

25-Year-Old Man With Recurring Headache and Confusion

FATTA B. NAHAB, MD*; GREGORY A. WORRELL, MD, PhD†; AND BRIAN G. WEINSHENKER, MD‡

A 25-year-old right-handed man was brought to our emergency department because of confusion and right arm and right leg weakness. Two days earlier, during an evening meal, he developed a severe left-sided headache that lasted several hours and forced him to bed; he was afebrile and had no other neurologic symptoms. He had “migraines” in the past that occurred only once a year. He also had frequent, less severe headaches that were controlled with aspirin. He suspected that the current headache was a migraine. On the evening of onset of the headache, he was examined at his local emergency department; he was afebrile and had no focal neurologic findings. Findings on a computed tomographic (CT) scan without contrast were normal. He was treated with ketorolac methamine, hydroxyzine, and sumatriptan and discharged.

The next morning, the patient’s headache had not resolved. His temperature was 38.6°C, and his physician prescribed ceftriaxone. Throughout the rest of the day, his headache did not improve. Family members noted that the patient appeared “confused.” The next morning, 2 days after onset of the headache, the patient’s family brought him to our emergency department because of worsening confusion, disorientation, and unsteadiness when walking.

A general examination revealed an athletic man in no acute distress. He was afebrile, and vital signs were normal. He was drowsy and inattentive; neglect of his right hemispace was apparent. He had nonfluent aphasia with poor naming and repetition and followed only simple 1-step commands. The patient was able to move all 4 extremities spontaneously, although he moved his right arm and leg less than his left arm and leg. A pronation drift of the outstretched right upper extremity was evident. Reflexes were symmetrical, and the plantar responses were flexor. No nuchal rigidity was noted. A complete blood cell count was unremarkable, and no leukocytosis was present.

*Visiting student from Loma Linda University School of Medicine, Loma Linda, Calif.

†Resident in Neurology, Mayo Graduate School of Medicine, Mayo Clinic, Rochester, Minn.

‡Adviser to student and resident and Consultant in Neurology, Mayo Clinic, Rochester, Minn.

See end of article for correct answers to questions.

Individual reprints of this article are not available. Address correspondence to Brian G. Weinschenker, MD, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (e-mail: weinb@mayo.edu).

1. Which one of the following diagnoses is most likely in this patient?

- a. Encephalitis
- b. Subarachnoid hemorrhage (SAH)
- c. Meningitis
- d. Migraine with prolonged aura
- e. Seizure

Headache, altered level of consciousness, and confusion are consistent with each of these diagnoses. Encephalitis, specifically herpes simplex encephalitis, seems most likely considering the sequence: headache followed by fever and confusion accompanied by focal neurologic findings. However, our patient did not have a fever at the earliest presentation, and 92% of patients with confirmed herpes encephalitis have fever on presentation.¹

Subarachnoid hemorrhage usually presents with a sudden, severe “thunderclap” headache, often accompanied by vomiting, altered consciousness, and focal neurologic deficits. Our patient had some of these symptoms, but the temporal course of the headache, which developed over several hours, makes SAH less likely. Furthermore, no meningism was evident. The normal findings on a CT scan make SAH less likely. The sensitivity and specificity of a CT scan without contrast for SAH are high,² approximately 93% for patients seen within the first day of onset of the headache. This high sensitivity decreases to 50% after day 5 and to zero by day 10. A cerebrospinal fluid (CSF) examination to search for xanthochromia, the breakdown product of hemoglobin, is usually indicated to rule out SAH when the index of suspicion is high and findings on a CT scan are normal.

Meningitis, regardless of the cause, typically presents with fever, headache, altered level of consciousness (less common with aseptic viral meningitis), nuchal rigidity, nausea, and vomiting. The absence of meningeal irritation and the lack of persistent fever make this possibility less likely. Furthermore, meningitis is associated with focal neurologic findings in only 15% of patients. Therefore, meningitis is unlikely but is possible.

Migraine with prolonged aura refers to a migraine symptom complex accompanied by neurologic deficits that persist for more than 1 hour but fewer than 7 days. Complicated, hemiplegic, ophthalmic, hemisensory, aphasic, basilar, and confusional migraine are all part of the migraine

with aura category according to the current International Headache Society classification system; however, some of these disorders are clinically distinct, and the underlying genetic basis has been established for others. A neurologic deficit secondary to migraine is a diagnosis of exclusion. The following entities should also be ruled out: head trauma, vascular and nonvascular disorders, substance withdrawal, noncephalic infection, metabolic disorder, and disorders of the cranium, neck, eyes, nose, sinuses, teeth, and mouth.³ Migraine would not explain the patient's fever, but the fever did not persist and was absent when he was evaluated at our emergency department. At this point, migraine with prolonged aura should be kept in the differential diagnosis, although encephalitis seems more likely.

No tonic-clonic seizures were witnessed despite close observation of the patient. While postictal confusion may be associated with focal findings that mimic acute encephalopathy or encephalitis, this confusional state usually recedes over several hours. Possibly, this patient had non-convulsive status epilepticus, but it is atypical for status epilepticus to be preceded by headache.

On presentation to our emergency department, the patient was given intravenous acyclovir therapy because of the possibility of herpes encephalitis. Computed tomography, lumbar puncture, and electroencephalography (EEG) were performed. The CT scan suggested subtle effacement of the sulci of the left cerebral hemisphere. Analysis of the CSF revealed the following: opening pressure, 9 cm H₂O (reference ranges shown parenthetically) (8-20 cm H₂O); total nucleated cells, 1/mL (<5/mL); erythrocytes, 1/mL; protein, 29 mg/dL (14-45 mg/dL); glucose, 76 mg/dL; negative gram stain; and no xanthochromia. The EEG suggested diffuse left hemisphere dysfunction with delta frequency activity but no epileptiform discharges. The patient was admitted to the hospital for further evaluation, which included cranial magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) of the head and cervical vessels, and magnetic resonance venography (MRV). The MRI scan (Figure 1) showed a diffuse high signal throughout the left cerebral hemispheric gray matter, best seen on the fluid attenuated inversion recovery images, along with widening of the gyri and obliteration of the sulci secondary to lateralized cerebral edema. Findings on MRA and MRV were normal.

2. Based on the laboratory and neuroimaging findings, which one of the following diagnoses is now most likely in this patient?

- a. Cerebral venous thrombosis (CVT)
- b. Acute arterial infarct
- c. Migraine with prolonged aura
- d. Encephalitis
- e. Mitochondrial encephalopathy

Often, a clue to the diagnosis of CVT is a hemorrhagic infarct that does not pertain to a single arterial territory or an elevated CSF opening pressure. Thus, CVT is unlikely in our patient. Moreover, CVT is unlikely with normal findings on MRV. In a patient with a unilateral headache and focal neurologic deficit referable to the same hemisphere, a carotid or vertebral dissection leading to arterial infarction should be considered. A major cerebral arterial infarction can produce a similar picture on CT, with hemispheric edema and obliteration of sulci as the earliest findings; however, the MRI appearances in our patient are atypical for an arterial infarct in light of the wide extent of the cortical changes without apparent involvement of the subcortical white matter. The normal findings on MRA of the head and neck vessels make arterial dissection unlikely. Furthermore, although unilateral, the MRI changes do not pertain to the territory of any single major vessel, as would be expected with an embolic or thrombotic cerebral infarction.

Migraine with prolonged aura is a diagnosis of exclusion. Based on the normal findings on CSF analysis and the subtle MRI abnormalities, this is the most likely diagnosis. Similar MRI findings have been reported in patients with migraine with aura.

The extensive involvement of the cortical ribbon over the entire hemisphere is unusual in viral encephalitis. Herpes simplex encephalitis is associated with focal MRI abnormalities, but these abnormalities are usually in the medial temporal structures. The normal CSF results argue against encephalitis.

Mitochondrial encephalopathies are inherited disorders associated with mitochondrial dysfunction. Mitochondrial disorders are often associated with myopathy and lactic acidosis. The imaging changes most commonly seen in the brain in patients with MELAS (*m*itochondrial *e*ncephalopathy, *l*actic *a*cidosis, and *s*troke-like episodes) syndrome are multifocal cerebral infarcts, rather than confluent signal changes involving the cortical ribbon of an entire hemisphere.

On further discussion with family members, we discovered that the patient had a history of recurrent events similar to the current episode. At 1 year of age, he fell from a chair, sustaining minor head trauma; a protracted course of emesis required hospitalization for rehydration. At 9 years of age, the patient was hit in the head by a ball; over the course of several hours, he developed headache, nausea, vomiting, and confusion. He was hospitalized for 1 week; during that time, CSF analysis and head CT showed normal findings, but EEG demonstrated diffuse left hemispheric delta activity, suggesting diffuse left hemisphere dysfunction. Over the course of hospitalization, the patient's symptoms resolved completely. At 10 years of age, the patient fell from a tree, sustaining minor head trauma; a severe headache, nausea, vomiting, and confusion developed. An EEG demonstrated right hemispheric delta frequency activity.

A detailed family history revealed that the patient's mother had migraine headaches. A maternal first cousin also had recurrent headaches associated with transient aphasia and motor neurologic deficits requiring hospitalization.

3. With the information obtained thus far, which one of the following disorders is most likely in this patient?

- a. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- b. MELAS
- c. Familial hemiplegic migraine (FHM)
- d. Antiphospholipid-antibody syndrome (APLAB)
- e. Syndrome of headache, neurologic deficit, and CSF lymphocytosis (HaNDL)

Recurrent migraine is common to CADASIL, MELAS, FHM, HaNDL, and APLAB. The inherited disorders CADASIL and MELAS are consistent with a family history that could be explained by autosomal dominant or mitochondrial inheritance. However, the lack of a progressive neurologic decline in our patient argues against these 2 diseases. In addition, the relatively subtle abnormalities on MRI are not consistent with CADASIL or MELAS. In these conditions, patients ultimately experience dementia. Patients with CADASIL have substantial white matter abnormality on MRI, an abnormality not present in our patient. Characterized by recurrent migraine and hemiplegia, FHM is a genetic disorder, and often there is a strong family history. Results of laboratory and imaging studies are relatively unremarkable, although subtle imaging findings, as in our patient, have been reported. Patients with FHM recover completely from each episode. In our patient, FHM is the most likely diagnosis. His clinical presentation is typical for FHM, which has an autosomal dominant inheritance pattern with variable penetrance. Antiphospholipid-antibody syndrome, like MELAS and CADASIL, should also be considered in the differential diagnosis of migraine accompanied by stroke. Our patient's radiological findings were unlike those typically seen in patients with APLAB, which usually show ischemic strokes. HaNDL, a migrainous syndrome with CSF pleocytosis and focal neurologic deficits, has a benign course.⁴ Our patient's normal CSF results during a clinical episode make this diagnosis unlikely.

Based on the patient's family history and findings on imaging and laboratory studies, FHM was diagnosed.

4. Which one of the following tests would help to confirm the diagnosis made in this patient?

- a. Muscle biopsy
- b. Antiphospholipid antibodies
- c. Skin biopsy
- d. Temporal artery biopsy
- e. Genetic mutation testing and linkage studies

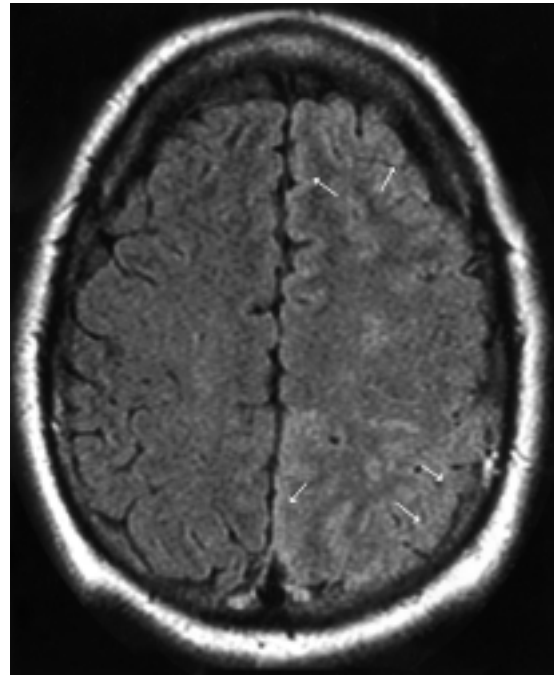


Figure 1. Magnetic resonance fluid attenuated inversion recovery image reveals hyperintensity (arrows) diffusely throughout the cortical gray matter of the left hemisphere. Effacement of the cortical sulci in the left hemisphere is due to edema.

A muscle biopsy would help to confirm a mitochondrial encephalomyopathy such as MELAS, which might present with recurrent migraine attacks and stroke. Antiphospholipid antibodies, including anticardiolipin antibodies, may be found in systemic autoimmune disorders such as systemic lupus erythematosus and can be associated with arterial and venous strokes. A skin biopsy might be useful in the diagnosis of CADASIL. A superficial temporal artery biopsy may help to confirm an inflammatory vasculopathy.

Based on our patient's symptom complex, the most likely diagnosis is FHM. Direct mutation analysis or, if unrevealing, genetic linkage studies are indicated to determine whether the patient has inherited a causative mutation in either of the known loci for FHM in chromosome 19p or 1q31.

The patient made steady improvement over the course of hospitalization. He was discharged and had only a subtle aphasia. At follow-up 2 weeks later, findings on examination were normal.

5. Which one of the following medications is least appropriate for this patient if he experiences a future attack?

- a. Sumatriptan
- b. Prochlorperazine
- c. Nonsteroidal anti-inflammatory drugs
- d. Verapamil
- e. Acetazolamide

Many options exist to treat acute migraine. Among the most potent and specific agents are dihydroergotamine and triptan drugs, the prototype of which is sumatriptan. The use of serotonin agonists and ergot derivatives is contraindicated in the treatment of FHM since transient hemiplegia and ischemic stroke are possible complications.^{5,6} Prochlorperazine, a dopamine antagonist with antiemetic properties, and nonsteroidal anti-inflammatory drugs are useful for early treatment of migraine. Long-term prophylactic treatment to reduce the frequency of migraine includes the use of calcium channel antagonists such as verapamil. Some reports have also described patients with specific *CACNA1A* gene mutations on chromosome 19 who responded to acetazolamide.⁷

DISCUSSION

First described by Clark⁸ in 1910 as recurrent motor paralysis in migraine, FHM was poorly understood until the past decade. Genetic linkage analyses have clarified the pathogenesis of the disease and suggest that it is a calcium channelopathy in a high proportion of cases.

Attacks typically begin in childhood and are frequently precipitated by minor head trauma that leads to alterations in consciousness, ranging from confusion to coma. Hemiparesis is frequently mild, and confusion or aphasia dominates the clinical picture. Recurrent encephalitis is commonly diagnosed. The focal features are a component of the aura and last less than 1 hour to days or weeks before complete resolution. Usually, no sequelae are permanent. However, 20% to 40% of patients with the 19p calcium channel mutation have progressive cerebellar atrophy.⁹

Because of the broad differential diagnosis of acute encephalopathy, FHM can be difficult to diagnose. When confusion punctuated by acute attacks of migraine dominates the clinical picture, other entities to consider are MELAS, CADASIL, and APLAB. This case shows how clinical and radiological assessments, such as MRI with fluid attenuated inversion recovery sequences, can distinguish among these entities. Electroencephalography may also be useful in identifying lateralized hemispheric high-voltage, slow-wave activity, but this finding is nonspecific and can be seen in various focal encephalitides. Several patients with FHM have been studied with transcranial Doppler ultrasonography or angiography to assess cerebral blood flow both during and after the headache phase and were found to have unstable cerebrovascular tone with wide rapid fluctuations in cerebral blood flow. Whereas initial phases of vasodilatation are likely responsible for the migrainous headache, vasoconstriction that leads to ischemia is responsible for the subsequent neurologic deficits.^{10,11}

Once the diagnosis of FHM is established clinically, the mutation status of the proband and other family members

can be assessed directly. Direct mutation testing can be performed in a limited number of research institutions that use allele-specific polymerase chain reaction and single-strand conformational polymorphism analysis to screen for common missense mutations.¹² When no mutations are found, linkage analysis may help to detect the responsible locus if sufficient numbers of affected and unaffected persons in the pedigree are identified and agree to participate. Mutations in chromosomes 1 and 19 have been described in affected families with 50% of pedigrees linked to a chromosome 19p13 locus encoding the *CACNLIA4* gene, a neuronal voltage-gated calcium channel α subunit. Several causative mutations have been identified in different families. Major deletions, missense mutations, and trinucleotide repeats in this gene cause episodic ataxia type 2, FHM, and spinocerebellar ataxia type 6, respectively.⁹ In our patient, direct mutation testing for 5 specific mutations and single-strand conformational polymorphism analysis of 2 other exons failed to reveal a mutation in selected exons of the *CACNLIA4* gene. The number of affected and unaffected persons available for linkage analysis was insufficient.

REFERENCES

- Whitley RJ. Herpes simplex virus. In: Scheld WM, Whitley RJ, Durack DT, eds. *Infections of the Central Nervous System*. 2nd ed. Philadelphia, Pa: Lippincott-Raven Publishers; 1997:73-89.
- Sames TA, Storrow AB, Finkelstein JA, Magoon MR. Sensitivity of new-generation computed tomography in subarachnoid hemorrhage. *Acad Emerg Med*. 1996;3:16-20.
- Olesen J, Lipton RB. Migraine classification and diagnosis: International Headache Society criteria. *Neurology*. 1994;44(6, suppl 4):S6-S10.
- Bartleson JD, Swanson JW, Whisnant JP. A migrainous syndrome with cerebrospinal fluid pleocytosis. *Neurology*. 1981;31:1257-1262.
- Luman W, Gray RS. Adverse reactions associated with sumatriptan [letter]. *Lancet*. 1993;341:1091-1092.
- Rose FC. Adverse reactions and sumatriptan [letter]. *Lancet*. 1993;341:1663-1664.
- 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.
- Clark J. On recurrent motor paralysis in migraine. *BMJ*. 1910;1:1534-1538.
- Gardner K, Hoffman EP. Current status of genetic discoveries in migraine: familial hemiplegic migraine and beyond. *Curr Opin Neurol*. 1998;11:211-216.
- Friberg L, Olsen TS, Roland PE, Lassen NA. Focal ischaemia caused by instability of cerebrovascular tone during attacks of hemiplegic migraine: a regional cerebral blood flow study. *Brain*. 1987;110(pt 4):917-934.
- Pierelli F, Pauri F, Cupini LM, Fiermonte G, Rizzo PA. Transcranial Doppler sonography in familial hemiplegic migraine. *Cephalalgia*. 1991;11:29-31.
- Ophoff RA, Terwindt GM, Vergouwe MN, Frants RR, Ferrari MD, Dutch Migraine Genetics Research Group, Wolff Award 1997: involvement of a Ca^{2+} channel gene in familial hemiplegic migraine and migraine with and without aura. *Headache*. 1997;37:479-485.

Correct answers: 1. a, 2. c, 3. c, 4. e, 5. a