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Chapter 115

# Pseudomigraine with Pleocytosis

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**Other terms:** migraine variants, headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL)

## INTRODUCTION

Pseudomigraine is a term first introduced in 1983 to describe attacks of temporary neurologic deficit accompanied or followed by migrainous headache and cerebrospinal fluid (CSF) pleocytosis of unknown origin and automatic relief (10). Similar clinical presentations were reported previously under different names, such as migraine variants (1,13).

## EPIDEMIOLOGY

Fewer than 100 cases of HaNDL are reported in the literature (2,7), but it may be underdiagnosed as estimates of its annual incidence are up to 0.2 cases per 100,000 inhabitants (11). Contrary to migraine, this syndrome is more frequent in males (male:female ratio 2–3:1). Reported ages have ranged from 7 to 51 years, but most patients are around 30 years old (2,7,8).

## PATHOPHYSIOLOGY

The cause of HaNDL remains elusive. Proposed mechanisms are (11):

1. A rare variant of migraine with aura
2. Infectious meningoencephalitis
3. Autoimmunity

Episodes of HaNDL can be induced by cerebral angiography, which implicates a vascular etiopathology of the syndrome. The vascular theory of HaNDL is supported further by transcranial Doppler findings of asymmetrical changes in blood flow velocity and pulsatility index of middle cerebral artery (9). Alternatively, imaging studies suggest that neurologic deficits of HaDNL might be caused by cortical spreading depression (5,6), as in migraine with aura. Furthermore, overlap of clinical presentations between HaNDL and familial hemiplegic migraine triggered a search for mutations in the CACNA1A gene, which were not found (4). Finally, the CSF inflammatory picture of HaNDL suggests an inflammatory, autoimmune, or postinfectious etiology, and supportive data are awaited.

## PRESENTATION AND EVALUATION

Diagnostic criteria (Revised International Classification for Headache Disorders [ICHD-II]) of HaNDL are listed in Table 115-1. The clinical characteristics of HaNDL are: (1) more than two discrete episodes of temporal focal neurologic (most often sensory plus aphasic) symptoms followed by moderate to severe headache and (2) complete and spontaneous relief of the condition after a few weeks or months. Characteristic paraclinical findings are: (1) CSF pleocytosis with lymphocytic predominance, whereas all serologic or CSF microbiologic studies are negative, and (2) ictal transient changes in brain single photon emission computed tomography (SPECT) and electroencephalogram (EEG) in the absence of any other abnormality in brain imaging (3,7). A combination of these clinical features and findings raises suspicion of HaNDL, but a 3-month follow-up period is necessary to establish the diagnosis, since the condition lasts from 6 hours to 49 days (mean $\pm$ SD $= 14 \pm 10$ days, [7]).

Nonheadache clinical features of HaNDL include premonitory symptoms such as general malaise, cough, diarrhea, or rhinitis, which precede the clinical presentation by up to 3 weeks (11); symptoms of cortical dysfunction; and rarely symptoms of cerebellar or brainstem disturbance (Table 115-2).

Combinations of neurologic symptoms are not uncommon, particularly aphasia with sensory and motor

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**TABLE 115-1 Diagnostic Criteria for the Syndrome of Transient Headache and Neurologic Deficits With Cerebrospinal Fluid Lymphocytosis, Code 7.8, ICHD-II**

A. Episodes of moderate or severe headache lasting hours before resolving fully and fulfilling criteria C and D.
B. Cerebrospinal fluid pleocytosis with lymphocytic predominance (>15 cells/$\mu$L) and normal neuroimaging, CSF culture, and other tests for etiology.
C. Episodes of headache are accompanied by or shortly follow transient neurologic deficits and commence in close temporal relation to the development of CSF pleocytosis.
D. Episodes of headache and neurologic deficits recur over <3 months.

complaints. Interestingly, most patients (75%) experience left hemispheric neurologic deficits (7). The neurologic symptoms of HaNDL last minutes to several days (mean $\pm$ SD $= 5 \pm 13$ hours, [8]) and may spread as in migraine aura. All patients are asymptomatic between episodes.

Headache, which typically, although not invariably, follows the neurologic symptoms, resembles migraine, and is throbbing, usually nonlocalizing and bilateral (60%), moderate to severe, and lasting hours to days (6 to 19 hours on average [7,11]). When unilateral, the headache is always contralateral to the neurologic deficit. Isolated headache attacks without neurologic symptoms may occur in approximately 30% of cases (7).

Signs of meningeal irritation are absent in patients with HaNDL. Routine laboratory tests, including erythrocyte sedimentation rate and immunologic studies, are normal in most patients. Rarely, a slight leucocytosis, increased levels (<100 U/L) of transaminases, or positive antinuclear antibodies (<1/80) can be discovered. Serologies or cultures for virus, brucella, borrelia, mycoplasma, treponema, and tuberculosis are negative. A HaNDL-like clinical picture has been described due to cytomegalovirus (CMV) infection (12); however, in most HaNDL cases, CMV serology remains negative (2,4,7,11).

CSF opening pressure is high in more than half the cases (7,11). CSF glucose is always normal, but protein levels are elevated in more than 90% of cases (mean 94 mg/dL, maximum 250 mg/dL). CSF pleocytosis (range 10 to 760 cells/mm$^3$, mean 200 cells/mm$^3$) is observed in all, with lymphocytic predominance (>90% in most cases). Immunoglobulin (Ig) G and adenosine deaminase levels are within normal limits, and oligoclonal bands are absent. Other CSF studies, including bacterial, viral, fungal, and immunologic studies, are normal (2,4,7,11).

Neuroimaging studies (computed tomography [CT] and magnetic resonance imaging [MRI]) are normal except for occasional nonspecific $T_2$ hyperintensities (4). MR diffusion-weighted imaging during temporary focal symptoms was normal in a HaNDL patient (5). More than two-thirds of patients show unilateral ictal EEG slowing over the symptomatic side, which normalizes with recovery of the clinical condition. During and up to 1 day after the episodes, $^{99}$mTc-HMPAO SPECT usually detects focal areas of decreased radionuclide uptake, coincident with the neurologic symptoms. SPECT becomes normal when repeated more than 2 days after the transient neurologic symptoms (2,3,5) (Fig. 115-1). Conventional cranial angiograms are usually normal, even in the symptomatic phase. Irregularities suggestive of inflammation of the wall have occasionally been described in opercular arteries (7). Angiograms should be avoided because they frequently trigger new episodes (7,11).

**TABLE 115-2 Nonheadache Clinical Features of Headache and Neurologic Deficits With Cerebrospinal Fluid Lymphocytosis**

| *Clinical Features* | *Frequency* |
|---|---|
| Sensory symptoms | 78% |
| Speech difficulties | 66% |
| Motor dysfunction | 56% |
| Nausea and vomiting | 54% |
| Premonitory symptoms of a viral-like illness | Up to 33% of patients |
| Fever (37.5 to 39°C) | 22% |
| Visual deficits | 18% |
| Photophobia or phonophobia | 16% |
| Cerebellar and/or brainstem symptoms | Rare |
| Confusion | Rare |

From refs. 5 and 7.

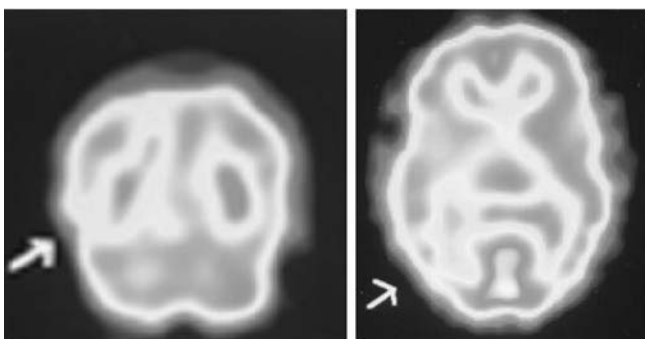

***FIGURE 115-1.*** Coronal (left) and horizontal (right) single photon emission computed tomography (SPECT) images showing 99mTc-HMPAO distribution in a typical patient with pseudomigraine with pleocytosis 12 hours after an episode of headache accompanied by left sensory and motor symptoms. There is decreased tracer uptake posteriorly in the right hemisphere (arrows). A SPECT study performed on this patient 1 week later was normal. This 26-year-old man had had two previous episodes with aphasia and right sensory symptoms.

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**TABLE 115-3 Differential Diagnosis of Headache and Neurologic Deficits With Cerebrospinal Fluid Lymphocytosis**

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|---|
| Migraine, including basilar and sporadic hemiplegic migraine |
| Cerebral edema |
| Viral meningitis |
| Mollaret meningitis |
| Neuroborreliosis |
| Neurosyphilis |
| Neurobrucellosis |
| Mycoplasma infection |
| Neoplastic meningitis |
| Granulomatous meningitis |
| Autoimmune disease with central nervous system manifestations (e.g., neuro-Behçet, systemic lupus erythematosus) |
| HIV infection |
| Multiple sclerosis |
| Seizures and nonconvulsive status epilepticus |

The differential diagnosis of HaNDL includes conditions with headache and transient neurologic deficits (Table 115-3).

## TREATMENT AND PROGNOSIS

No treatment has been reported either to abort the acute episodes or to prevent their recurrence. The self-limiting character of this condition indicates that only symptomatic and supportive treatment is needed. The only reported complications were related to diagnostic workup, especially cerebral angiography, and not to the syndrome itself. Therefore, the recognition of this benign syndrome is very important to avoid unnecessary testing.

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