Letter to the Editor: New Observation

Transient Headache and Neurological Deficits with Cerebrospinal Fluid Lymphocytosis following COVID-19

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Headache is a common symptom of coronavirus disease 2019 (COVID-19) during and after infection.1,2 The syndrome of headache and neurologic deficit with cerebrospinal fluid lymphocytosis (HaNDL) is a unique phenotype commonly associated with viral infection but with only one case reported following COVID-19 infection to date.3 We report a second case and an approach to patients presenting with headache and focal neurological symptoms after COVID-19 (Figure 1).

A 27-year-old non-obese woman with a history of migraine without aura for over 10 years, developed new headaches 3 weeks following a mild COVID-19 infection. She also had a recent history of acne, and depression, managed on bupropion and isotretinoin for the last 6 months. Over 2 weeks, she developed increasing holocranial, mixed pressure and throbbing, headaches lasting 5–120 minutes, occurring up to 6 times per day, without provocation. There was associated photophobia, phonophobia, nausea, and occasional vomiting. These episodes were more severe and frequent than her typical migraines, and she had never had any visual or somatosensory aura previously. Twice, she experienced migratory hemibody paresthesias following headache; the first involved...

Figure 1: Approach to persistent headache following COVID-19. Red flags for secondary headaches adapted from the SNNOOP10 list4. CSF = cerebrospinal fluid; HaNDL = headache and neurologic deficit with cerebrospinal fluid lymphocytosis.

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and investigations were felt to be in keeping with HaNDL, also known as migraine with cerebrospinal pleocytosis or pseudomigraine with lymphocytic pleocytosis, as presents as a constellation of self-limited migraine-like headaches, neurological symptoms, and CSF lymphocytosis. 

Headaches resemble migraines (often moderate to severe, throbbing, unilateral or bilateral, lasting hours, with nausea, vomiting, and photophobia) occurring in association with neurological symptoms (most commonly hemiparesthesia, followed by hemiparesis or dysphasia, and rarely positive visual phenomena) typically lasting from 15 minutes to 2 hours or longer. 

Examination showed no meningismus or fever. She was alert and oriented with fluent speech. Severe photophobia made pupil examination challenging although there did not appear to be papilledema. Visual acuity was 20/20 in each eye, with full visual fields. The remainder of the neurological examination was unremarkable. Given several red flag features, urgent outpatient neurology opinion was requested.

Isotretinoin was discontinued.

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Table 1: Cerebrospinal fluid results

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Clear, colorless</td>
<td>Clear, colorless</td>
</tr>
<tr>
<td>Volume removed</td>
<td>8 ml</td>
<td>16 ml</td>
</tr>
<tr>
<td>Opening pressure (cmH2O)</td>
<td>28</td>
<td>20.5</td>
</tr>
<tr>
<td>White cells (cells/μL; ref 0–5)</td>
<td>44</td>
<td>31</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>&gt; 90%</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Xanthochromia</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Protein (g/L; ref 0.15–0.45)</td>
<td>0.72</td>
<td>0.60</td>
</tr>
<tr>
<td>Glucose (mmol/L; ref 2.3–4.1)</td>
<td>3.4</td>
<td>4.0</td>
</tr>
<tr>
<td>Bacterial culture</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Viral PCR (HSV1, HSV2, VZV, enterovirus)</td>
<td>Negative</td>
<td>–</td>
</tr>
<tr>
<td>Cryptococcal antigen</td>
<td>Negative</td>
<td>–</td>
</tr>
<tr>
<td>Fungal culture</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>AFB</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Cytology</td>
<td>–</td>
<td>No abnormal cells</td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>–</td>
<td>Negative</td>
</tr>
</tbody>
</table>

HSV = Herpes simplex virus; PCR = polymerase chain reaction; VZV = varicella zoster virus.

Table 2: ICHD-3 diagnostic criteria for HaNDL

1. accompanied or shortly preceded by onset of at least one of the following transient neurological deficits lasting > 4 hours
   a) hemiparesis
   b) dysphasia
   c) hemiparesis

2. associated with cerebrospinal fluid (CSF) lymphocytic pleocytosis (> 15 white cells per μl), with negative etiological studies

3. 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

4. Not better accounted for by another ICHD-3 diagnosis.

ICHD-3 = International Classification of Headache Disorders, 3rd edition; IHS = from the International Headache Society.

After 6 weeks, her headaches had gradually resolved with symptomatic treatment, and there was no recurrence of transient neurologic symptoms.

IIH should be normal, and rare cases that report lymphocytosis (Table 2). After 6 weeks, her headaches had gradually resolved with symptomatic treatment, and there was no recurrence of transient neurologic symptoms.

Idiopathic intracranial hypertension (IIH) was also considered in our case, given isotretinoin exposure and elevated opening pressure. However, IIH symptomatology generally develops soon after isotretinoin exposure (mean time to diagnosis 2.3 months) and resolves gradually over weeks to months with medication discontinuation. 

Additional factors such as regular follow-up visits, treatment adherence, and ongoing monitoring of vision and neurologic symptoms.

Diagnosis was confirmed by the absence of structural abnormalities on imaging and normalization of CSF findings.

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Diagnosis was confirmed by the absence of structural abnormalities on imaging and normalization of CSF findings.
requiring treatment with acetazolamide or shunting. There were no neuro-ophthalmologic or neuroimaging features in our case to suggest IIH. There have been rare reports of IIH associated with COVID-19 occurring during active infection but again with normal CSF composition. To date, there is only one other report of HaNDL following COVID-19 infection. Headache is a common symptom of both active COVID-19 infection and in the postinfectious period, with several proposed mechanisms including inflammation, cytokine release, endothelial dysfunction, raised intracranial pressure, and venous congestion. The absence of detectable virus in inflammatory CSF of patients with neurological symptoms supports an indirect autoimmune mechanism. Furthermore, the timing of symptom onset in our case 3 weeks following infection would support a postinfectious hypothesis as described in other cases of HaNDL. It is proposed that viral infection could trigger activation of the immune system, producing antibodies to antigens in cranial vessels and aseptic inflammation accounting for headaches and CSF lymphocytosis, and transient cerebral hypoperfusion leading to neurological symptoms. This is also reflective of the often-monophasic course, with resolution within 3 months, also seen in our case. The most common chronic headache phenotypes following COVID-19 are migraine or tension, which may be part of a wider spectrum of the so-called “long-Covid syndrome” which can also include fatigue, rash, respiratory symptoms, and mental health and cognitive symptoms including anxiety, depression, and insomnia. A monophasic course with focal neurological symptoms atypical for migraine aura makes HaNDL unique. Recognition of this uncommon syndrome is important and should be included in the differential diagnosis in a patient presenting with headache and focal neurological symptoms after viral illness including COVID-19. However, it remains important to exclude other potentially serious conditions presenting in a similar fashion.

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Statement of authorship. SM: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. AP: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept and design; analysis or interpretation of data.

References