

Syndrome of Transient Headache and Neurological Deficits with Cerebrospinal Fluid Lymphocytosis (HaNDL): A Case Report - Is there an Association with the COVID-19 Vaccine?

Bartleson, 1981 described the syndrome of transient headache and neurologic deficits with cerebrospinal fluid (CSF) lymphocytosis (HaNDL) for the first time.^[1] HaNDL is classified as a “headache attributed to nonvascular intracranial

disorder” and is included in the third edition of the International Classification of Headache Disorders.^[2] HaNDL, a rare clinical entity, is diagnosed according to the following criteria: (1) episodes of migraine-like headache; (2) accompanied

or shortly preceded by the onset of at least one transient neurological deficit lasting >4 h, and CSF lymphocytic pleocytosis (>15 white cells/mL), with negative etiological studies; (3) development or significant worsening of headache and transient neurological deficits in temporal relation to the onset or worsening of the CSF lymphocytic pleocytosis or led to its discovery, and/or have significantly improved in parallel with the improvement in the CSF lymphocytic pleocytosis; and (4) not better accounted for by another diagnosis. The syndrome resolves within 3 months.^[2] Although the etiology of HaNDL is not precisely known, based on CSF lymphocytic pleocytosis, it is assumed to be associated with an autoimmune or infectious inflammatory disease. Cortical spreading depression may also cause neurologic deficits.^[3]

CSF lymphocytosis may be accompanied by elevated CSF total protein and CSF pressure that supports possible inflammation. Electroencephalography (EEG) may demonstrate focally abnormal areas consistent with focal neurological deficits. The neurological manifestations include sensory symptoms in approximately three-quarters, aphasia in two-thirds, and motor deficits in a little more than half of the cases.^[2]

Neurologic adverse events such as fever, headache, fatigue, and myalgia following coronavirus disease (COVID-19) vaccination are generally mild and transient. One of the most frequent neurological complaints reported after the COVID-19 vaccination is a headache.

Twenty-eight-year-old female patient with migraine reported to our outpatient clinic with severe headache, speech disturbances, and right-sided sensory symptoms. She had a throbbing pain localized to the left hemisphere, accompanied by nausea and vomiting, and sensitivity to light and sound. The migraine attacks occurred once every 2 months and were responsive to simple analgesics.

After the second dose of COVID-19 (BNT162b2-BioNTech) vaccination, the frequency and character of headache attacks changed. Distinct severe headaches were noted, and the frequency of headache attacks was increased to 15 days a month with a significantly reduced analgesic response. After 2 months of vaccination, severe headache attacks became chronic and right-sided hemi-hypesthesia and dysarthria appeared. There was no recent viral disease history except for the COVID-19 infection 8 months back during which she had mild symptoms. There was a minimal increase in the frequency of headaches without any change in character. However, dramatic changes occurred post-vaccination.

Neurologic examination revealed mild dysarthria, and right hemi-hypesthesia with normoactive tendon reflexes, without any motor disturbance, neck stiffness, meningeal irritation signs, pathological reflexes, or cognitive dysfunction.

A detailed blood work-up was performed, including vitamin B12 levels, and serological tests, all of which were within normal limits. Antinuclear antibody (ANA) was weakly positive (1/100) in the vasculitis panel. Detailed

autoimmune and paraneoplastic antibody panels were all negative. Ophthalmological examination revealed no papilledema. Contrast-enhanced cranial magnetic resonance imaging (MRI), non-contrast computerized tomography (CT), MR angiography (MRA), venography, and EEG were unremarkable. Lumbar puncture (LP) showed leukocytic pleocytosis with lymphocytic dominance (45 leukocytes-80% lymphocytes without erythrocytes). CSF opening pressure was 10 cm/CSF and analysis revealed normal protein (40 mg/dL) and normal glucose levels (61 mg/dL-serum: 79 mg/dL). The CSF viral panel, Gram stain, and culture were negative.

After the exclusion of other differential diagnoses, HaNDL secondary to the COVID-19 vaccination was diagnosed and was followed closely with symptomatic treatment. The patient's clinical symptoms lasted for approximately 3 weeks and then disappeared spontaneously. During the 6-month follow-up period, there was no recurrence of neurologic deficits despite the occasional headache.

There are different views on the etiology of HaNDL syndrome. The presence of inflammatory CSF findings suggests that infection and/or inflammation triggers the condition. Additionally, it is hypothesized that viral infection may activate the immune system and cause HaNDL syndrome.^[4] The most important finding in support of this hypothesis is that some patients had a viral infection before the onset of symptoms.^[5]

After infection with COVID-19, persistent or new symptoms may develop for weeks or months, called long COVID or post-COVID syndrome. The symptoms may exceed 12 weeks. Common symptoms in people with long COVID are fatigue, headache, breathlessness, cough, chest pain, myalgia and weakness, insomnia, memory and concentration problems, and worsened quality of life.^[6] Although the frequency of the patient's headache increased post-COVID-19 infection, it was vaccine-related rather than infection since the main change in headache character was post-vaccination.

A known adverse event of COVID-19 vaccination is a headache. Patients with migraine-type headaches develop more headaches after COVID-19 vaccination compared to healthy controls.^[7] In BNT162b2 clinical trials (manufactured by BioNTech and Pfizer), a higher incidence of headache was noted after the second dose than the first dose, with approximately 52% of patients reporting mild to moderate headaches.^[8]

In accordance with the literature data, headaches increased in our patients with a history of migraine, particularly after the second vaccination dose.

Studies emphasize that the risk of headache after vaccination is increased twice and has a migrainous character in one-third of patients. Although the mechanisms underlying vaccine-induced headaches are still unclear, it may be owing to a systemic inflammatory response.^[9] Vaccination with COVID-19 mRNA may cause an immunomodulatory response. The immune system stimulation following vaccination induces

a strong T-cell response and increases CD8+ T cells and CD4+ T cells.^[10]

Although the neurological deficit developed in our patient 2 months after the vaccination, there was a significant and constant change in the frequency and character of the headaches immediately post-vaccination. Therefore, the neurological deficit added 2 months later was considered a continuation. In light of all these data and after excluding other differential diagnoses, the COVID-19 vaccination may be considered as a possible cause of HaNDL syndrome by triggering inflammation in our patient.

HaNDL should be considered in the differential diagnosis after excluding other probable causes in patients with neurological deficits and headaches post-COVID-19 vaccination.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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