

# Residents And Fellows: Opinions In Headache Education

## COVID-19 and Headache: A Primer for Trainees

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**Objective.**—To summarize for the trainee audience the possible mechanisms of headache in patients with COVID-19 as well as to outline the impact of the pandemic on patients with headache disorders and headache medicine in clinical practice.

**Background.**—COVID-19 is a global pandemic caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2, of which a large subset of patients features neurological symptoms, commonly headache. The virus is highly contagious and is, therefore, changing clinical practice by forcing limitations on in-person visits and procedural treatments, more quickly shifting toward the widespread adaptation of telemedicine services.

**Design/Results.**—We review what is currently known about the pathophysiology of COVID-19 and how it relates to possible mechanisms of headache, including indirect, potential direct, and secondary causes. Alternative options for the treatment of patients with headache disorders and the use of telemedicine are also explored.

**Conclusions.**—Limited information exists regarding the mechanisms and timing of headache in patients with COVID-19, though causes relate to plausible direct viral invasion of the nervous system as well as the cytokine release syndrome. Though headache care in the COVID-19 era requires alterations, the improved preventive treatment options now available and evidence for feasibility and safety of telemedicine well positions clinicians to take care of such patients, especially in the COVID-19 epicenter of New York City.

**Key words:** COVID-19, headache, trainees, telemedicine

**Abbreviations:** ADEM acute disseminated encephalomyelitis, ANE acute necrotizing encephalopathy, ARBs angiotensin II receptor blockers, CAR chimeric antigen receptor, CNS central nervous system, CRS cytokine release syndrome, CVT cerebral venous thrombosis, DIC disseminated intravascular coagulation, hCoV human coronavirus, MERS-CoV Middle East respiratory syndrome coronavirus, NSAIDs nonsteroidal anti-inflammatory drugs, SARS-CoV1 severe acute respiratory syndrome coronavirus, SARS-CoV2 severe acute respiratory syndrome coronavirus 2, TRP transient receptor potential, VTE venous thromboembolism

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### INTRODUCTION

COVID-19 was identified as a global pandemic by the World Health Organization in early March 2020. COVID-19 is caused by the novel coronavirus severe

acute respiratory syndrome coronavirus 2 (SARS-CoV2), a single-stranded RNA virus that is now 1 of the 7 coronaviruses known to infect humans. Though most human coronaviruses cause mild respiratory diseases,

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other fatal coronavirus infections have emerged in the past 2 decades, namely the severe acute respiratory syndrome coronavirus (SARS-CoV1) and the Middle East respiratory syndrome coronavirus (MERS-CoV).<sup>1</sup> The novel SARS-CoV2 has already proven itself to be deadly, primarily acting on the lungs but with effects on several other organ systems, notably the renal, hematologic, and nervous systems.

A sizeable subset of patients with SARS-CoV2 feature neurological symptoms, often including headache. As the literature continues to grow, we are largely seeing the neurologic manifestations of SARS-CoV2 occur in 3 categories: central nervous system (dizziness, headache, cerebrovascular disease, seizure, altered consciousness), peripheral nervous system (anosmia, ageusia, visual impairment, neuropathic pain, Guillain-Barre Syndrome, and variants), and skeletal muscular injury.<sup>2</sup> In 1 observational study from Wuhan, 36.4% of COVID-19 patients who showed neurologic manifestations, the most common symptom was dizziness (16.8%) followed closely by headache (13.1%).<sup>2</sup> In another prospective analysis out of Wuhan, headache was present in 8% of all patients, overall the most common neurological symptom.<sup>1</sup> Neither of these studies collected data on milder nervous system symptoms and, therefore, likely failed to capture those with anosmia and ageusia to offer direct quantitative comparison to those with headache.

Additionally, the care of patients with preexisting headache disorders has been drastically impacted by the COVID-19 pandemic. Where we practice in New York City, the COVID-19 epicenter, trainees in headache and neurology had been subject to redeployment to directly manage patients with COVID-19, to evaluate neurological complications in such patients, and of course to contend with managing existing patients with headache disorders.<sup>3</sup> Targeting the trainee audience, we undertook a narrative review searching PubMed indexed publications through May 12<sup>th</sup>, 2020 for headache and neurologic complications associated with SARS-CoV2. Articles shared on social media relevant

to this topic were also collected and considered for this review. Here, we aim to provide a brief summary regarding COVID-19 as it relates to headache as a symptom, headache as a disease, and headache medicine practice in areas with high COVID-19 prevalence.

## HEADACHE AS A SYMPTOM OF COVID-19

Respiratory viruses in general can cause neurologic symptoms with headache being among the most common (alongside encephalopathy, seizure, and encephalitis).<sup>4</sup> In fact, headache is an accepted symptom of a systemic viral infection according to the International Classification of Headache Disorders (Table 1).<sup>5</sup> The exact mechanisms of headache attributed to systemic infection are not yet fully investigated, though with

**Table 1.—ICHD3: Headache Attributed to Systemic Viral Infection**

### 9.2.2 Headache Attributed to Systemic Viral Infection

#### *Description*

Headache caused by and occurring in association with other symptoms and/or clinical signs of a systemic viral infection, in the absence of meningitis or encephalitis.

#### *Diagnostic criteria*

- A. Headache of any duration fulfilling criterion C
- B. Both of the following:
  1. Systemic viral infection has been diagnosed
  2. No evidence of meningitic or encephalitic involvement
- C. Evidence of causation demonstrated by at least two of the following:
  1. Headache has developed in temporal relation to the onset of the systemic viral infection
  2. Headache has significantly worsened in parallel with worsening of the systemic viral infection
  3. Headache has significantly improved or resolved in parallel with the improvement in or resolution of the systemic viral infection
  4. Headache has either or both of the following characteristics:
    - (a) Diffuse pain
    - (b) Moderate or severe intensity
- D. Not better accounted for by another ICHD-3 diagnosis

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possible causes attributed to fever and exogenous or endogenous pyrogens, direct effects of the microorganisms themselves, and activation of several immunoinflammatory mediators (cytokines, glutamate, cyclooxygenase-2/prostaglandin E2 system, nitric oxide system, and reactive oxygen species).<sup>5</sup> In 2009, the most frequent neurological sign reported of the H1N1 pandemic was headache (35%) in 1 retrospective study.<sup>4</sup> A more recent report from 2016 on human coronavirus (hCoV) in hospitalized children noted headache to be the most recurring neurological symptom.<sup>6</sup> Without robust pathological data, the exact way in which the SARS-CoV2 virus affects the nervous system is not yet fully realized, though many possible causal or contributory mechanisms are under investigation.

More generic indirect mechanisms for headache causality in SARS-CoV2 may exist that are not disease-specific, including hypoxia, dehydration, systemic inflammation, and metabolic disturbances. Further, SARS-CoV2 could directly invade the central nervous system (CNS) via the olfactory bulb, akin to a similar mechanism already described in mice for the familial hCoV virus.<sup>7</sup> Upon hCoV cellular viral infection, there is a release of inflammatory cytokines with resultant neuronal damage appearing similar to demyelination.<sup>4</sup> Although there is no confirmation of such a mechanism of SARS-CoV2, the frequent presence of anosmia (51%) in conjunction with cough and fever and even as an isolated symptom (17%)<sup>8</sup> suggests a possibility of olfactory nerve invasion, though specific neuronal or glial mechanisms do remain unclear. SARS-CoV2 binds to angiotensin-converting enzyme 2 (ACE2) receptors to gain entry inside cells and such receptors are also expressed on neurons and glial cells.<sup>9,10</sup> Herein results the potential for direct viral infection as the cause of headache, perhaps even in the severe forms of infectious meningoencephalitis as case reports suggest<sup>11,12</sup> or even as acute disseminated encephalomyelitis (ADEM) which has not yet been reported in SARS-CoV2 but has in hCoV.<sup>13</sup>

Another important consideration for the mechanism of headache in SARS-CoV2 is related to cytokine release syndrome (CRS). CRS is a supraphysiological response that typically occurs following the use of immunotherapy that activates or engages T-cells and/or other immune effector cells<sup>14</sup> and is often associated

with neurotoxicity. In patients with severe SARS-CoV2, higher concentrations of pro-inflammatory cytokines (such as IL-6, IL1B, and IFN $\gamma$ ) have similarly been measured in plasma.<sup>1</sup> The presence of these cytokines is known to result in direct tissue injury<sup>2</sup> and a further inflammatory cascade. In immunotherapy, neurotoxic symptoms seen with chimeric antigen receptor (CAR) T cells include headache (in as high as 42% of patients),<sup>15</sup> encephalopathy, somnolence or obtundation, tremors, seizures, and focal weakness.<sup>15,16</sup> Cerebral edema has led to deaths in a small number of patients with CAR T cell neurotoxicity<sup>16</sup> and is, likewise, considered to be a potential cause of death in COVID-19.<sup>9</sup> Further, SARS-CoV2 has shown an association with acute necrotizing encephalopathy (ANE),<sup>17</sup> a rare complication of influenza and other viral infections with suggested mechanisms related to intracranial cytokine storms that result in the blood-brain barrier breakdown but without direct viral invasion or parainfectious demyelination.<sup>18</sup> Treatments aimed at CRS in COVID19 include convalescent plasma, immunoglobulin, thymosin, cytotoxic T cell, and B cell epitopes, as well as tocilizumab,<sup>19</sup> which is also an effective treatment for the important secondary headache disorder giant cell arteritis.<sup>20</sup>

Secondary effects of the systemic inflammation of CRS in SARS-CoV2 include an increase in other inflammatory markers, such as D-dimer and calcitonin gene-related peptide (CGRP), which play a role in headache. Firstly, D-dimer elevation in COVID-19 is common and has even shown to be a predictor of mortality in hospitalized patients<sup>21</sup> tied to its role in disseminated intravascular coagulation (DIC) and venous thromboembolism (VTE).<sup>22</sup> Neurological complications of elevations in D-dimer, therefore, include stroke and cerebral venous thrombosis (CVT), both of which lead to headache. Secondly, CGRP is a neuropeptide that has now been highly implicated in migraine pathophysiology with a suspected link to transient receptor potential (TRP) channels.<sup>23</sup> In the case of SARS-CoV2, there is presumptive viral activation of TRP channels that are involved in cough, anosmia, and gastrointestinal disturbances. This activation results in CGRP release which is then thought to polarize the T cell response in some patients toward a more proinflammatory state, characterized by Th17

and IL-17, as has similarly been elucidated in MERS-CoV.<sup>24</sup> In fact, a new agent for the acute treatment of migraine, intranasal vazegepant (a CGRP receptor antagonist), is currently in a phase 2 trial for the treatment of the lung inflammation in COVID-19.<sup>25</sup>

Anecdotally in our practice in the United States epicenter of COVID-19, we have observed many patients who have headache earlier in their course, often correlating with fever, myalgias, and cough, akin to other systemic viral illnesses. However, some patients seem to develop a headache later, after initial COVID-19 symptom onset, which may be more related to CRS. Prospective studies are needed to capture the clinical characteristics and timing of headache in SARS-CoV2 infection.

### **IMPACT OF COVID-19 ON PATIENTS WITH HEADACHE DISORDERS AND ON HEADACHE PRACTICE**

Clinicians across all fields of medicine are applying “physical distancing” in the care of patients in order to limit the spread of infection. Practically, this means abstaining from all nonessential healthcare visits in person, including procedural visits. Patients with headache disorders often depend on therapies like onabotulinumtoxinA, trigger point, and nerve block injections, and have therefore been especially vulnerable to the possibility of inadequate care during this uncertain time. Though headache clinicians have delineated alternative treatment options that minimize patient-physician contact, while still maximizing headache health, we recognize such stringent restrictions in care are not necessarily universal to all headache clinical practices at this time.

In migraine prevention, onabotulinumtoxinA injections should be avoided when possible and supplemented with other preventive therapies like self-injectable CGRP monoclonal antibodies and oral agents such as beta-blockers<sup>26</sup> and angiotensin II receptor blockers (ARBs),<sup>27</sup> among the many other common preventive drug classes. In regards to nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme inhibitors/ARBs in particular, though initial speculation suggested use of them might be associated with a worse COVID-19 clinical course, no such evidence has been identified.<sup>28</sup> In the

acute treatment of migraine, status migrainosus, and cluster headache, procedural visits for nerve blocks and patient visits to the emergency department for parenteral medications should also be avoided when possible. Alternative therapies include oral NSAIDs, neuroleptics, triptans, and use of any available neuromodulation devices.<sup>27</sup> Oral corticosteroids may be superior to nerve blocks for the remission of status migrainosus within 24 hours (31% of patients compared to 24%<sup>29</sup> respectively) as well as a transitional treatment for cluster headache,<sup>30</sup> however, should be used cautiously given the Center for Disease Control’s warning that corticosteroids may prolong viral replication in SARS-CoV2, as was observed in MERS-CoV.<sup>31</sup>

One positive and likely long-lasting change coming out of the COVID-19 crisis is headache medicine’s swift adoption of telemedicine services. Several pre-COVID-19 era studies have already shown the benefits of telemedicine in headache practice. In 2017, 1 randomized trial found telemedicine consultations for non-acute headache to be as efficient and safe as traditional consultation.<sup>32</sup> A pediatric headache clinic’s prospective analysis from 2018 similarly showed telemedicine to be convenient, cost-effective, and patient-centered, thereby providing high patient and family satisfaction for routine follow-up visits.<sup>33</sup> Further, in 1 randomized cohort of patients with severe migraine-related disability, telemedicine proved a feasible and effective mode of treatment when compared to in-office visits for migraine follow-up care.<sup>34</sup> COVID-19 has forced faster changes in practice than would have otherwise occurred, though fortunately with long-term improvements in both patient and clinician satisfaction, in efficiency, and in healthcare costs likely to result.

### **CONCLUSION**

The COVID-19 pandemic has been notable for high transmissibility, morbidity, and mortality, requiring rapid adaptations of care. Neurological complications are proving common, with headache certainly included. Treatments under investigation have also been studied for secondary and primary headache disorders. Headache medicine clinicians in New York City in particular have had to prioritize minimizing emergency department visits and hospitalizations as well as face-to-face visits and procedural treatments.<sup>27</sup>

We know that headache, particularly migraine, may worsen or begin after a major stressful life event, and an expected rise in post-traumatic stress disorder may accompany migraine worsening or onset in many patients. Consideration of the characteristics of patients with COVID-19 who also develop headache is one area in need of future study, along with the geographical differences in COVID-19-related headache prevalence. Further investigations are also needed to understand both the acute and long-term effects of SARS-CoV2 on the nervous system, on patients with pre-existing headache disorders, and on the current generation of headache providers.

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