Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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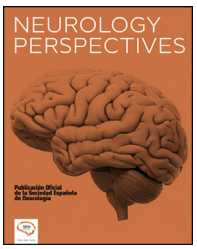

SCIENTIFIC LETTER

HaNDL syndrome after COVID-19

Síndrome de HaNDL tras infección por COVID-19

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Dear Editor:

Headache and neurological deficits with cerebrospinal fluid (CSF) lymphocytosis, also known as HaNDL syndrome, is characterised by episodes of migraine-like headache associated with motor, sensory, or language deficits lasting several hours and recurring within less than 3 months.[1] Diagnosis is confirmed by predominantly lymphocytic pleocytosis and normal results in other complementary tests.[2]

The aetiopathogenic mechanism of HaNDL syndrome is unclear, although the condition is thought to be a transient inflammatory process caused by an immune response to viral infection (e.g., HHV-7, EBV, CMV, HHV-6)[3–6] or other pathogens; this would trigger the production of antibodies and/or inflammatory cytokines, which would act on leptomeningeal vessels,[1] causing vasoconstriction and vasodilation.[7]

We present the case of a 14-year-old boy with no relevant personal or family history who visited the emergency department due to an episode of sudden-onset, moderate-intensity holocranial pulsatile headache, associated with nausea, photo- and phonophobia, and language impairment in the form of paraphasia and blocking. Symptoms persisted for over 4 h. He had not presented fever or any other systemic symptoms in the previous days, but in the previous month he had presented a mild upper respiratory tract infection, with odynophagia and mild fever, and a PCR test had yielded positive results for SARS-CoV-2.

The patient was asymptomatic and haemodynamically stable, and presented no fever. Blood analysis did not reveal elevated levels of acute-phase reactants or blood count alterations, and a urine toxicology screening test yielded negative results. Eye fundus examination did not reveal signs of intracranial hypertension, and a head CT scan detected no relevant alterations. CSF opening pressure was 20 cm H_2O, and a biochemical analysis revealed pleocytosis (525 cells/μL, mostly lymphocytes [99%]), elevated protein levels (98.2 mg/dL), and lack of glucose consumption. A CSF culture did not detect bacterial growth. We started empirical treatment with intravenous aciclovir and lacosamide, and the patient was admitted to the neurology ward.

During hospitalisation, the patient presented 2 additional episodes of headache with the same characteristics, accompanied by language alterations and sensory alterations affecting the left limbs, after which he recovered completely. Complementary analyses showed normal thyroid, liver, and kidney function; a normal lipid profile; and normal autoimmune test results. Serology tests for HCV, EBV, CMV, HSV, VZV, HHV-6, HHV-7, HHV-8, syphilis, *Rickettsia*, *Toxoplasma gondii*, *Borrelia*, and *Brucella* yielded negative results, as did CSF PCR assays for viral infection. Magnetic resonance angiography revealed no parenchymal alterations or intravenous contrast uptake. A video EEG study did not detect focal slowing or epileptogenic foci. In view of the negative viral PCR test results and the lack of additional episodes, antiviral and antiepileptic treatment was discontinued. A second CSF analysis performed before discharge

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Table 1 International Classification of Headache Disorders (ICHD-3) diagnostic criteria for HaNDL syndrome.

Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL syndrome).
A) Episodes of migraine-like headache fulfilling criteria B and C.
B) Both of the following:
1. Accompanied or shortly preceded by onset of at least one of the following transient neurological deficits lasting >4 h:
a) hemiparaesthesia
b) dysphasia
c) hemiparesis
2. Associated with CSF lymphocytic pleocytosis (>15 white cells/μL), with negative aetiological studies
C) Evidence of causation demonstrated by either or both of the following:
1. Headache and transient neurological deficits have developed or significantly worsened in temporal relation to onset or worsening of the CSF lymphocytic pleocytosis, or led to its discovery.
2. Headache and transient neurological deficits have significantly improved in parallel with improvement in the CSF lymphocytic pleocytosis.
D) Not better accounted for by another ICHD-3 diagnosis.

showed improvements, with a leukocyte count of 150 cells/μL and normal protein levels.

HaNDL syndrome is included in the International Classification of Headache Disorders[8]; the diagnostic criteria for this rare entity are listed in Table 1.

In younger patients, the condition may be misdiagnosed as hemiplegic migraine (associated with a mutation in *CACNA1A*)[2] or familial hemiplegic migraine type 1.[1] In fact, the mechanism believed to cause the neurological symptoms is cortical spreading depression, similarly to what occurs in migraine aura.[9] In older individuals, the condition may present as a stroke mimic, which, when in doubt, is managed with fibrinolytic treatment.[1] Differential diagnosis of HaNDL syndrome includes a wide range of diseases; in addition to the conditions mentioned previously, it also includes CNS vasculitis, infectious or inflammatory encephalitis, neoplastic arachnoiditis, Mollaret meningitis, and posterior reversible encephalopathy.[9]

Although diagnosis is established by exclusion, other complementary findings have been identified in recent years, including leptomeningeal contrast uptake on brain MRI, focal or diffuse slowing of EEG activity,[2,7,9] cerebral hypoperfusion predominantly in the temporal lobe,[10,11] and vasospasm in transcranial Doppler ultrasound studies.[7] Given its excellent prognosis without specific treatment and the monophasic course of the disease,[1,2] recurrence should lead us to reconsider the diagnosis of HaNDL syndrome.

As occurs with other neurotropic viruses, SARS-CoV-2 may cause HaNDL syndrome due to its capacity to trigger a "cytokine storm,"[12] resulting in the vasomotor alterations that are believed to cause the syndrome. History of SARS-CoV-2 infection should therefore be taken into account when HaNDL syndrome is suspected.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical considerations

The authors observed their centre's protocols for the publication of patient data. The patient gave informed consent for the publication of this case report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2022.06.007.

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