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Treatment of sporadic hemiplegic migraine with calcium-channel blocker verapamil

Wengui Yu, MD, PhD; and Steven H. Horowitz, MD

Abstract—Gene mutations within the P/Q type neuronal calcium channel in familial hemiplegic migraine (FHM) suggest a therapeutic role for calcium-channel blockade. The authors have previously reported abortive therapy of FHM with IV verapamil. Here the authors describe four cases of sporadic hemiplegic migraine (SHM) responsive to verapamil, administered either orally or IV. The findings indicate that verapamil is effective therapy for both SHM and FHM.

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Hemiplegic migraine was initially described in 1910 as a type of migraine consisting of recurrent headaches associated with transient hemiparesis.¹ There are two forms: familial and sporadic. Familial hemiplegic migraine (FHM) is an autosomal dominant disorder, the diagnosis of which is dependent upon first-degree family members having similar attacks. In the absence of family history, migraine attacks with accompanying motor weakness constitute sporadic hemiplegic migraine (SHM). Although hemiplegic migraine is well described in the literature, very little was known about its pathogenesis until 1996, when gene mutations within the P/Q type neuronal calcium channel $\alpha 1A$ subunit (CACN1A1) were identified in patients with FHM.² The possibility of calcium-channel dysfunction in FHM suggests a potential therapeutic role for calcium-channel blockade. In our previous report,³ we showed that IV verapamil reproducibly aborted acute attacks of hemiplegic migraine in a patient with FHM. Here we report four cases of SHM and their successful treatment with the calcium-channel blocker verapamil.

Case reports. Four women, aged 30 to 35, were diagnosed with SHM based on International Headache Society criteria. The clinical features are summarized in the table. All patients had classic migraine headaches beginning at age 11 to 18. Although each had a family history of migraine, no first-degree relative with migraine had accompanying attacks of hemiparesis. Each patient developed hemiparesis during severe attacks of migraine 1 month to 3 years before evaluation. Hemiplegic migraine attacks occurred 1 to 12 times per month, and lasted from minutes to 2 days. Three of the four patients had hemiparesis on the same side as the headache. The motor weakness ranged from 0/5 to 4/5 (Medical Research Council) during acute attacks. Extensive investigations, including CT, MRI/MRA, and EEG, all had normal results. Each patient had failed therapy with numerous migraine medications, including amitriptyline, propranolol, antiemetics, analgesics, narcotics, and triptans. Before the treatment with verapamil, all patients were screened with an electrocardiogram to rule out Wolff-Parkinson-White syndrome and other major conduction abnormalities.

Patient 1 was started on oral verapamil 120 mg/d. Patient 2 was started on a higher initial dose (120 mg twice a day) because she had 8 to 12 attacks/mo. Both patients became hemiplegic migraine free 1 to 2 weeks after initiation of verapamil treatment and remained headache free during 12-month follow-up periods.

Patient 3 experienced four hemiplegic migraine attacks a month, approximately half of which were associated with confusion and coma during the event. These clinical features resemble acetazolamide-responsive FHM.⁴ She was initially started on acetazolamide 250 mg twice a day. However, she could not tolerate that medication owing to dizziness and orthostatic hypotension. She was then given verapamil 120 mg/d for a week and 120 mg twice a day thereafter. She reported a more than 50% reduction in severity and frequency of hemiplegic migraine attacks within 1 month and started to resume outdoor activities for the first time in 3 years. She continued to improve and had only one severe attack with accompanying confusion and coma 9 months later while under stress. The dose of verapamil was then increased to 120 mg three times a day. She has only had occasional mild headaches without hemiparesis, confusion, or coma in the last 3 months.

Patient 4 had one to four hemiplegic migraine attacks per month for 7 months. Despite being refractory to other medications, including IV valproic acid, an acute attack responded to IV verapamil (5 mg over 5 minutes) with resolution of left-sided headache and ipsilateral weakness within minutes. IV verapamil was given under telemetry and blood pressure monitoring in the step-down unit of inpatient service without adverse effects. The patient experienced fewer and milder hemiplegic migraine attacks with an oral maintenance dose of verapamil (120 mg/d). Unfortunately, she reported frequent chest tightness while on verapamil and the medication was discontinued 2 months later. There was a gradual return to baseline hemiplegic migraine frequency with no improvement while receiving acetazolamide or topiramate.

Discussion. We describe four cases of SHM responsive to verapamil despite being refractory to other common migraine therapies. SHM is a rare disorder. However, to our knowledge, it is far more common than FHM, and frequent misdiagnosis suggests even greater prevalence. For example, three of the four patients in our report were initially diagnosed with transient ischemic attacks or mini-strokes by primary care physicians and other neurologists. Patient 3 was thought to have conver-

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Table Clinical features of patients with sporadic hemiplegic migraine

Characteristics	Patient			
	1	2	3	4
Sex/age, y	F/30	F/32	F/32	F/35
Age at onset, y, without/ with hemiparesis	11/30	14/30	12/29	18/34
Headache features				
Localization	Left side	Left temporal	Retro-orbital	Left frontal
Duration	4–5 h	Hours	Hours–2 d	Minutes–hours
Attacks/mo	1–6	8–12	4	1–4
Other symptoms	VA, N/V, P/P	VA, P/P	VA, N/V, P/P, C/C	VA, N/V, P/P
Evaluations	CT, LP	CT, MRI/MRA, EEG	CT, MRI, EEG	CT, MRI/MRA

All patients had left-side hemiparesis.

VA = visual aura; N/V = nausea/vomiting; P/P = photophobia/phonophobia; C/C = confusion/coma; LP = lumbar puncture; MRA = MR angiography.

sion disorder and was advised to see a psychiatrist by numerous physicians, including a neurologist. All of these patients went through extensive investigation including repetitive imaging studies. Therefore, increased awareness and early recognition of SHM is essential to minimize unnecessary testing, health care expenses, and patient frustration. If the history of migraine is evident and initial stroke workup is unremarkable, an early diagnosis of SHM should be possible.

Nevertheless, even after correct diagnosis, patients with SHM often seek emergent care owing to disabling attacks refractory to common migraine medications. Current therapeutic recommendations are based on isolated case reports: propranolol,⁵ phenytoin,⁶ flunarizine,⁷ and verapamil.⁸ Despite anecdotal use of verapamil, its efficacy has not been well documented. Recent identification of gene mutations within *CACNA1A* in FHM provide a theoretical basis for a therapeutic role of calcium-channel blockade. We have previously reported successful responses of hemiplegic migraine to IV verapamil in a patient with FHM.³ The current report indicates that verapamil, administered either orally or IV, is also effective for SHM. Genetic studies have revealed de novo mutation or incomplete penetrance of *CACNA1A* in patients with SHM,^{9,10} thereby suggesting that SHM may be part of the spectrum of FHM syndrome. Taken together, our

findings suggest that neuronal calcium-channel dysfunction may underlie the pathogenesis of both forms of hemiplegic migraine, and the calcium-channel blocker verapamil is an effective therapy for both disorders.

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