

Case report

# Hemiplegic migraine: Hyperperfusion and abortive therapy with intravenous verapamil

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## Abstract

A 20-year-old female with hemiplegic migraine was treated during an acute attack with intravenous verapamil, which reproducibly resolved the headache within 20 min but did not affect her hemiplegia. Magnetic resonance (MR) and computed tomographic (CT) angiography and perfusion performed during the attack showed vasodilation and hyperperfusion. Cerebral hyperperfusion concurrent with hemiplegia suggests a dissociation between cerebral perfusion and neuronal function in hemiplegic migraine. The beneficial effect of verapamil on headache but not hemiplegia suggests a distinct mechanism for pain and neuronal dysfunction in hemiplegic migraine, with the beneficial effect on pain not due to vasodilation.  
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## 1. Introduction

Much has been learned about migraine physiology and biochemistry but a causative mechanism has remained elusive [1,2]. At baseline, neocortical neurons are diffusely hyperexcitable in migraineurs. With aura onset, there is focal hyperemia followed by spreading oligemia (cortical spreading depression, CSD). The oligemic phase may last into the headache phase and correlates with neuronal dysfunction. Migraine pain is associated with peripheral and central trigeminal activation, dural inflammation and plasma extravasation, central sensitization, and abnormal nociceptive

neuromodulatory centers in the brainstem; vasodilation is seen inconsistently [1,2].

The mechanism of hemiplegic migraine may or may not be the same as that for classic migraine. We present a patient with recurrent hemiplegic migraines associated with cerebral hyperperfusion concurrent with and contralateral to the hemiplegia. Her headaches but not hemiplegia resolved promptly with intravenous verapamil.

## 2. Case history

A 20-year-old female, followed by our Pediatric Neurology service for many years, was admitted with a severe right-sided throbbing headache associated with dense left hemiplegia.

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She has had 7 prior hemiplegic migraine attacks, from age 8 months to 19 years, alternating body sides. Attacks lasted from 20 min to 14 days. A typical attack starts with a visual aura and progresses to obtundation and clonic seizures on the hemiparetic side. The most severe attack occurred at age 8 years; it began with aphasia and right-sided hemiplegia and progressed to quadriplegia, severe encephalopathy, and respiratory depression requiring intubation. Brain MRI prior to this attack was normal; MRI 6 weeks after this attack showed mild cerebral atrophy. Gross motor function gradually improved but residual right-sided weakness persisted for more than 12 months. Cognitive impairment became apparent after this attack. Currently 20 years old, she has a cognitive level equivalent to 12 years.

Cerebrospinal fluid analyses, amino and organic acids, muscle biopsy, and mitochondrial DNA panels were normal.

Past migraine prophylaxis included amitriptyline, nortriptyline, valproic acid, acetazolamide, propranolol, and oral verapamil, with no benefit. Migraine abortive medications included aspirin/butalbital/cafeine,

ibuprofen, acetaminophen, sumatriptan, dihydroergotamine, haloperidol, lorazepam, and intravenous and oral steroid bursts, all with partial and variable benefit. For seizure prophylaxis, she was treated with carbamazepine in the past and receives valproic acid currently.

Her mother has mild migraines with aura; one attack in her 20s was associated with inability to move one leg for less than a day. A maternal aunt has severe migraines without hemiplegia.

On day 1 of the current hospital admission, brain MRI with MR angiogram showed right hemisphere dural enhancement, mild swelling and dilated arteries (Fig. 1). Dynamic gadolinium-enhanced perfusion studies showed abnormally rapid transit times, elevated cerebral blood volumes, and high relative blood flow in the right hemisphere [3]. She was given intravenous haloperidol, lorazepam, valproic acid, dexamethasone and oral gabapentin, without benefit. She became obtunded. On hospital day 3, she was given 5 mg of intravenous verapamil over 5 min. Within 20 min of the dose, her mental status cleared and her headache resolved, but she remained hemiplegic. On hospital day 6, CT studies

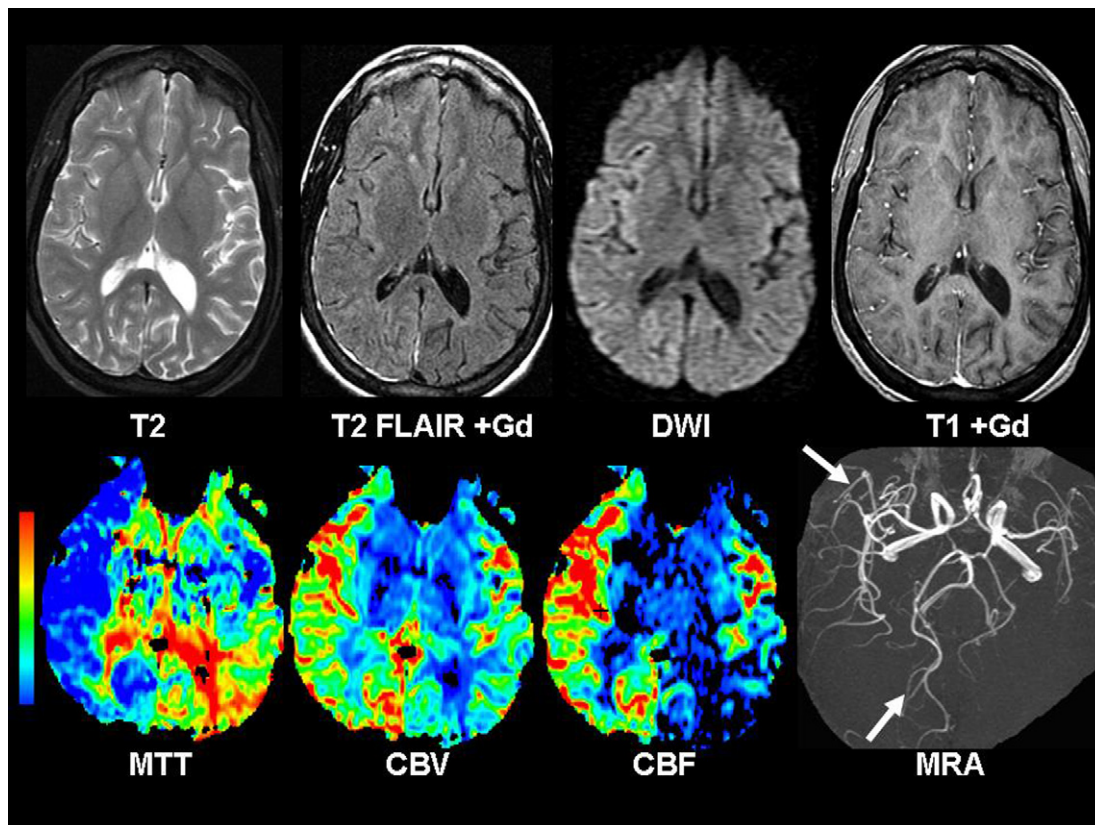


Fig. 1. MRI studies, day 1. There is subtle swelling of the right hemisphere, with slightly higher cortical signal on T2, T2 FLAIR, and diffusion-weighted images. Post-gadolinium (+Gd) images also show asymmetric dural enhancement over the right hemisphere. The perfusion parameter maps (rainbow scale; higher values toward red) show evidence for relative hyperemia in the right hemisphere: faster mean transit times (MTT), higher cerebral blood volumes (CBV), and elevated cerebral blood flow (CBF). Gross dilatation of right middle cerebral and posterior cerebral arteries is seen on MRA.

showed persistent cerebral vasodilation and persistent but less severe hyperperfusion in the right hemisphere (Fig. 2).

On hospital day 8, she redeveloped a right-sided headache. Intravenous verapamil again produced rapid resolution of the headache. Oral verapamil was started at 80 mg three times daily. By hospital day 11, strength began to return on her left side, but later that day, she developed a severe left-sided headache that resolved, for the third time, with intravenous verapamil.

She was discharged on hospital day 14 with intact, symmetric leg strength and mild left arm weakness. She was given extended-release verapamil 300 mg daily. CT studies at discharge showed resolution of vasodilation and hyperperfusion (Fig. 3).

Complications of this admission included one left-sided clonic seizure on hospital day 6 and one right arm clonic seizure with expressive aphasia on hospital day 11. Interictal EEGs showed diffuse slowing, more pronounced on the right, with no epileptiform discharges.

In the 2 years since discharge, two additional right-sided hemiplegic migraines were aborted with intravenous verapamil in a local emergency department; neither

episode required hospitalization. She continues on prophylactic verapamil, valproic acid, and gabapentin.

### 3. Discussion

Our patient had hyperperfusion with vasodilation of cerebral arteries ipsilateral to her headache, concurrent with contralateral hemiplegia. Cerebral hyperperfusion contralateral to hemiplegia has been previously reported in hemiplegic migraine [4,5] as well as in alternating hemiplegia of childhood [6–8].

Our patient's headaches were abolished by intravenous verapamil with no discernible effect on her hemiplegia. Use of intravenous verapamil has been previously reported in single cases of familial and sporadic hemiplegic migraine [9–11], although in two cases, hemiplegia resolved acutely as well as headache [9,10]. In our patient, the response to verapamil of headache but not hemiplegia suggests that the mechanism of headache and hemiplegia may be distinct, and that, in the setting of persistent hyperperfusion, the mechanism of verapamil in headache relief in our patient is not due to vasodilation.

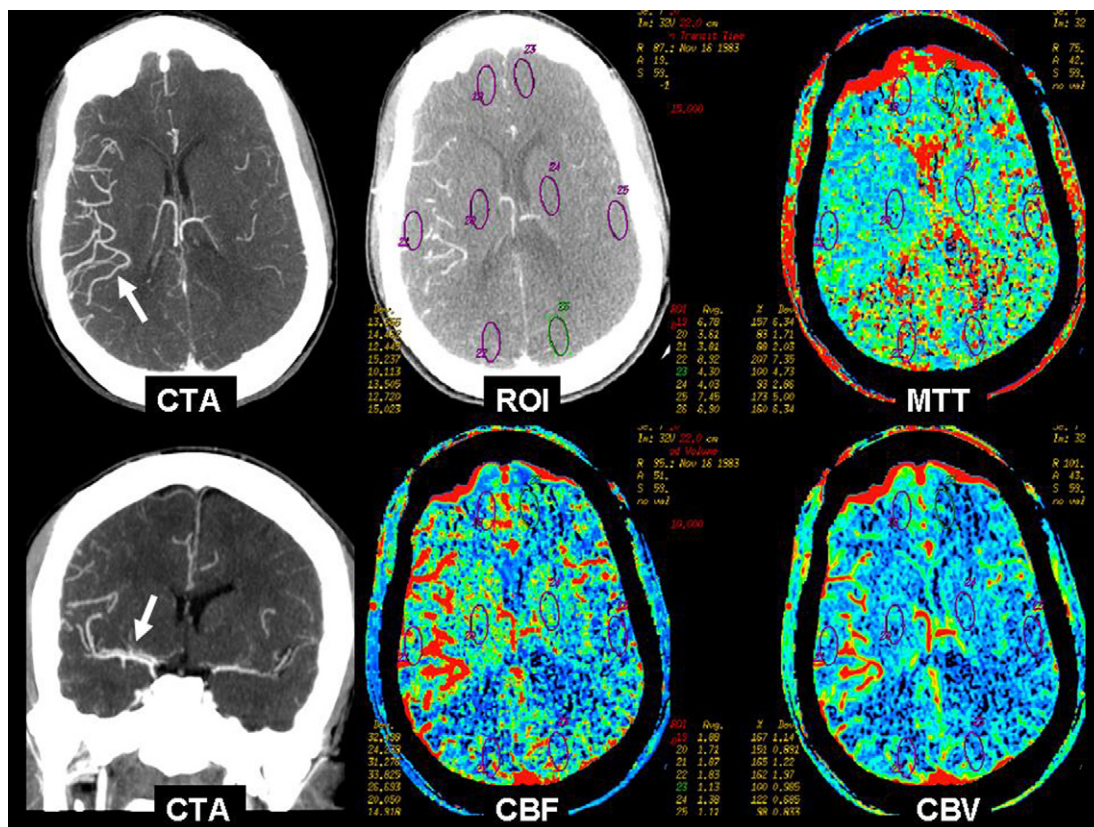


Fig. 2. CT studies, day 6. CTA (axial reconstruction, upper left, coronal lower left) shows persistent vasodilation in the right hemisphere (arrows). CT perfusion maps (same rainbow scale and abbreviations as defined in Fig. 1) show persistent but less severe relative hyperperfusion. Representative values comparing right to left for regions of interest (ROI) centered on the middle cerebral artery territory include MTT 3.8 vs. 7.4 s; CBV 1.9 vs. 1.1 ml/100 g; and CBF 38 vs. 14 ml/100 g/min.



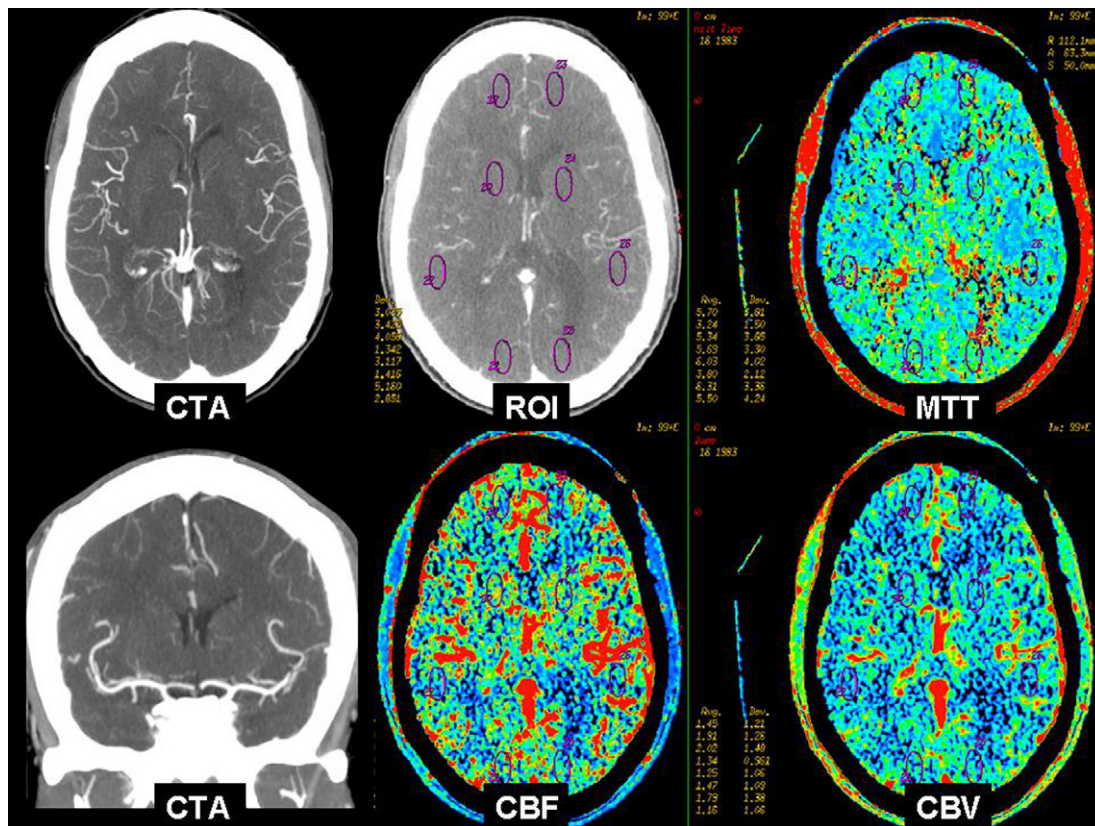


Fig. 3. CT studies, day 14. CTA (axial reconstruction, upper left, coronal lower left) shows symmetric, normal appearing vessels. Perfusion maps have also become qualitatively symmetric. Representative values comparing right to left for regions of interest (ROI) centered on the middle cerebral artery territory include MTT 5.7 vs. 5.5 s; CBV 1.3 vs. 1.8 ml/100 g; and CBF 19 vs. 22 ml/100 g/min.

Hemiplegic migraine and classic migraine may or may not share a common underlying mechanism, since the positive symptoms in classic migraine (e.g., the perception of visual scintillations) are associated with the initial focal hyperemia, while the negative symptoms (e.g., the perception of visual scotomas) are associated with the later oligemic phase (reviewed in Ref. [2]). The hyperemia is usually taken to be part of the pathophysiology of migraine, possibly related to neuronal hyperexcitability and to the extravasation of neuroactive proteins. In contrast, in our patient as in other patients with hemiplegic migraine, prolonged negative symptoms (hemiplegia and encephalopathy) are associated with hyperemia, not oligemia. Why should such striking negative symptoms be associated with hyperperfusion in hemiplegic migraine and not in classic migraine? It is possible that continued hyperperfusion leads to continued extravasation of neuroactive proteins, which then cause both headache and negative symptoms in hemiplegic migraine. But then why are negative symptoms in classic migraine associated with oligemia and not hyperemia?

Alternatively, the hyperperfusion seen in hemiplegic migraine, consisting of vasodilation of cerebral arteries and faster mean transit times with minimal evidence of

cerebral edema, may potentially represent a reaction to neuronal depression, and not the cause of it. That is, it may represent vascular recruitment in response to metabolic stress. In this case, one should be cautious about trying to reverse the hyperperfusion without reversing the underlying cause of neuronal depression.

A caveat is that our patient's clinical course, including seizures during her headache episodes and her cognitive delay, is rather more severe than in typical hemiplegic migraine. Therefore, the mechanism of our patient's symptoms may or may not be related to that of others with more typical hemiplegic migraine.

The differential effect of verapamil on headache and hemiplegia may lie in the different roles played by P/Q-type calcium channels in the brain [2]. P/Q-type calcium channels in neocortex are involved in the initiation and spread of CSD. Prophylactic blockade of these channels might decrease neuronal cortical excitability and increase resistance to CSD. P/Q-type calcium channels also modulate brainstem nociceptive centers. Thus, intravenous verapamil may act more directly on the brainstem nociceptive pathway, while CSD, once triggered, may not respond to P/Q-type channel blockade. Although verapamil is classically an L-type calcium channel blocker, at higher doses it can also block

P/Q-type channels [12]. The reason that our patient previously failed on oral verapamil as prophylaxis may be that she did not achieve high enough central nervous system concentrations to effect P/Q-type channel blockade. An intravenous route may be necessary to achieve levels high enough to abort an attack. Similarly oral gabapentin (at 600 mg every 6 h) did not work for our patient possibly because it is not reliably absorbed through the oral route, particularly during a migraine attack, and insufficient levels were achieved in the central nervous system.

#### 4. Conclusions

In hemiplegic migraine, headache and hyperperfusion are associated with contralateral hemiplegia, suggesting that hyperperfusion may be a reaction to neuronal dysfunction. In our patient, headache and encephalopathy, but not hemiplegia, rapidly reversed with intravenous verapamil, suggesting that the mechanism of headache and hemiplegia may be distinct and that, given concurrent hyperperfusion, the mechanism of headache relief may not be due to vasodilation.

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