaNDL), is an uncommon disorder characterized by episodic transient neurologic symptoms associated with moderate to severe headache and cerebrospinal fluid (CSF) lymphocytic pleocytosis.^{1,2} Pseudomigraine with lymphocytic pleocytosis appears to be more common in men and affects otherwise healthy individuals.³ Suggested diagnostic criteria include at least one episode of transient neurologic deficit accompanied or followed by moderate to severe headache, CSF pleocytosis with lymphocytic predominance, negative diagnostic studies, and spontaneous resolution of the clinical picture over a period of less than 4 months.^{2,3} Although most attacks of PMP occur spontaneously, angiography may be a trigger in some cases.²⁻⁴ Single photon emission computed tomography (SPECT) in patients with PMP has demonstrated a reduction of brain blood flow over the cortical region corresponding to neurologic deficits during the acute phase.⁵⁻⁷ These results are similar to SPECT studies performed in patients during migraine aura, and it has been suggested that the neurologic symptoms in PMP could be produced by spreading depression.⁶

Familial hemiplegic migraine (FHM) is an autosomal dominant disorder with features of migraine with aura. It is characterized by an aura of hemiplegia, which may also be associated with hemianopsia, hemisensory deficit, and aphasia followed by a moderate to severe headache.⁸ Cerebrospinal fluid lymphocytosis has been observed during attacks of FHM, and attacks can be triggered by minor head injury and angiography.⁸ Approximately 50% of reported families with FHM show genetic linkage to the α_{1A} subunit gene of the P/Q-type calcium channel (*CACNA1A*) gene on chromosome 19p13,⁸ and sporadic cases of hemiplegic migraine have been demonstrated to result from de novo *CACNA1A* mutations.^{9,10}

The neurologic symptoms, triggers, and CSF findings seen in PMP are similar to those seen in patients with hemiplegic migraine with mutations in the *CACNA1A* gene. The hypothesis that a mutation or a polymorphism in the *CACNA1A* gene may predispose individuals to PMP was tested.

METHODS

Utilizing retrospective chart review, we describe the clinical features of PMP in 10 patients.

Genetic Analysis.—Patients with a clinical diagnosis of PMP, who were able to provide informed consent, had venous blood taken for genetic analysis. Whole blood was used to extract DNA using standard techniques.⁹ Mutations known to cause FHM (R192Q, R195K, S218L, T666M, V714A, D715E, R583Q, T1385C, V1457L, I1811L, S218L) were initially screened using direct DNA sequencing.¹¹⁻¹⁵ The remainder of the *CACNA1A* gene was screened using heteroduplex analysis. Each of the 47 exons and their flanking intron/exon boundaries were polymerase chain reaction-amplified using primers previously described and were run on a heteroduplex gel.¹¹ If any migrational differences were detected, the DNA was sequenced. Sequencing was performed on an ABI 377 automated DNA sequencer. The sequences obtained from the patients with PMP were compared to the human genomic sequence of the *CACNA1A* gene in order to identify mutations or polymorphisms.

RESULTS

Patients.—Seven men and 3 women, with a mean age of 29 years (range, 20 to 51), were included in the study (Table). Clinical features included transient episodes of weakness, sensory and visual symptoms, aphasia, and confusion lasting minutes up to 4 hours. Sensory symptoms, typically affecting the face and arm, were the most common presentation. Localization of symptoms failed to conform to cerebrovascular territories. Headaches were most often described as bilateral, but could include unilateral and vertex presentations, with pain typically described as throbbing. The number of episodes ranged from 2 to 9, with a mean duration of 17 days (range, 7 to 36). Cerebrospinal fluid examination showed an elevated protein level and a lymphocytic pleocytosis in all cases (mean white blood count [WBC], 152/mm³; 95% lymphocytes). Events were preceded by viral illness or angiogram in 4 cases. None of the patients had a family history of hemiplegic migraine. Four of the patients described a family history of migraine without aura, and one patient had a prior history of migraine with visual

Clinical Features of Pseudomigraine With Lymphocytic Pleocytosis*

Patient	Age, y Sex	Symptoms	Precipitant	No. of Episodes	Duration of Episodes, days	CSF WBC, mm ³ (% lymphocytes)
1	28 M	Sensorimotor, Aphasia, Sometimes the L side was involved other times the R side	Viral Angiogram	9	20	108 (99)
2	33 M	Aphasia and bilateral peripheral vision loss, L-sided sensory symptoms, R visual field symptoms on one occasion	Viral Angiogram	3	17	67 (97)
3	28 M	Sensorimotor, Confusion, Symptoms spread from one side to the other over 20-45 minutes	No	3	13	140 (99)
4	51 M	Flashing wavy lines bilateral peripheral vision, R-sided sensory symptoms, Aphasia	No	4	29	31 (93)
5	22 F	Sensorimotor, Slurred speech, L-sided	No	3	7	143 (98)
6	31 F	Sensorimotor, Dysmetria, L-sided	No	3	9	122 (97)
7	27 M	Sensorimotor, Aphasia, Homonymous hemianopsia, R-sided	Viral	4	36	407 (96)
8	28 M	Sensorimotor, Aphasia, Homonymous hemianopsia, R-sided	No	4	13	118 (87)
9	20 F	Sensory, Homonymous hemianopsia, L-sided	No	2	8	159 (90)
10	22 M	Sensorimotor, Homonymous hemianopsia, L-sided	Viral	5	15	223 (90)

*CSF indicates cerebrospinal fluid; WBC, white blood count; L, left; R, right.

aura. No alternative etiology was found on investigations (which included CSF profile and microbiology, electrocardiogram, carotid ultrasound, echocardiogram, antiphospholipid antibody/anticardiolipin antibody, angiogram, and electroencephalogram). All patients had full neurologic recovery after each episode of headache and neurologic deficit.

Representative Case (Patient 3).—A 28-year-old, right-handed man was evaluated after 2 episodes of focal neurologic symptoms followed by headache. Both episodes involved bilateral sensory symptoms, with numbness gradually progressing up the right arm and right side of the head and then down the left side of the head and left arm over 20 minutes. His wife noted right facial weakness, unsteady gait, and confusion. This was followed by a severe, throbbing, vertex

headache associated with nausea and vomiting lasting 45 minutes. Neurologic examination 3 days later was normal. Four days later, he had a third similar episode of numbness and weakness of the right arm and face. Computed tomography of the brain and a bilateral carotid ultrasound were normal. Analysis of the CSF demonstrated an elevated WBC (140 cells/mm³; 99% lymphocytes), elevated protein level (1062 mg/L), and a normal glucose level (3.6 mmol/L). Cerebrospinal fluid, blood cultures, VDRL test, and anticardiolipin antibodies were negative. Magnetic resonance imaging (MRI) of the brain revealed multiple periventricular hyperintensities on T2- and proton density-weighted images, raising speculation about a vasculitic process, but a cerebral angiogram was normal. Follow-up MRI of the brain was unchanged, and no further episodes

occurred. The patient had a history of headaches as a child but not as an adult, and a positive family history of migraine without aura. No further episodes had occurred at last follow-up, 18 months after the initial event.

Genetic Analysis.—No mutations or shared polymorphisms were identified in the exons or the intron/exon boundaries of the *CACNA1A* gene in 8 patients with PMP. Two of the 10 patients were lost to follow-up and did not have genetic analysis performed.

COMMENTS

The syndrome of recurrent episodes of neurologic dysfunction followed by migraine-like headache with a CSF lymphocytic pleocytosis, seen in this series of 10 Canadian patients, is consistent with previous reports of PMP. Pseudomigraine with lymphocytic pleocytosis may be more common than previously recognized. Similarities between FHM and PMP include recurrent headache with reversible neurologic deficit, CSF lymphocytic pleocytosis, and triggers such as angiography. These similarities suggest that PMP may also be a calcium channelopathy. Although familial PMP has not been documented, the commonalities between FHM and PMP suggest that either a sporadic mutation or a polymorphism in the *CACNA1A* gene on 19p13 may predispose individuals to PMP. Even so, after screening the *CACNA1A* gene in the patients with PMP by heteroduplex analysis and sequencing, no mutations or shared polymorphisms were identified in the exons or the intron/exon boundaries of the *CACNA1A* gene. These results do not support a role of the *CACNA1A* gene in the etiology of PMP.

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