



Review Article

Headache Pain Res 2024;25(1):24-33
pISSN: 3022-9057 · eISSN: 3022-4764
<https://doi.org/10.62087/hpr.2024.0008>

COVID-19 Infection-related Headache: A Narrative Review

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Abstract

Severe acute respiratory syndrome coronavirus 2 is the virus responsible for coronavirus disease 2019 (COVID-19), which caused a global pandemic and then became an endemic condition. COVID-19 infection may be associated with clinical manifestations such as respiratory symptoms and systemic diseases, including neurological disorders, notably headaches. Headaches are a common neurological symptom in individuals infected with COVID-19. Furthermore, with the transition to endemicity, COVID-19 infection-related headaches may reportedly persist in the acute phase of COVID-19 infection and in the long term after COVID-19 infection resolves. Persistent headaches after COVID-19 infection can be a significant concern for patients, potentially leading to disability. The present review discusses the clinical characteristics and potential underlying mechanisms of COVID-19 infection-related headaches.

Keywords: COVID-19, Headache, Headache disorders, Migraine disorders, SARS-CoV-2

INTRODUCTION

In December 2019, an outbreak of a severe respiratory illness, later identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was initially reported in Wuhan, China. This outbreak rapidly escalated into a global pandemic, garnering widespread international focus due to its significant infectious potential. In February 2020, the World Health Organization officially designated this illness as coronavirus disease 2019, abbreviated as COVID-19. In populations with comorbid conditions such as atrial fibrillation, heart failure, liver disease, seizures, dementia,

and insulin resistance, the prognosis following COVID-19 infection tends to be poor.¹⁻⁴ Even in the current era of endemic COVID-19, COVID-19 infection remains a major global health issue.⁵⁻⁷

In addition to the respiratory symptoms, the effects of COVID-19 are more widespread, encompassing a spectrum of neurological issues.⁸ The complications associated with COVID-19 vary from mild symptoms such as headaches and dizziness to more serious conditions including strokes and seizures.⁹ Findings from a comprehensive systematic review and meta-analysis showed that headache was a common symptom in COVID-19 cases, with a com-

Received: February 11, 2024; **Revised:** February 25, 2024; **Accepted:** February 26, 2024

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bined prevalence rate of approximately 25%.¹⁰ Evidence indicates that headaches are the most frequently observed neurological symptom of COVID-19 and they can sometimes appear as the initial indication of COVID-19 infection.¹¹ In addition to the direct association of headaches with COVID-19, increased cases of headaches have occurred among the general population and individuals with a prior history of headaches, which may be attributed to lifestyle changes during the COVID-19 period.¹²

Because headaches are the most frequent non-respiratory symptom associated with COVID-19, recognizing their various types and underlying causes could have important clinical consequences. To date, the characteristics of COVID-19 infection-related headaches have been explored in only a few studies. Thus, in the present narrative review, clinical characteristics of COVID-19 infection-related headaches are presented, and potential pathophysiology and treatment options of COVID-19 infection-related headaches explored.

CHARACTERISTICS OF AN ACUTE HEADACHE DURING COVID-19 INFECTION

Headaches typically begin early in the course of COVID-19 symptoms and can start on the first day of the illness in approximately 40%–55% of patients, and for approximately 25% of patients, it may be the first symptom of COVID-19.^{13–20} In approximately 10% of cases, a headache is the only symptom of COVID-19.^{13,21,22} For 50%–80% of patients who have a history of headaches, especially primary headaches, a COVID-19 infection-related headache can show different characteristics than their usual headaches. The COVID-19 infection-related headaches typically develop gradually and are bilateral, ranging from moderate to severe intensity, and are pressing or tightening types.^{23,24} The COVID-19 infection-related headaches are often accompanied by photophobia in 14%–49% of cases, phonophobia in 5%–41%, and nausea and/or vomiting in 14%–43%.^{13,18,21,22} Although in most studies, tension-type headaches (TTHs) were reported the most common form, in several studies, migraines were suggested to be more frequent.^{13,18,21,22} Overall, the nature of post-COVID-19 headaches can be considered as somewhere between TTHs and migraines.

As the COVID-19 pandemic progressed, various strains

of the virus have been identified, each showing different characteristics and prevalence of symptoms like headache. Earlier research, which didn't include data on the Omicron variant, found a higher frequency of headache at the onset of infection in patients with the Delta variant (33%–62%) compared to the Wild-type (21%) and Alpha (12%–56%) variants.^{25,26} However, not all studies support this finding.²⁷ Currently, the Omicron variant is the most prevalent, and there is conflicting information regarding its association with headaches.²⁸ Reports indicate that headaches are a common symptom of the Omicron variant, but recent findings suggest a decline in headache cases following the rise of Omicron.²⁹ Infections from the Omicron variant are reportedly associated with headaches more often than those from the Wild-type and Alpha variants, though the incidence is somewhat lower than with the Delta variant.^{29–31}

SECONDARY HEADACHES DUE TO COVID-19 INFECTION BASED ON THE INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS 3RD EDITION CLASSIFICATION

The most frequently observed headache disorders associated with the ongoing pandemic, classified according to the International Classification of Headache Disorders 3rd Edition (ICHD-3) codes, are discussed below.

1. Acute headache attributed to systemic viral infection

According to the ICHD-3, to diagnose an acute headache caused by a systemic infection, individuals must experience headache episodes that are diffuse and/or moderate to severe in intensity. These headaches should develop, intensify, and subside in temporal correlation with a confirmed systemic viral infection, without any signs of meningitis or encephalitis.³² Headaches are a frequent symptom among COVID-19 patients, and those associated with the infection can exhibit characteristics of either migraine, TTH, or a combination of both. The nature of these headaches is not restricted to a single type.^{33,34} With the Omicron variant of the virus, headaches are a very common symptom, ranking as the second most likely symptom following upper respiratory issues.³⁵

2. Headache attributed to viral meningitis or encephalitis

Headaches attributed to viral meningitis or encephalitis typically present as either holocranial (affecting the entire head) or nuchal (in the neck area) and often occur with fever and neck stiffness. The presence and variety of neurological symptoms are dependent on the severity of the infection in individuals who have been diagnosed with meningitis or encephalitis.³² For headaches attributed to viral encephalitis, diagnosis is established in cases where there is either multifocal or widespread brain swelling or the presence of at least one of the following symptoms: altered mentality, seizure, or focal neurologic deficit.³²

Acute brain inflammation and encephalitis are most commonly caused by viruses such as herpes simplex virus, influenza virus, varicella-zoster virus, enterovirus, and cytomegalovirus. However, other respiratory viruses, including SARS-CoV and Middle East respiratory virus, also lead to brain swelling and inflammation.^{36,37} Typically, headaches associated with these conditions are widespread, intense, and can be either throbbing or pressing, often concentrated in the frontal or retroorbital area.³² Viral encephalitis can also present with milder symptoms such as fever and mild headache or may occur without any symptoms.³⁸

In cases where individuals experience either unilateral or bilateral headaches accompanied by fever and neck stiffness, which worsen with physical activity and the Valsalva maneuver, and sometimes associated with nausea, vomiting, photophobia, then, viral meningitis or encephalitis can be suspected.³⁹ To confirm the diagnosis for viral meningitis or encephalitis, neuroimaging assessments may be helpful, specifically revealing the enhancement of the leptomeninges.³² As the COVID-19 pandemic advanced, the frequency of reported encephalitis cases related to COVID-19 increased.⁴⁰ In a systematic review in which the neurological manifestations of COVID-19 were investigated, acute viral meningitis or encephalitis was the most common initial diagnosis in patients with confirmed COVID-19 infection.⁴¹

3. Headache attributed to other non-infectious inflammatory intracranial diseases

During a COVID-19 infection, the development of headaches is influenced by cytokine release, which also alters the pain threshold. Headaches induced by a cytokine storm, a significant immune response, typically arise between the 7th and 10th day following the onset of the disease. These headaches can be classified as headaches attributed to other non-infectious inflammatory intracranial disease according to ICHD-3 criteria.³² In a previous cross-sectional study in which the effects of systemic inflammatory molecules in COVID-19 patients were investigated, serum levels of Nod-like receptor pyrin domain-containing 3 (NLRP3), high mobility group box-1 (HMGB1), angiotensin-converting enzyme 2 (ACE2), and interleukin (IL)-6 were significantly elevated in COVID-19 patients experiencing headaches compared with subjects without headaches.⁴² In this previous study, the authors concluded that increased levels of these mediators might contribute to the sensitization of the trigeminal system, leading to headache as a secondary symptom of SARS-CoV-2 infection.⁴² Furthermore, in a case-control study, cytokine and IL profiles in COVID-19 patients were assessed and compared between subjects with and without headaches. The authors found that IL-10 and IL-23 levels were significantly higher in patients suffering from headaches than in subjects without headaches among the COVID-19 cohort.⁴³

4. Headache attributed to cranial or cervical vascular disorder

Increasing evidence indicates that COVID-19 may lead to an increased risk of a hypercoagulable state and thromboembolic events. The occurrence of acute stroke in COVID-19 patients is estimated to be approximately 1.5%,⁴⁴ with a potentially higher rate in severe cases requiring intensive care unit admission compared with patients treated in general wards.⁴⁵ This increased thrombosis risk is thought to be due to endothelial damage caused by cytokine release syndrome. Rare complications of COVID-19, such as cerebral venous sinus thrombosis (CVST), ischemic stroke, and hemorrhagic stroke, have been documented. Although focal neurological signs and reduced

consciousness levels are more common than headaches in many conditions, especially in ischemic and hemorrhagic strokes, headaches often serve as a primary early warning sign in CVST and subarachnoid hemorrhage. In addition, recognizing the correlation between these cerebrovascular disorders and COVID-19 infection-related headaches is crucial.

5. Headache attributed to increased cerebrospinal fluid pressure

Under the ICHD-3 diagnostic criteria, for a headache to be classified as one attributed to increased cerebrospinal fluid (CSF) pressure, the CSF pressure must be over 250 mm and the composition should be normal.³² In addition, at least two of the following criteria must be met: presence of papilledema, the headache developing in temporal relationship with intracranial hypertension, and the headache improving in temporal relationship with reduced CSF pressure. A possibility also exists that headaches might develop due to increased CSF pressure following a COVID-19 infection. Therefore, if headaches persist after a COVID-19 infection, assessing whether they are related to increased CSF pressure is necessary.

6. Headache attributed to hypoxia and/or hypercapnia

A particular type of headache syndrome emerges and intensifies following exposure to low oxygen levels (hypoxia) and/or high carbon dioxide levels (hypercapnia), and shows significant improvement as the balance between oxygen and carbon dioxide is restored.³² In more severe instances, SARS-CoV-2 infection can result in widespread inflammation in the alveoli and throughout the body as well as disruptions in gas exchange, leading to headaches caused by hypoxia-induced neuroinflammation.⁴⁶ In a study of hospitalized COVID-19 patients, subjects experiencing silent hypoxemia (low blood oxygen levels without respiratory distress) were more likely to report new-onset headaches.⁴⁷

PRIMARY HEADACHE DUE TO COVID-19 INFECTION BASED ON THE INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS 3RD EDITION CLASSIFICATION

1. Cough headache

Cough headache is an uncommon type of headache that typically emerges following coughing or other straining actions such as sneezing, bending over, or performing a Valsalva maneuver, and occurs without any abnormalities visible on imaging. A cough headache is generally bilateral and posterior, short-lived, and resolves on its own. A cough headache usually persists for a maximum of 30 minutes, although it can last up to 2 hours in some cases. In approximately 40% of cases, cough headache syndrome is symptomatic, arising as a secondary condition to other disorders.³² This type of headache, triggered by coughing, has also been observed in COVID-19 patients.^{15,48} In a cross-sectional study of hospitalized COVID-19 patients, 26% of subjects with COVID-19-related headaches reported experiencing cough headaches.²² In addition, cough headache occurrences have been reported with frequencies ranging from 2–10%.^{15,23} Some research indicates that cough headaches associated with systemic infections may be due to changes in vascular tone within the cranial vessels.⁴⁹

POSSIBLE MECHANISM OF COVID-19 INFECTION-RELATED HEADACHES

There are several possible mechanisms of COVID-19 infection-related headaches (Figure 1).

1. Direct involvement of trigeminal nerve

ACE2, a metalloproteinase, serves as the specific entry receptor for SARS-CoV-2 in cells. In numerous studies, results indicated that SARS-CoVs can lead to damage in multiple organs by reducing ACE2 expression on cells, a mechanism also supported by research on influenza.⁵⁰ Within the central nervous system (CNS), ACE2 is primarily found in neurons but is also present in glial cells. Notably, ACE2 is located in areas, such as the brainstem and motor cortex, thalamus, caudate nucleus, putamen, raphe nucleus, tractus solitarius, rostral ventrolateral medulla, and nucleus

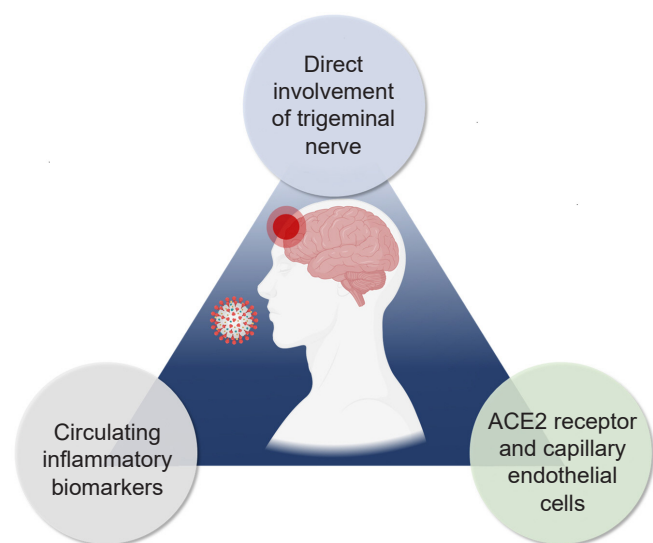


Figure 1. Possible mechanisms of COVID-19 infection-related headaches.

ambiguous.^{51,52} In previous research, the renin-angiotensin system in the trigeminal ganglia was suggested to possibly facilitate the direct invasion of the trigeminal nerve endings through the nasal or oral cavities.^{53,54} In *in vivo* studies in which the molecular mechanisms of COVID-19 were investigated, the virus was shown to enter the CNS via the olfactory bulb and then spread to other regions retrogradely through trans-synaptic routes. Pathways associated with ACE and the olfactory system are also considered potential routes for virus neuroinvasion.⁵⁵

2. Circulating inflammatory biomarkers

An additional hypothesis for the cause of headaches associated with COVID-19 is the effect of circulating inflammatory biomarkers including cytokines.⁵⁴ Cytokines play a role in altering the pain threshold and in rendering the trigeminal nerve fibers more sensitive.^{56,57} Typically, headaches in the context of COVID-19 are accompanied by other systemic infection symptoms and thought to be triggered by cytokine release syndrome. This syndrome is a result of an intense immune reaction to the infection, marked by a surge in various cytokines including tumor necrosis factor-alpha (TNF- α), IL-2, IL-6, IL-7, IL-10, granulocyte colony-stimulating factor, monocyte chemoattractant protein 1, interferon-gamma inducible protein 10, and

macrophage inflammatory protein 1-alpha.^{58,59} This cytokine storm is a key feature of cytokine release syndrome. The involvement of cytokines such as TNF- α in developing headaches was previously reported.⁶⁰ Evidence indicates TNF- α contributes to headache formation, including observations of elevated serum TNF- α levels during migraine episodes and the onset of headaches following TNF- α infusions.⁶¹ Increases in inflammatory cytokines, including IL-1, which shares many functions with TNF- α , have also been reported.^{58,59} In other research, patients receiving granulocyte-macrophage colony-stimulating factor treatment experienced headaches,⁶² and headaches were identified as a primary side effect of IL-2 therapy.⁶³ Experimental models have shown that coronaviruses can infect macrophages and glial cells, leading to the release of inflammatory mediators. However, attributing the early and isolated occurrence of headaches solely to a cytokine storm remains unconvincing and more data are required to fully understand this phenomenon.

3. ACE2 receptor and capillary endothelial cells

Elevated ACE2 expression levels in the capillary endothelium indicate potential vascular damage and activation of the trigeminovascular system, which can lead to headaches.⁴⁶ The interaction of the SARS-CoV-2 spike protein with ACE2 receptors on the capillary endothelium can compromise the blood-brain barrier.⁶⁴ This activation of the trigeminovascular system results in the release of neurotransmitters known to induce pain, such as substance P and calcitonin gene-related peptide (CGRP). The headaches that result from this process may resemble migraines in their symptoms, including throbbing pain, nausea, photophobia, and phonophobia.⁶⁵

TREATMENT FOR HEADACHES RELATED TO COVID-19 INFECTION

To date, randomized clinical trials on treating headaches related to COVID-19 infection have not been conducted. Therefore, the results of recent observational studies or expert opinions are described and summarized in this section (Table 1). The effectiveness of corticosteroids in treating headaches after COVID-19 infection has not been proven. Based on observational data from institutions that

Table 1. Summary of treatment for COVID-19-related headaches

Possible medication	Study result	Caution	Reference
Corticosteroids	There was no significant difference in the frequency or intensity of headaches that occurred after COVID-19 infection depending on whether corticosteroids were administered. In another study, patients receiving corticosteroids were more likely to respond well to nonsteroidal anti-inflammatory drugs (NSAIDs) for headaches that occurred after COVID-19 infection.	The effectiveness of corticosteroids in treating headaches after COVID-19 infection has not been proven. Corticosteroids can cause immune deficiency, which may be associated with opportunistic infections.	20, 66
Acetaminophen, NSAIDs, metamizole, triptans, or a combination of these oral medications	Several oral medications, including combination therapy, may lead to complete or partial relief (about 25% to 54%) for COVID-19-related headaches.	The effectiveness of oral medications may be insufficient, and if accompanied by nausea and vomiting, administration can be challenging.	15
Paracetamol	About 60% of patients with headaches after COVID-19 infection showed improvement after an intravenous administration of 1 g of paracetamol.	Usually, paracetamol can be prescribed as parenteral formulations.	67
Lidocaine	Lidocaine can be used to block the greater occipital nerve, leading to relief in 85% of COVID-19-related headaches that do not respond to paracetamol.	Lidocaine can be applied for occipital nerve block.	67
NSAIDs (ibuprofen)	Concerns were raised that NSAIDs, especially ibuprofen, might be associated with worse outcomes and increased infectivity of SARS-CoV-2. However, this hypothesis was not confirmed in subsequent studies. Usually, NSAIDs can be prescribed as oral or parenteral formulations.	Care should be taken regarding renal dysfunction caused by NSAIDs. NSAID administration can mask COVID-19-related symptoms.	68

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

administered corticosteroids to patients with moderate to severe COVID-19, association was not found between the administration of corticosteroids and occurrence, frequency, or intensity of headaches.⁶⁶ Conversely, in another study in which a similar hospital protocol was followed, patients with COVID-19 of moderate to severe intensity who were administered corticosteroids, subjects who responded poorly to analgesics for headaches were more often in the group that did not receive steroids.²⁰

In a European study on the treatment of headaches following COVID-19 infection, the medications used were acetaminophen (75%), nonsteroidal anti-inflammatory drugs (NSAIDs), metamizole, triptans, or a combination of these (25%).¹⁵ Complete relief of headaches was reported in 26% of all patients and 54% experienced partial improvement.¹⁵ In another study, 59% of patients with headaches post-COVID-19 infection showed improvement after an intravenous administration of 1 g of paracetamol. For subjects who did not respond to paracetamol, lidocaine was used to block the greater occipital nerve, leading to relief in 85% of these cases.⁶⁷ Early in the COVID-19 pandemic, concerns were raised that NSAIDs, especially ibuprofen,

might be associated with worse outcomes and increased infectivity of SARS-CoV-2. However, this hypothesis was not confirmed in subsequent studies.⁶⁸ However, monitoring might be necessary when using NSAIDs because the kidneys are a target organ affected by COVID-19.

PERSISTENT HEADACHE AFTER COVID-19 INFECTION

Reports vary, however, among individuals who experience headaches during the acute phase of COVID-19, 6%–45% continue to suffer from headaches beyond the initial phase of the infection (typically 2–4 weeks).²⁴ Factors associated with persistent headache include being younger, female, having a history of primary headaches (especially migraines), experiencing headache as the first COVID-19 symptom, and having thyroid disorders.^{18,33} In studies in which persistent headaches post-COVID-19 infection were monitored, 16.5% of patients continued to experience headaches for 60 days, 10.6% for 90 days, and 8.4% for more than 180 days.⁶⁹ Therefore, the prevalence of persistent headaches apparently decreases over time. In

addition, these persistent headaches can exacerbate existing primary headaches.⁶⁹

If serious secondary headache causes are excluded, treatment similar to that for new daily persistent headache (NDPH) can be considered. Although NDPH can be diagnosed as secondary to a systemic viral infection, the possibility of NDPH, especially following COVID-19 infection, cannot be dismissed. Viral infections can trigger NDPH and reportedly, NDPH after COVID-19 infection can occur.⁷⁰⁻⁷² Regarding treatment, because clinically proven trials have not been conducted, empirical treatment may be considered. In previous reports, treatments such as steroids and venlafaxine, as well as anticonvulsants, onabotulinum toxin, or CGRP antibody therapies were suggested.⁷⁰⁻⁷²

CONCLUSION

Headaches following COVID-19 infection are not uncommon and often improve within 3 months but can sometimes persist for a longer period, necessitating differentiation from secondary headaches. Typically, these headaches resemble TTHs or migraine headaches and can be managed with general analgesics and NSAIDs. However, in cases where headaches do not improve over a long period, various medications can be tried. The exact mechanisms underlying these headaches are poorly understood, highlighting the need for further research into their causes and the management of prolonged headaches after COVID-19 infection.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization: TJS; Data curation: TJS; Formal analysis: TJS; Investigation: TJS; Methodology: TJS; Software: TJS; Validation: TJS; Writing—original draft: YC, TJS; Writing—review and editing: YC, TJS.

CONFLICT OF INTEREST

Tae-Jin Song is the Editor of *Headache and Pain Research*

and was not involved in the review process of this article. All authors have no other conflicts of interest to declare.

FUNDING STATEMENT

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2023-00262087 to TJS). The funding source had no role in the design, conduct, or reporting of this study.

ACKNOWLEDGMENTS

Not applicable.

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