



# Headache as a Significant Central Nervous System Manifestation of COVID-19 Infection

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## Dear Editor,

In recent years, the world has witnessed the emergence of dangerous respiratory diseases with coronaviruses, including the severe acute respiratory syndrome (SARS) by the SARS-CoV, Middle East respiratory syndrome (MERS) by the MERS-CoV, and coronavirus disease 2019 (COVID-19) by the SARS-CoV-2. The disease now affects most countries in the world. Coronavirus is generally known to cause respiratory disease, but clinical and experimental studies show that this disorder affects several organs including the central nervous system (CNS).<sup>1-3</sup>

The CNS effects of COVID-19 are not well-known owing to being an emerging phenomenon, however, it is worth understanding. The virus enters the cells of the human body using the cellular receptor angiotensin-converting enzyme 2 (ACE2). In a normal condition, this receptor is expressed in very small amounts in the CNS. The virus can be transmitted to the CNS through systemic circulation or across the cribriform plate of the ethmoid bone in the early and secondary stages of COVID-19 infection. Broad spectrum of neurological manifestations such as ageusia, anosmia, headache, sensory disturbances and epilepsy have been observed in some patients. Anosmia and ageusia are common, and can occur in the absence of other clinical features. Unexpectedly, acute cerebrovascular disease due to hyper coagulation state is also emerging as an important complication. Altered level of consciousness and encephalitis are other presentations in patients with COVID-19.<sup>4,5</sup> Almost all the articles reviewed focused on macro-and microscopic changes in the lungs, and only a handful of information from other organs and systemic findings were presented. Comprehensive study after autopsy in

the brain is very important and more research needs to be done.<sup>6-9</sup> A better understanding of the function of coronavirus in the CNS and accurate identification of the damage can help in treatment planning and prognosis of the disease.<sup>10,11</sup> In addition, hypoxia may occur in the CNS (hypoxic ischemic encephalopathy) due to respiratory failure. Thrombotic microangiopathy can also occur.<sup>12</sup> Hence, it is of paramount importance that in the early and uncomplicated stages of coronavirus infection, the patient's CNS be examined. There is still insufficient information to provide a complete picture of the pathophysiology of SARS-CoV-2 infection. Careful clinical, diagnostic, and epidemiological studies are needed to help define the manifestations and burden of neurological disease caused by SARS-CoV-2. Precise case definitions must be used to distinguish non-specific complications of severe disease (e.g. hypoxic encephalopathy and critical care neuropathy).<sup>4</sup> In light of the above mentioned, further studies on patients with progressive or worsening CNS findings should be performed more carefully to make the undiscovered effects of this virus on the CNS clearer to the world.

So far, we have mentioned CNS involvement in general and now we aim to give a brief summary of studies on headache attributed to COVID-19 infection. The reports on the neurological presentations are rising significantly and headache has the lead on the symptom list.

Headache associated with systemic infections is usually nonspecific and actually there are no particular distinguishing or characteristic features. It was reported that headache was a frequent symptom in COVID-19 infection and there was an extreme diversity in its characteristics.

In one observational case study that included patients

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who were consulted due to headache and had COVID-19 illness spontaneously, up to one-third of the hospitalized patients reported headache. The fact that might possibly be ignored in asymptomatic patients with COVID-19 is that headache can be isolated or the earliest symptom during the disease course.

Severe, rapid onset, continuing headache with migraine pattern that lasted up to 3 days has been specified in 70% of the patients and relieved in all patients during 2 weeks. Most of the patients were women and not suffering from primary headaches.

The pathophysiology of COVID-19 is complex and interacts with migraine. The angiotensin system, Calcitonin gene-related peptide (CGRP), inflammatory cytokines, and trigeminovascular activation with further basic and clinical studies should be assessed. It should be noted that headache associated with COVID-19 is more probably related to the peripheral mechanisms of infection in contrast to the migraine that primarily has a central origin.<sup>13</sup> Another study has confirmed that the possible pathophysiological mechanisms of headache is activation of peripheral trigeminal nerve endings by the SARS-CoV-2 directly or through the vasculopathy and/or increased circulating pro-inflammatory cytokines and hypoxia. In this study, headache with variable features including sudden to gradual onset, poor response to common analgesics, high relapse rate, limited to the active phase of COVID-19 was reported in 11%-34% of admitted patients with COVID-19.<sup>14</sup>

In another study, generally 64.4% of patients with COVID-19 reported severe, diffuse headaches, that had mostly begun on the first day of symptoms and 94% of them experienced bilateral headache. 15% of the patients presented a continuous headache, which was moderate to severe, and lasted for at least 15 days. More than half of patients had presenting severe intensity with migraine phenotype. In some patients, headache was triggered by coughing. Patients who reported hyposmia/anosmia or hypogeusia/ageusia experienced headache and phono phobia (38.4% and 39.7%, respectively) more frequently than those without these symptoms. Another interesting point that can be extracted from this study is that the migraine phenotype was observed more frequently in those experiencing previous migraine.<sup>15</sup> Another study revealed that more than half of patients had a diffuse, pressing headache with a median intensity of 7/10. Patients with moderate COVID-19, fever, dehydration, comorbidities, female sex had significantly higher frequency and intensity of COVID-19-related headache. For precise management, these prognostic factors can be considered as predictors.<sup>16</sup>

In a recent study on 121 patients, before the pandemic, 64.5% had migraine and 9.1% experienced a tension-type headache whereas 26.4% reported new onset headache post COVID-19 infection. Patient had significant increase

in headache days and analgesic consumption rather than before. There was evidence of statistically significant rise in severity and frequency of headache attacks with tension type headache. Another noteworthy point is that de novo headache was mostly resolved within 1 month. Besides, bi-frontal and temporal headache were the most reported. Patients younger than 40 years had longer duration of headache attack. Unlike previous studies, men suffered more severe headache compared with women.<sup>17</sup>

An observational study was done to estimate the frequency of headache in COVID-19 patients and classify the characteristics of related headache. Headache was reported by 23.4% of the patients. Given the fact that headache was the most frequent first symptom of COVID-19, near to half of patients reported prior history of headache. Median headache onset and duration were within 24 hours and 7 days respectively. However, it persisted after one month in 13% of patients. Pain was bilateral (80%), with frontal preference (71%), with pressing quality (75%), of severe intensity. Systemic symptoms were present in 98% of the patients. Headache frequency and phenotype was similar in patients with and without need for hospitalization and when comparing male and female patients, it was more intense in women.<sup>18</sup>

It was reported in a recent study that headache associated with COVID-19 has multiple phenotypes. Most patients had a less intense pain with the characteristics of tension-type headache, however one-fourth of patients suffered from severe and migraine-like headache. This migraine-like phenotype was observed in other studies previously mentioned. Another outstanding point is that, anyone could potentially experience headache similar to a migraine attack in the context of the pandemic, reflecting an activation of the trigeminovascular system.<sup>19</sup>

As a result, it can be concluded from these studies that headache is really common in COVID-19 patients and it can be the earliest or isolated symptom during the course of COVID-19. It is more common in women. Patients experience bilateral, diffuse, migraine-like, moderate to severe headache that mostly recovered within 2 weeks. Although, there are contradictory findings, most results about headache characteristics are consistent and similar.

Notwithstanding, all we have learned about headache related to COVID-19, may be defined as "Headache attributed to systemic viral infection" in the International Classification of Headache Disorders (ICHD) in a not-so-distant future.<sup>19</sup>

#### Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

#### Ethical Statement

Not applicable.

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