Clinical Reasoning:
A 48-year-old woman with recurrent headache, transient neurologic symptoms, and CSF pleocytosis

SECTION 1
A 48-year-old woman was admitted to our department with recurrent episodes of throbbing right parietal headache lasting for hours. The patient was afebrile and neurologic examination disclosed no signs of meningeal irritation or papilledema. Blood pressure (BP) levels and heart rate were normal (<140/90 mm Hg, 70 bpm) on repeat measurements.

Before onset of headache she experienced a transient sensory deficit on the right half of her body. The patient reported having the first episode of headache 2 weeks prior to admission, while on a trip in Colombia. The pain was of pulsating nature and was aggravated by physical activity. She occasionally reported that the headache was accompanied by nausea, vomiting, alldynia of the skin of the head, and phonophobia and photophobia. The headache attacks were not preceded by any symptoms of aura and were relieved by nonsteroid inflammatory drugs followed by periods of rest and sleep. The headache episodes lasted less than 24 hours and the patient recovered completely from her symptoms. The patient had no history of headaches and no family history of migraine.

Questions for consideration:
1. What is your differential diagnosis at this time point?
2. What additional diagnostic tests would you consider at this time point?
SECTION 2
The differential diagnosis included meningoencephalitis, temporal arteritis, cerebral venous sinus thrombosis (CVST), intracranial bleeding, reversible vasoconstriction syndrome, and posterior reversible encephalopathy.

The patient underwent immediate brain MRI during her present hospitalization. Axial T2, fluid-attenuated inversion recovery, T1-weighted imaging, 2-dimensional time-of-flight cerebral magnetic resonance angiography (MRA), and diffusion-weighted imaging sequences were negative for acute cerebral ischemia, posterior reversible encephalopathy, vasoconstriction syndrome, and intracerebral bleeding, and no signs of CVST were observed.

The initial EEG showed slowing over both occipital lobes with no epileptiform activity (figure, A). The duplex and Doppler sonography of the cerebral vessels and the external temporal artery revealed no signs of cerebral vasospasm or temporal arteritis (halo sign). The CSF examination documented a lymphocytic pleocytosis with 14 cells (100% lymphocytes), normal protein (462 mg/L), pressure (60 mm H₂O), glucose (85 mg/dL), and lactate (16 mg/dL). HIV, syphilis, and sarcoidosis testing (angiotensin-converting enzyme in serum and CSF, chest X-ray) were negative and cytology/flow cytometry studies had normal results. The patient was placed on IV acyclovir medication at dosage of 3 × 10 mg/kg body weight until we received the negative CSF PCR results of herpes simplex virus 1 and 2, varicella zoster, cytomegalovirus, and Epstein-Barr.

Question for consideration:
1. Which is the final diagnosis?
SECTION 3

Her neurologic condition was attributed to a pseudomigraine with transient neurologic deficit and lymphocytic pleocytosis. Consequently she received an IV therapy with 250 mg methylprednisolone/day. The pseudomigrainous headache improved substantially within 48 hours. Repeat EEG was then normal (figure, B).

DISCUSSION

The patient fulfilled the criteria of the International Headache Society for the syndrome of transient headache and neurological deficits with CSF lymphocytosis (HaNDL), which should always be considered in the differential diagnosis of headache with transient neurologic symptoms. The diagnostic criteria consist of 1) episodes of moderate to severe headache lasting hours before resolving fully, 2) CSF pleocytosis with lymphocytic predominance (>15 cells/μL) and normal neuroimaging, CSF culture, and other tests for etiology, 3) episodes of headache are accompanied by or shortly follow transient neurologic deficits and commence in close temporal relation to the development of CSF pleocytosis, 4) episodes of headache and neurologic deficits recur over <3 months.

Our diagnostic evaluation in combination with the patient’s history excluded other causes of transient neurologic dysfunction accompanied by headache including meningoencephalitis, CNS vasculitis, intracranial bleeding, reversible vasoconstriction syndrome, posterior reversible encephalopathy, and CVST. This can be tricky especially in the case of the reversible vasoconstriction syndrome and convexal subarachnoid hemorrhage where extensive radiologic workup is necessary (MRI with diffusion-weighted images, fluid-attenuated inversion recovery, T1-weighted imaging, 2-dimensional time-of-flight cerebral MRA, transcranial Doppler ultrasonography, and conventional transfemoral angiography).

Several reports of this syndrome used various terms including headache with neurologic deficits and CSF pleocytosis and pseudomigraine with temporary neurologic symptoms and lymphocytic pleocytosis. Patients with this condition are usually men between 15 and 40 years of age.

The self-limited syndrome consists of 1 to several episodes of variable neurologic deficits accompanied by moderate to severe headache and in some cases fever. Each episode lasts hours, with total duration of the syndrome being from 1 to 70 days. The neurologic manifestations, involving either cerebral hemisphere or the brainstem/cerebellum, are most commonly sensory symptoms (78% of reported cases), aphasia (66%), and motor deficits (56%). Migraine aura–like visual symptoms are relatively uncommon (18%).

CSF abnormalities include a lymphocytic pleocytosis (10–760 cells/μL), elevation of CSF protein (20–250 mg/dL) in >90% of cases, and increased CSF opening pressure (100–400 mm H2O) in >50% of cases. MRI and CT are invariably normal, but EEG often shows focal or diffuse slowing. SPECT studies demonstrate focal or widespread areas of decreased blood flow on the side of origin of the neurologic deficits, suggestive of the spreading depression–like mechanism similar to that proposed for migraine. Results of the microbiologic studies are always negative.

The cause of the syndrome is unclear, although there are numerous theories like the infectious-autoimmune, neurogenic inflammation, dysfunction of the blood–brain barrier, spread cortical depression, and trigeminal-vascular activation. Pseudomigraine with temporary neurologic symptoms and lymphocytic pleocytosis could result from an activation of the immune system secondary to a recent viral infection, which would produce antibodies against neuronal or vascular antigens. This autoimmune attack may induce an aseptic leptomeningeal vasculitis causing a CSF pleocytosis and accounting for the headache and the transient symptoms likely through a spreading depression–like mechanism.

Some obvious similarities to migraine with aura exist. In migraine vasodilator peptides such as calcitonin gene-related peptide (CGRP), substance P, neurokinin A, neuropeptide Y (NPY), and galanin are found in trigeminal neurons and could be involved in vascular nociception, supporting the neurogenic inflammation theory that proposes CGRP release from trigeminal sensory afferents causing vasodilation and plasma extravasation from dural vessels. This procedure may lead to a “sterile neurogenic inflammation.” However, the duration of the focal symptoms in migraine is longer than in HaNDL. The most important difference between migraine and HaNDL is the CSF pleocytosis.

The present case highlights the importance of diagnosing the syndrome of transient HaNDL in patients with or without history of migraine with transient neurologic deficits. The diagnosis of HaNDL is one of exclusion, as extensive paraclinical testing should be obtained to exclude other differential diagnoses.

AUTHOR CONTRIBUTIONS

A. Kerasnoudis acquired, analyzed, and drafted the content of this clinical reasoning including medical writing. R. Gold revised the manuscript for content and did the supervision of this clinical reasoning. M.-S. Yoon analyzed and revised the content of this clinical reasoning.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.
REFERENCES


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*Neurology* 2012;79;e59-e62
DOI 10.1212/WNL.0b013e3182648b3c

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