A 30-year-old man without previous attacks of migraine, despite a family history of migraine, presented with moderate headache and temporary focal neurological signs and symptoms. The patient had had, two weeks previously, a prodromic flu-like illness. Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis and increased total protein. Extensive microbiological determinations were negative. Routine hematological, immunological, blood and urine tests were normal. Electroencephalography showed a focal slowing in the right temporal area. Brain SPECT, performed during a symptom-free period, revealed decreased tracer uptake in the left temporal and insula cortices, topographically consistent with abnormalities on brainstem auditory evoked potentials. Computed tomography and magnetic resonance imaging of the brain were normal. A cardiovascular examination provided normal results. The patient completely recovered within 2 days. This condition is suggestive of “headache with neurologic deficits and CSF lymphocytosis” (HaNDL syndrome). I hypothesize that this syndrome could be produced by the direct action of a virus.

**Key words** Headache • Migraine • Pseudomigraine • Headache with neurologic deficits and CSF lymphocytosis • SPECT

**Introduction**

The occurrence of a severe headache with temporary neurological symptoms and lymphocytic pleocytosis is highly suggestive of a benign and self-limiting syndrome with typical clinical and laboratory features and unknown etiopathogenesis. This syndrome has been called “HaNDL syndrome” (headache with neurologic deficits and cerebrospinal fluid lymphocytosis) by Berg and Williams [1] and “PMP syndrome” (pseudomigraine with temporary neurological symptoms and lymphocytic pleocytosis) by Gómez-Aranda et al. [2]. I prefer the term HaNDL syndrome, because it describes this illness completely.

This syndrome was first described independently by Swanson et al. [3] and Martí-Massó et al. [4] in the 1980’s; a similar case had been published earlier by Kremenitzer and Golden in 1974 [5]. In recent years, there has been an increase in the number of cases reported, and about 100 cases of this disease have now been reported. In particular, Berg and Williams [1] published diagnostic criteria based on the clinical and laboratory data for 40 cases reported prior to 1995, and the Spanish Headache Study Group [2] reviewed the clinical and laboratory data of 50 cases. The onset of HaNDL occurs between the ages of 14 and 39 years, with a mean of 28 years; the syndrome is more frequent in males, and a 3:1 male-to-female ratio has been reported [2]. This syndrome should be suspected in patients with the following clinical and laboratory presentation [1, 2]:

1. One or more episodes of moderate-to-severe bilateral and/or hemi-cranial headache accompanied by temporary neurological deficits;
2. Each neurological deficit resolves within 3 days;
3. Total resolution of this syndrome within 3 months;
4. Absence of signs and symptoms between episodes;
5. Cerebrospinal fluid lymphocytosis with negative etiological results;
6. Normal neuroradiological studies, except for transient focal, decreased radionuclide uptake on single photon emission computed tomography (SPECT) of the brain.
Frequently associated features are:
- Increased total protein concentration in the CSF,
- Increased opening pressure,
- Transient focal, non-epileptic changes on electroencephalography
- Viral-like prodrome or fever.

The precise mechanism underlying this syndrome is still not known and the etiology has been debated in the literature. Some authors attributed this clinical picture to primary viral meningoencephalitis [1, 6]; others considered it to be the result of severe migraine [7, 8]. Still others hypothesized that a viral infection could activate the immune system, and thereby cause an aseptic inflammation of the leptomeningeal vasculature [2].

Recently, my colleagues and I described a new type of cytomegalovirus (CMV)-induced meningoencephalitis with paroxysmal course [9]. This disease shows the same clinical and laboratory features as the recurrent type of HaNDL syndrome, except for the demonstration of CMV in the CSF.

**Case report**

A 30-year-old man with a family history of migraine and without previous attacks of migraine experienced a sudden left hemiparesis with homolateral paresthesias and a throbbing frontal headache of moderate intensity with phonophobia, photophobia, nausea and vomiting. The neurological symptoms lasted about 4 h, while the headache lasted 2 days. He was given only symptomatic therapies, analgesics and antiemetics. Two weeks previously, he had had a flu-like syndrome without fever.

On admission, the results of a general examination, including temperature, pulse and blood pressure, were normal, while the neurological evaluation showed a motor deficit in the left hemiface.

Routine hematological, immunological, blood and urine analyses were normal. Tests for human immunodeficiency virus (HIV), Borrelia burgdorferi and syphilis were negative.

Lumbar puncture revealed an opening pressure of 24 cm H2O, lymphocytosis (65 cells/mm3), elevated total protein (112 mg/dl) and IgG (8 mg/dl), and normal glucose (65 mg/dl), relative to serum. CSF cultures for bacteria, fungi and yeast were negative. CSF was tested by polymerase chain reaction (PCR) for the presence of nucleic acids of neurotrophic viruses. A repeat lumbar puncture, 15 days later, showed lymphocytosis (390 cells/mm3), elevated total protein (190 mg/dl) and normal glucose (70 mg/dl). The first EEG examination showed a slow-waves activity (2-6 Hz) in the right temporal area, consistent with transient neurological symptoms. This slow activity disappeared within 15 days. Visual evoked potentials (VEP) and median somatosensory evoked potentials (SEP) were normal, while brainstem auditory evoked potentials (BAEP) showed an increased left III-V interpeak latency. Technetium Tc 99m HMPAO brain SPECT, performed 20 days later during a symptom-free period, showed a decreased tracer uptake in the left temporal and insula cortices, topographically consistent with BAEP abnormalities. The SPECT results became normal when repeated two months after the transient neurological symptoms. Results of computed tomography (CT) and magnetic resonance imaging (MRI) of the head, cerebral MR angiography, Duplex sonography of the cervix and vertebral arteries, and transcranial Doppler ultrasonography were within normal limits. A cardiovascular examination with electrocardiography (ECG) and transthoracic and transesophageal echocardiography provided normal results. A third lumbar puncture, 40 days from the episode, revealed lymphocytosis (57 cells/mm3), elevated total protein (78 mg/dl) and IgG (7.8 mg/dl) and normal glucose (64 mg/dl). The patient refused a fourth lumbar puncture. At follow-up after 2 years, the patient is symptom-free.

**Discussion**

This patient fulfills the diagnostic criteria for “headache with neurologic deficits and CSF lymphocytosis“ (HaNDL syndrome) [1]. In fact, the patient experienced a transient syndrome consisting of focal neurological deficits, migraine-like headache and CSF pleocytosis. As in all previously reported cases [1, 2, 6], a definite etiology was not found.

There was increased left III-V interpeak latency on BAEP examination, indicating a defect in conduction between the caudal pons and midbrain.

Brain SPECT, performed 20 days from the onset of the symptoms and during a symptom-free period, showed a decreased tracer uptake in the left temporal and insula cortices, topographically consistent with BAEP abnormalities and inconsistent with the transient focal neurological symptoms and EEG focal slowing. SPECT abnormalities have been reported during attacks or 8–20 days after the onset of symptoms [2, 10, 11]. Focal areas of decreased radionuclide uptake have been observed in one or both hemispheres, but the left hemisphere was always found to be involved, both during the symptomatic period and during a headache-free period; the most affected area was the frontotemporal cortex [2, 10, 11].

Recognition of HaNDL syndrome is important for the differential diagnosis in neurology, especially for migraine with aura and transient ischemic attacks (TIAs). TIAs are characterized by temporary focal neurologic deficits of sudden onset that usually last, by definition, less than 24 hours, but typically last less than 15 minutes. TIAs are usually life events that do not cause headache. On the contrary, symptoms of migraine aura progress gradually over several minutes or occur in succession and generally last around 30 minutes; migraine aura is often followed by a severe, throbbing, unilateral headache associated with phonophobia, photophobia, nausea or vomiting. Other important diseases to consider in the differential diagnosis with HaNDL are Lyme neuroborreliosis [12, 13], neurosyphilis [14], neurobrucellosis [15], mycoplasma infections [16], granulomatous