# Familial hemiplegic migraine and its abortive therapy with intravenous verapamil

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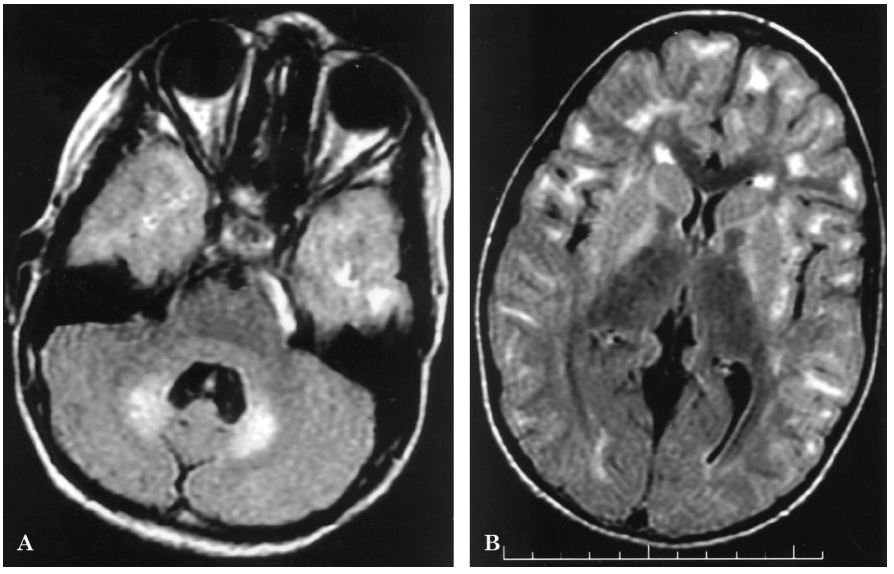


*Figure. Fluid attenuated inversion recovery MRI shows T2-hyperintensities in the subcortical white matter and the dentate.*



**References**

1. Duran M, Kamerling JP, Bakker HD, van Gennip AH, Wadman SK. L-2-hydroxyglutaric aciduria: an inborn error of metabolism? J Inherit Metab Dis 1980;3:11–15.
2. Barth PG, Hoffman GF, Jaeken J, et al. L-2-hydroxyglutaric acidaemia: a novel inherited neurometabolic disorder. Ann Neurol 1992;32:66–71.
3. Warmuth–Metz M, Becker G, Bendszus M, Solymosi L. Spinal canal stenosis in L-2-hydroxyglutaric aciduria. Arch Neurol 2000;57:1635–1637.
4. Barbot C, Fineza I, Diogo L, et al. L-2-hydroxyglutaric aciduria: clinical, biochemical, and magnetic resonance imaging in six Portuguese pediatric patients. Brain Dev 1997;19:268–273.
5. Topcu M, Erdem G, Saatci I, et al. Clinical and magnetic resonance imaging features of L-2-hydroxyglutaric aciduria: report of three cases in comparison with Canavan disease. J Child Neurol 1996;11:373–377.
6. D'Incerti L, Farina L, Moroni I, Uziel G, Savoiardo M. L-2-hydroxyglutaric aciduria: MRI in seven cases. Neuroradiol 1998;40:727–733.

## Familial hemiplegic migraine and its abortive therapy with intravenous verapamil

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

Familial hemiplegic migraine (FHM) is an inheritable subset of migraine headache with motor paralysis. In 1996, gene mutations within the P/Q gated neuronal calcium channel α1A subunit (CACNA1A) were identified in patients with FHM.[1] Subsequent genetic studies established multiple missense mutations in CACNA1A and genetic linkage to chromosomes 19p13 and 1q in various families with FHM.[2-4] These findings suggest calcium channel dysfunction and implicate a role for calcium channel blockers in the treatment of hemiplegic migraine. We report a case of FHM and its abortive therapy with IV verapamil.

*Case report.* A 28-year-old white woman had classic migraine headaches with visual aura since age 11. The headaches were throbbing in nature and accompanied by nausea and vomiting. They usually lasted for 3 to 4 hours and occurred every 4 to 5 months. However, during the past few months the patient started to have progressively more severe and frequent migraine attacks associated with left side hemiparesis and eyelid ptosis. She had no seizure activity, anisocoria, extraocular muscle weakness, or diplopia. At the time of assessment she averaged two episodes of left hemiparetic migraine headaches per day, each attack lasting for 3 to 4 hours, with left-sided strength 1/5 per Medical Research Council (MRC) Scale at the time the headache was most severe. Strength then returned to 4/5 (MRC) at the end of each migraine headache with mild weakness persisting between attacks. The patient had a family history of hemiplegic migraine. Her mother had migraine headaches at a young age, and her sister had severe migraine attacks with hemiparesis for several months a few years ago. The patient had an extensive workup, including CT, MRI/magnetic resonance angiography, cerebral arteriogram, and multiple EEG, the results of which were all negative. Although gene testing was not available for us to confirm the diagnosis, family history and clinical features were consistent with familial hemiplegic migraine. The patient's symptoms failed to improve despite therapy with amitriptyline, nonsteroidal anti-inflammatory drugs, propanolol, Duradrin (Duramed Pharmaceutical Inc., Cincinnati, OH), Imitrex (GlaxoWellcome, Research Triangle Park, NC), Zomig (Zeneca Pharmaceuticals, Wilmington, DE), Decadron (Merck & Co., West Point, PA), Neurontin (Parke-Davis, Morris Plain, NJ), and aspirin/butalbital/caffeine. Due to bradycardia secondary to the use of propanolol, the patient was started on a very low dose of verapamil (40 mg PO twice a day) after discontinuation of propanolol. However, oral verapamil at increasing doses up to 60 mg tid, IV Toradol (Roche Laboratories, Nutley, NJ), morphine sulfate, and dexamethasone were not effective. Nevertheless, the patient responded quickly to low dose IV verapamil (5 mg) (table). The first dose of verapamil was given by IV push over 2 minutes under cardiac monitoring. Initially, the patient felt some tightness in the chest and a flush in her forehead. Her headache, left hemiparesis, and ptosis resolved within a few minutes. Verapamil (5 mg) given by IV push within a few minutes to half an hour of migraine onset over 3 days reproducibly aborted each of five hemiplegic migraine attacks. Thereafter, as the patient received increasing doses of oral verapamil, the frequency of the attacks abated and she was discharged with a prescription for 120 mg bid. At 2-month follow-up, the patient reported only mild headaches with minimal left arm weakness occurring once a week. We speculate that both abortive therapy with IV verapamil and prophylactic treatment with a higher dose of oral verapamil were responsible for the subsequent improvement.

***Table*** *Effects of intravenous medications on familial hemiplegic migraine*

| IV medication* | Headache | Ptosis | Hemiparesis |
|---|---|---|---|
| Toradol | +/− | − | − |
| Morphine | +/− | − | − |
| Dexamethasone | +/− | − | − |
| Verapamil† | ++ | ++ | ++ |

* Doses were 60 mg (toradol), 2 mg (morphine sulfate), 4 mg (dexamethasone), and 5 mg (verapamil). Each medication was administered at least 3 times.
† Verapamil was administered under cardiac monitoring by IV push over 2 to 5 minutes.

− = No effect; +/− = mild effect; ++ = significant effect.

*Discussion.* Familial hemiplegic migraine is a rare and difficult-to-treat disorder. Serendipitously, oral flunarizine[5] and verapamil[6] were shown to prevent hemiplegic migraine even prior to the identification of gene mutations within the neuronal calcium channel. IV verapamil was shown recently to reverse the vasospasm during a hemiplegic migrainous process by transcranial duplex ultrasound.[7] Here we report a case of FHM and its successful abortive therapy with IV verapamil. Our patient had recurrent disabling hemiplegic migraine attacks that failed to respond to multiple medications, including IV Toradol, morphine sulfate, and dexamethasone. However, low dose IV verapamil reproducibly aborted headaches, ptosis, and hemiparesis within minutes. Although controlled study in large numbers of patients is necessary to evaluate the effect, our report suggests a role for IV verapamil and, possibly, other calcium channel blockers in the treatment of hemiplegic migraine attacks.

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### References

1. Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the $Ca^{2+}$ channel gene CACNL1A4. Cell 1996;87:543–552.
2. Ducros A, Denier C, Joutel A, et al. Recurrence of the T666M calcium channel CACNA1A gene mutation in familial hemiplegic migraine with progressive cerebellar ataxia. Am J Hum Genet 1999;64:89–98.
3. Battistini S, Stenirri S, Piatti M, et al. A new CACNA1A gene mutation in acetazolamide-responsive familial hemiplegic migraine and ataxia. Neurology 1999;53:38–43.
4. Carrera P, Piatti M, Stenirri S, et al. Genetic heterogeneity in Italian families with familial hemiplegic migraine. Neurology 1999;53:26–33.
5. Silver K, Andermann F. Alternating hemiplegia of childhood: a study of 10 patients and results of flunarizine treatment. Neurology 1993;43:36–41.
6. Razavi M, Razavi B, Fattal D, et al. Hemiplegic migraine induced by exertion. Arch Neurol 2000;57:1363–1365.
7. Ng TM, Kohli A, Fagan SC, et al. The effect of intravenous verapamil on cerebral hemodynamics in a migraine patient with hemiplegia. Ann Pharmacother 2000;34:39–43.

## Daily headache as a manifestation of lithium intoxication

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Drugs may cause headache or may exacerbate a preexisting headache disorder. The International Headache Society (IHS) groups them as "headaches associated with substances or their withdrawal."[1] When these drug-induced headaches have an abrupt development and do not remit, they are sometimes classified as "new daily persistent headaches."[2] We present a case of daily headache as the main clinical manifestation of lithium intoxication.

*Case report.* A 62-year-old white woman had had bipolar disorder for 12 years and had been treated with lithium carbonate (1200 mg daily), diazepam (5 mg daily), and thioridazine (25 mg daily) for 3 years. She had good control of the psychiatric symptomatology, showing only a mild depression. Her last manic exacerbation occurred 6 years previously. Two weeks before initial examination (12/99), she had daily bilateral, intense holocranial headache, which she described as being "heavy"; it was without photophobia but with phonophobia and nausea. On the day of examination the patient awoke with headache, and she reported that she was occasionally awakened during the night by headache. The patient did not remember any previous need for headache medication but had been taking analgesics several times a day since the onset of symptoms. Her family reported no alterations in her mood or behavior.

Ten days before the patient presented, she was seen by a psychiatrist who considered the symptomatology part of the basic disease exacerbation. Thioridazine was then replaced with pipotiazine (10 mg daily).

Examination showed that the patient was conscious, aware, and presenting extrapyramidal (bradykinetic gait with generalized, toothed-wheel rigidity) and cerebellar (staccato voice, discrete bilateral dysmetria) syndromes and globally alive stretch reflexes. The eye fundus was normal, and the cranial nerves showed no alterations.

Magnetic nuclear resonance examination and CSF tap including pressure measurement were also normal. Results of laboratory examinations were normal, except for a serum lithium concentration of 2.5 mEq/L (normal value up to 1.5 mEq/L).

The lithium carbonate concentration was then reduced. Lithium concentration was measured every 2 days for 10 days and then measured each week. One week later the patient was free of headache (lithium concentration of 1.4 mEq/L) and showed partial improvement in the extrapyramidal and cerebellar signs and symptoms. The patient was followed-up for 2 months and had no recurrence of headache (last lithium concentration of 1.3 mEq/L) and a normal neurologic examination (figure).

*Discussion.* Since lithium was introduced for the treatment of bipolar disorders in the 1950s, it has been considered the main therapeutic alternative for this type of disorder, although its therapeutic use has been extended to other psychiatric and neurologic diseases and to diseases of internal medicine.[3] Despite these applications, its mode of action is largely unknown. Lithium is known to interfere with circadian rhythms and REM sleep.[4] It has been suggested that lithium is able to induce inositol depletion, resulting in decreased production of inositol triphosphate (a second messenger) and other neuropeptides such as VIP and substance P, with repercussions on neuronal physiology. Lithium also seems to be involved in serotoninergic transmission.[5]

Adverse effects of lithium are not negligible and include weakness, nausea, tremor, staccato speech, confusion, nystagmus, extrapyramidal signs, convulsions, hypothyroidism, and others.[3]

It should be noted that, although the current patient showed an altered neurologic examination, it was the appearance of new daily headache that led to the visit.

Headache is rarely reported as an adverse effect of lithium therapy and has been secondary to idiopathic intracranial hypertension in cases previously described. In 9 of 10 well-documented cases, regression of the clinical picture and of CSF hypertension was observed after discontinuation of lithium carbonate. It has been proposed that lithium reduces fluid absorption by the arachnoid villi because of dysfunctional blockage of the sodium/potassium pump.[6] This probably was not the case in our patient: Fundoscopic examination was normal, and there was no alteration in CSF pressure.

In contrast, there are no reports in the literature regarding new daily headache related to lithium intoxication. Reports showed worsening of migraine control caused by lithium prophylaxis.[7] In contrast, our patient did not report previous headaches.

Lithium is frequently used in medical practice. We described the case of a new daily headache associated with lithium intoxication as the main clinical manifestation. Therefore, more attention

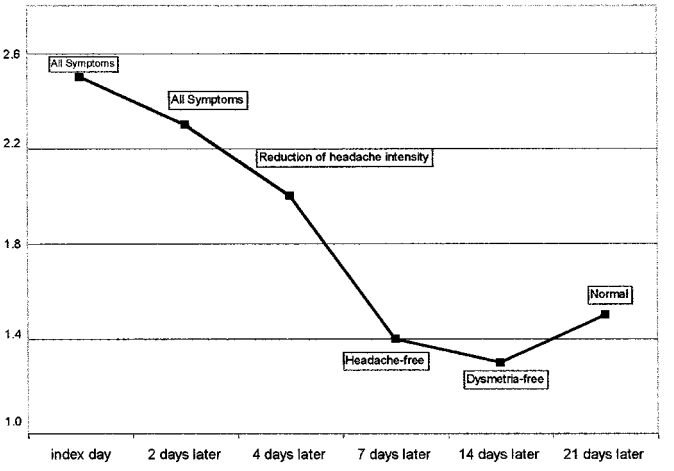


*Figure. correlation between serum lithium concentration and clinical manifestations.*