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**Review Article**

# COVID-19 and headache

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**Abstract**

A headache is a major symptom of COVID-19 and can indicate the development of systemic and neurologic symptoms. The clinical features of headache in COVID-19 are variable and underlying mechanisms have not been established yet. It should be considered that a headache can be an isolated presenting symptom of COVID-19 and can become a persistent daily headache after recovery. We think that there is a need for future studies to evaluate headache mechanisms and the relation of headaches with other symptoms and infection severity to improve care and optimize management for COVID-19.

***Keywords***: COVID-19, headache, trigeminovascular system

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## INTRODUCTION

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a pathogen with the potential to cause epidemics. The virus involves airways predominantly, resulting in many clinical conditions in a spectrum from asymptomatic infections to acute respiratory distress syndrome [coronavirus disease-2019 (COVID-19)] (1,2). Clinical features of COVID-19 consist of fever, cough, myalgia, shortness of breath, as well as neurological signs and symptoms including headache, dizziness, and impairments in taste and smell (2,3). In the International Classification of Headache Disorders, headaches caused by influenza and common cold viruses are classified under the following heading, "Headache Attributed to Systemic Viral Infection" (4). Although it is hypothesized that cytokines from immune cells, which are released in response to viral infection, induce headaches in the presence of upper respiratory tract infections, the underlying mechanism has not been fully understood (5). A recent systematic review about the global prevalence of headache in COVID-19 reported the cumulative prevalence of headache in COVID-19 patients as 25.2%, approximately twice more common than that of non-COVID-19 patients (patients with other viral infections of the respiratory system) (6).

A headache is an important symptom of COVID-19 infection and may occur as an initial and isolated symptom, indicating the development of further systemic and neurological symptoms. Moreover, it may become persistent over long periods as a possible chronic sequel of COVID-19 (7). The aim of this review is to perform a detailed review of the features of headaches seen in COVID-19 in detail in light of current data.

### *Pathophysiology of the COVID-19 headache*

No consensus has been achieved on the pathophysiology of headaches in COVID-19 although the effects of SARS-CoV-2 on the nervous system have been suggested to result from direct neuroinvasion, activities of proinflammatory cytokines, and indirect effects accompanied by hypoxia (7). While the mechanisms underlying the headache associated with COVID-19 remain to be established, a leading hypothesis is the direct invasion of the trigeminal nerve endings in the nasal cavity (8). Previous experimental studies have reported the spread of the infectious agent from peripheral nerves such as the olfactory nerve to the nervous system via retrograde axonal transport (9). Angiotensin-converting enzyme 2 (ACE2) is expressed in several areas of the brain, including neurons of the motor cortex, caudoputamen, thalamus, raphe nucleus, solitary tract, and nucleus ambiguous (10). ACE2 is known to be a cell receptor for SARS-CoV (11). Zhou et al. showed that SARS-CoV-2 could use a transmembrane metalloproteinase, ACE2, as an entry receptor to cells expressing the enzyme (12). Deregulation of the angiotensin-converting enzyme-2 (Ang II)/ACE2/angiotensin 1-7 in headache was previously reported and the availability of the angiotensin system in human trigeminal ganglia supports the trigeminal theory (13). However, trigeminovascular activation induced by endothelial inflammation takes a significant part in the etiology of headache. The inflammatory reaction is mediated by the interaction between the virus and endothelial cells with high expression levels of ACE2 (14). Vascular pathogenesis due to extensive endothelial damage caused by cytokine release in SARS-CoV 2 provides the grounds for a potential pathophysiological mechanism for cerebrovascular diseases and headaches (15).

Another potential mechanism is that the release of proinflammatory mediators and cytokines in SARS-CoV-2 infection may cause headaches by triggering the perivascular trigeminal nerve endings (16). Inflammatory mediators such as nitric oxide (NO), interleukin 1 beta (IL-1 beta), nuclear factor kappa B (NF-κB), and prostaglandin E2 (PGE2), and neuroinflammation are known to be involved in trigeminovascular activation (13). The release of these inflammatory mediators induces the activation of microglia, macrophages, and astrocytes, and leads to the disruption of the blood-brain barrier and pyrogenic hyperthermia of hypothalamic origin (17).

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***Features of the COVID-19 headache***

Headaches are among the most common neurological symptoms in COVID-19 (18). A headache may be an early-onset symptom of COVID-19 or may occur as an isolated symptom (19). In studies on patients with a confirmed diagnosis of COVID-19, headaches were reported to occur more commonly in women by a study, while others reported that they were observed more commonly in men (20-22). The majority of the patients had no previous history of chronic headaches but the majority of those with headaches were diagnosed with migraine and alterations were reported in the pain pattern in the presence of COVID-19 (23,24). COVID-19 patients with headaches were shown to have a higher number of comorbid diseases such as hypertension and diabetes (22). It has been reported that patients with a headache most commonly experienced cranial symptoms such as anosmia/ageusia and ocular pain, accompanying sore throat, myalgia, fatigue, fever, and gastrointestinal symptoms among other COVID 19 symptoms (25-27).The presence of cranial nerve symptoms such as headache and anosmia/ageusia coexisting with common COVID-19 symptoms supports the view that SARS-CoV-2 invades peripheral nerve terminals, causing activation of the trigeminovascular system, and that the virus can enter the central nervous system through transsynaptic pathways because of with its neurotropic characteristics (16). Increased circulating calcium gene-related peptide (CGRP) levels and various inflammatory mediators such as Interleukin-1β (IL-1β) and Interleukin-6 (IL-6) are thought to play a role in the development of gastrointestinal symptoms such as nausea and diarrhea accompanying headaches because increased CGRP is associated with headaches, an increase in gastrointestinal motility leading to diarrhea, vascular edema, and trigeminovascular activation, which induces inflammation (28,29) It was observed that headaches in COVID-19 patients usually started in the first days of infection, tended to improve with treatment, and completely resolved in the majority of patients in less than a month (30,31). In general, the headache was bifrontal and holocranial, and the pain had a throbbing and pressing character in most patients (20,31). Patients experienced mild to moderate headaches, mostly exacerbated by physical activity and coughing. The most common symptoms accompanying headache were photophobia, phonophobia, and nausea (15, 23).

Despite some migraine-like features of the headache seen in COVID-19, it was characterized by different features as well. Headaches in COVID-19 were more severe than primary headaches, they had a rapid course and high intensity, and they were resistant to analgesics (19). After the 3rd day of the disease, along with the alleviation of systemic symptoms, tenderness in the cervical and trapezius muscles and bilateral mild pain resembling tension-type headache occurred (32). However, it was reported that patients with a history of primary headaches experienced more frequent, prolonged, and severe attacks during COVID-19 than those without (33,34). In a study conducted on COVID-19 inpatients with most patients having pneumonia, it was shown that headaches were incapacitating symptoms causing significant disability (35). Found that most patients with COVID-19, who were discharged from the hospital with a diagnosis of covid, or another diagnosis during covid-19, had at least one of the symptoms of fatigue or muscle weakness, sleeping difficulties, anxiety, or depression after 6 months (36-41). In a similar study on patients with the diagnosis of COVID-19 presenting with a headache at admission, it was shown that the prevalence of headache and fatigue increased 7 months after discharge (30). However, studies have reported that the presence of headache among other symptoms of COVID-19 is associated with shorter disease duration and it is an independent predictor of a lower risk of death (16,27)

***Treatment***

COVID-19 has led to an increase in headache severity and patients' use of analgesics. It has been observed that patients most frequently use paracetamol for symptomatic relief, followed by nonsteroidal anti-inflammatory drugs (NSAIDs), metamizole, triptans, or a combination of these (23,31). Karadaş et al. reported that COVID-19 patients, who did not respond to

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paracetamol, had more severe headaches with higher blood IL-6 levels (22). Parenteral and oral corticosteroids are indicated for the management of headaches in the acute period and for prevention, respectively (42). Because of the potential immunosuppressive effects of corticosteroids, it is recommended that it will be best to avoid the orally used 1 mg/kg doses and give other therapeutic options to patients with headaches during the pandemic (43). Furthermore, it is suggested that carbamazepine should not be the first choice for the prophylactic treatment of headaches during the pandemic because of the risk of leukopenia associated with its use; which may further aggravate lymphopenia of COVID-19 (43).

The putative links between an increased risk of COVID-19 infection and certain drugs, such as Renin-Angiotensin System (RAS) inhibitors and ibuprofen, have raised concerns regarding their use during the pandemic. This concern is based on the fact that such medications increase the expression of ACE2, however, adequate evidence is not available to prevent their use (44). It is emphasized that paracetamol (acetaminophen) should be the first choice for headaches before starting NSAIDs because of its demonstrated favorable tolerability in studies (45).

## CONCLUSION

Headache pain is common in COVID-19 and characterized by variable clinical features. The underlying mechanism of headaches accompanying COVID-19 is not fully understood. In general, it was observed that headache pains started in the first days of the disease and progressed with mild or moderate severities having benign and short-lived pain characteristics. Despite reports of increased frequency and more severe course of headaches in patients with a history of primary headaches before COVID-19, no unique pain characteristics have been reported for the differentiation of COVID-19-associated headaches from other types. It should be noted that a headache may be an isolated symptom of COVID-19 and become a permanent daily headache after recovery. We think that further studies are needed to evaluate the mechanisms of headache and the relationship of pain with other symptoms and disease severity so that improved care and optimal management can be achieved for COVID-19.

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