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# Headache in Acute and Post-Acute Sequelae of SARS-Cov-2 (PASC) or Long COVID

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## Abstract

Headache is a prevalent symptom of COVID-19 and long COVID, and they can be debilitating. If you experience headaches, it is essential to seek medical attention immediately to ensure proper diagnosis and treatment. It has been observed that a considerable proportion of individuals (ranging from 6-45%) diagnosed with COVID-19 and exhibiting symptoms of headache during the acute phase, tend to experience persistent headaches in the post-symptomatic phase. This observation highlights the need for further research into the long-term effects of COVID-19, particularly concerning its neurological impact on patients. It is imperative to conduct more studies to understand the underlying mechanisms and pathophysiology of such headaches in order to provide appropriate treatment and management strategies for those affected. The pathophysiology is not clear. Headaches during COVID-19 can stem from both direct effects of the virus and broader systemic reactions like inflammation and hypoxemia. Key symptoms such as headache, loss of smell, and loss of taste suggest the virus's potential to cause local inflammation early in the infection. Neurological findings, including microhemorrhages in the olfactory bulb, underline the virus's impact on the nervous system. Inflammatory markers are elevated in patients with severe headaches, indicating an inflammatory response. The trigeminovascular system's activation due to olfactory and nasal inflammation, alongside a hypoxic state from reduced oxygen levels, are believed to contribute to headaches. SARS-CoV-2's entry into the central nervous system (CNS), possibly through the olfactory pathway or a compromised BBB, can lead to a range of neurological symptoms, with inflammation and coagulopathy playing roles in headache development. Persistent headaches post-infection suggests a lasting inflammatory response, necessitating further research and clinical attention for management.

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## Introduction

Headaches are a prevalent symptom of COVID-19 and long COVID, and they can be debilitating. If someone experiences headaches, seeking immediate medical attention is essential to ensure proper diagnosis and treatment. Don't suffer in silence; take action and prioritise their health. It has been observed that a significant proportion of individuals (ranging from 6-45%) diagnosed with COVID-19 and exhibiting symptoms of headache during the acute phase, tend to experience persistent headaches in the post-symptomatic phase (Chhabra et al., 2022). This observation highlights the need for further research into the long-term effects of COVID-19, particularly concerning its neurological impact on patients. It is imperative to conduct more studies to understand the underlying mechanisms and pathophysiology of such headaches in order to provide appropriate treatment and management strategies for those affected.

A recent study, after examining 130 patients, discovered that after six weeks. During the follow-up period, headaches continued in 37.8% of patients, and half of them had no prior history of headaches (Caronna et al., 2020). 21.4% of patients reported having a headache as a prodromal symptom. Daily and persistent headaches were experienced by 61% of patients. There was a noticeable female predominance among these cases.

Another study examined the duration of headaches during the acute and post-COVID period in a comprehensive systematic review of 36 clinical trials. They found that 16.5% of patients experienced headaches for up to 60 days, 10.6% experienced them within 90 days, and 8.4% experienced them for more than 180 days after the disease started (Fernández-de-Las-Peñas et al., 2021). As a result, headache frequency gradually declines over time. A decline in the prevalence of headache over time was also observed, according to an analysis of data from six Spanish cohort studies that included 905 adults with headache in the acute phase of COVID-19 (1% at 31 months, 3% at 19 months, 6.16% at 8 months, and 9% at 16 months) (Garcia-Azorin et al., 2022). Furthermore, after nine months, a stronger headache during the acute stage of the illness was linked to a higher prevalence of persistent headache notes.

One of the trickiest problems in the correlation between coronavirus infection and headaches is still how primary cephalgia functions in the post-COVID era. Another study explored the association between a history of migraine and long-term post-COVID symptoms, particularly fatigue, after severe acute respiratory SARS-CoV-2 infection. It found that while patients with a history of migraine who recovered from COVID-19 exhibited more long-term post-COVID symptoms like fatigue, the presence of headache as a long-term post-COVID symptom was not associated with a prior history of migraine (Fernández-de-Las-Peñas et al., 2021a) However, individuals with a history of headaches before contracting COVID-19 experienced worsening conditions after developing long COVID (Rodrigues et al., 2023). Headaches in long COVID patients have been observed to change in characteristics, showing tendencies towards chronification, longer durations, and symptoms like photophobia. Patients also reported a reduced response to analgesic treatments, indicating

a shift in the headache experience post-COVID-19 (Rodrigues et al., 2023). Daily persistent headache (NDPH) occurring after COVID-19, has been the subject of numerous studies. For instance, a study focused on participants across 11 Latin American countries who had experienced NDPH following COVID-19 infection highlighted that the majority of these participants began experiencing persistent headaches within the first two weeks of their COVID-19 onset. Notably, characteristics such as the headache's occipital location, severe intensity, burning character, and radiating pain were more prevalent among those diagnosed with NDPH compared to those with non-NDPH headaches (Carrión et al., 2023).

Another study also addresses this condition, indicating a growing recognition of NDPH as a post-COVID syndrome (Liu et al., 2020). In every situation, symptomatic headaches should be ruled out due to the challenges in validating this kind.

The impact of COVID-19 on individuals with migraine has been documented in a study that investigated the effects of quarantine on migraine characteristics. The research, part of the Italian National Headache Registry, aimed to explore changes in migraine frequency, severity, and medication use during the quarantine, considering lifestyle, emotions, and the pandemic's spread. Results indicated some reduction in headache days and acute medication intake during quarantine compared to pre-quarantine periods. This suggests that the pandemic and associated lockdown measures may have influenced migraine patterns in some individuals, which is often associated with the influence of psychosocial stressors associated with the pandemic Delussi et al., 2020). These observations are in logical agreement with the data that patients with a previous history of primary headache with COVID-19 disease are more likely to have severe cephalgic syndrome compared to those without a history of headache (52.9 vs 47.1%) (Magdy et al., 2020). The negative impact of the COVID-19 pandemic, in general, has also been demonstrated in patients.

It makes sense that individuals who have previously experienced primary headaches and are infected with COVID-19 are more likely to have more severe headaches than those who have not. In fact, 52.9% of those infected with COVID-19 who have a history of primary headaches experience severe headaches compared to 47.1% who do not have a history of primary headaches (Magdy et al., 2020).

## Pathophysiology

In the acute phase of SARS-CoV-2 infection, headaches can occur due to both specific and non-specific pathways. Non-specific mechanisms that may contribute to the onset of headache in COVID-19 include direct viral damage, inflammation, hypoxemia, coagulopathy, and endothelial dysfunction.

The presence of headache, anosmia (loss of smell), and ageusia (loss of taste) in COVID-19 patients suggests that the virus may invade the body and cause local inflammation, resulting in painful symptoms. These symptoms are often strongly associated with headache and typically occur at the beginning of the disease's clinical phase (Trigo et al., 2020) (Rocha et al., 2020). Recent studies have shown that individuals with COVID-19 and anosmia, a condition characterized by loss of smell, have been found to exhibit microhemorrhages in the olfactory bulb, which is the area responsible for the sense of smell. These microhemorrhages can be observed through magnetic resonance imaging (MRI). Additionally, persistent headache has also been reported in COVID-19 patients with anosmia. These findings provide valuable insights

into the neurological effects of COVID-19 and highlight the importance of monitoring patients with anosmia for potential underlying brain damage. It is widely recognized that COVID-19 symptoms such as chills, fever, sore throat, exhaustion, and myalgia are commonly associated with headaches (Sampaio Rocha-Filho et al., 2022) However, a significant number of people who had previously experienced headaches related to viral infections reported that their cephalgic symptoms were similar to those of COVID-19, with between 46% and 62% of them identifying COVID-19 as the cause of their headache.

Studies have shown that patients with severe headaches had higher levels of inflammatory serum interleukins and cytokines compared to those without headaches (Trigo et al., 2020) (Bolay et al., 2021) This suggests that headaches may be a result of an inflammatory response to the virus. Furthermore, people with headaches were found to be more likely to experience rhinosinusitis symptoms (Straburzyński et al., 2022), which include nasal congestion, runny nose, and sinus pain. It is important to note that while headaches are a common symptom of COVID-19, they can also be caused by other factors such as stress, dehydration, or eye strain.

Thus, these data support the assumption of the role of direct viral and vascular damage, as well as a local inflammatory process, in the origin of headache in COVID-19. In principle, both damage to the olfactory tract and inflammation of the nasal cavity can activate the trigeminovascular system (FAS) and cause headache (Messlinger et al., 2022) Another non-specific mechanism that may be involved in these processes is the hypoxic state, which can lead to vasodilation of the cerebral vessels and hence the onset of headache (Sampaio Rocha-Filho et al., 2022).

Based on the available data, it appears that headaches in individuals with COVID-19 may be caused by direct viral and vascular damage, as well as a localized inflammatory process. Specifically, damage to the olfactory tract and inflammation of the nasal cavity may activate the trigeminovascular system and cause headaches (Messlinger et al., 2022). The trigeminovascular system is a pathway that is implicated in headache disorders, including migraines.

Moreover, a hypoxic state, which is characterized by low oxygen levels, may also contribute to the onset of headaches. This may occur due to the vasodilation of cerebral vessels, which can result from reduced oxygen supply to the brain (Sampaio Rocha-Filho et al., 2022). The hypoxic state can also cause inflammation in the brain and the release of certain chemicals that can trigger headaches. Taken together, these mechanisms may explain the occurrence of headaches in individuals with COVID-19. Understanding these underlying processes may help in the development of effective treatments for this symptom, which is one of the commonly reported symptoms of COVID-19.

SARS-CoV-2, the virus causing COVID-19, can trigger specific pathophysiological mechanisms that lead to headaches. This can happen through direct viral invasion of the nervous system or systemic factors. Even individuals without a prior history of migraines can experience migraine-like symptoms during COVID-19, which suggests that the virus may be targeting the trigeminal nerve, a possible path for the virus to cause headaches.

The SARS-CoV-2 virus can directly invade the CNS due to its neurotropism, a characteristic also observed in SARS-CoV and MERS-CoV. This can result in a wide range of neurological complications in COVID-19 (Bergmann et al., 2006) (Altable et al., 2020). The virus can invade the CNS in two ways: the olfactory pathway and impaired blood-brain barrier

(BBB) permeability. The olfactory route is the most well-known, as it can explain the link between headache and anosmia. The virus invades the CNS by entering through peripheral terminals and spreading transsynaptically to other brain regions by retrograde transport. The angiotensin-converting enzyme 2 (ACE2) receptor is used as the main cell entry receptor for this process (Jackson et al., 2022). ACE2 receptors are present in the epithelial cells of the nasal mucosa. However, SARS-CoV-2 RNA is found not only in the nasal mucosa but also in the olfactory bulb and various terminals of the trigeminal nerve innervating the conjunctiva, cornea, palate mucosa, and trigeminal ganglion, and SARS-CoV-2 can spread through the bloodstream and reach the meningeal membranes(Zhang et al., 2021). This is because the cerebral vessels contain ACE2 receptors that allow the virus to pass through the intact blood-brain barrier (BBB) and penetrate the CNS.

Once the virus enters the endothelial cells of the cerebral vascular system, it triggers inflammatory responses by activating neutrophils, macrophages, and complementary pathways (Zhang et al., 2021). This inflammation can destabilize the BBB, which in turn may cause further brain damage and activate the trigeminovascular system (TVS). The activation of TVS can lead to headaches, which is a common symptom of COVID-19 (Brann et al., 2020).

Furthermore, COVID-19 is known to cause coagulopathy, which is a disorder that affects the body's ability to form blood clots. Coagulopathy contributes to the formation of microemboli in cerebral vessels, which may also play a role in headache generation (Tietjen et al., 2017). These microemboli can cause blockages in small blood vessels, leading to reduced blood flow and oxygen supply to the brain, which can trigger headaches.

Another route for SARS-CoV-2 entry into the CNS is through the BBB, which is primarily composed of brain endothelial cells. These cells express tight junction proteins that generally prevent the diffusion of substances between cells. Viruses that cross the BBB may do so by being transported via mechanisms such as adsorptive transcytosis or by altering BBB properties to permit direct entry. Experiments have shown that the S protein of SARS-CoV-2, a key component of the virus, can disrupt the integrity of the BBB, although this finding requires careful consideration due to variable dosages of S protein used in studies. It has been observed that inflammation can cause minor leakage of the S protein across the BBB, but this does not significantly alter the main transport mechanism (Fujimoto et al., 2022). Furthermore, brain endothelial cells express receptors associated with viral invasion, such as ACE2 and TMPRSS2, playing a significant role in SARS-CoV-2's potential to invade the brain. While SARS-CoV-2 has a low replication capacity in brain endothelial cells without inflammatory conditions or ACE2 overexpression, the virus and its spike proteins can cross the BBB and enter the brain, possibly affecting the brain endothelial cells directly and indirectly through the immune system.

For a comprehensive understanding of SARS-CoV-2 neuroinvasive mechanisms and its potential impact on neurological symptoms such as headaches, further research is essential. The studies mentioned provide valuable insights into the complex interactions between SARS-CoV-2 and the CNS, highlighting the need for ongoing investigation in this area. For more detailed information, you can explore the full articles on Frontiers in Neuropathological Aspects of SARS-CoV-2 Infection and Neurotropism and blood-brain barrier involvement in COVID-19 (Silva et al., 2022).

In summary, the ability of SARS-CoV-2 to penetrate the CNS and cause inflammation can destabilize the BBB and activate TVS, leading to headaches. Coagulopathy and the formation of microemboli in cerebral vessels also contribute to

the development of headaches. Additionally, SARS-CoV-2 can enter the brain through areas of BBB damage and directly affect the brain tissue, which may exacerbate headache symptoms.

COVID-19 is known to damage the brain through various systemic factors. One of these factors is the ability of the virus to induce a state of hyperinflammation known as a cytokine storm. This storm can lead to the activation of interleukin 6 (IL-6), a molecule that is linked to the dysregulation of coagulation factors and inflammatory biomarkers. This dysregulation can be a contributing factor to the manifestation of migraines (Yan et al., 2012).

Another molecule that may be involved in the formation of headaches in COVID-19 patients is calcitonin gene-related peptide (CGRP). CGRP can cause vasodilation and modify vascular permeability, allowing for the recruitment of inflammatory cells in local areas. This can contribute to tissue inflammation and sepsis. CGRP levels have been observed to increase during migraine attacks [40] and COVID-19 headaches (Sampaio Rocha-Filho et al., 2022).

It is worth noting that a new targeted drug designed to treat COVID-19 patients by targeting CGRP has been developed and is currently in clinical trials (Caronna et al., 2021). This drug offers hope for effective treatment of COVID-19 patients experiencing migraines and other related symptoms.

It is critical to consider the various mechanisms that can lead to persistent headaches in COVID-19 patients. These mechanisms may differ from the headaches experienced during the acute phase of the disease. A certain proportion of patients who did not experience headaches before contracting COVID-19 report persistent headaches for an extended period, which may indicate their post-infectious nature. This includes new daily persistent headaches (Caronna et al., 2021), which are caused by the sensitization of Trigeminal Autonomic Cephalalgia (TAC) due to persistent inflammation caused by microglial activation and the release of inflammatory mediators such as glutamate, interleukins, complement proteins, tumour necrosis factor alpha, and quinolinic acid. The increase in levels of these mediators can lead to the activation of glutamate and NMDA (N-methyl-D-aspartate) receptors, which can cause headaches (Boldrini et al., 2021).

It is believed that microglial activation and the release of inflammatory mediators could be responsible for the sensitization of TAC, leading to persistent headaches. Further research is required to understand the exact pathophysiology of COVID-19-induced headaches. Nevertheless, it is important to recognize the possibility of post-infectious headaches in COVID-19 patients who experience persistent headaches after recovery. It is recommended that patients who experience persistent headaches seek medical attention to determine the cause of their headaches and receive appropriate treatment.

## Structural and functional brain changes

Recent research has suggested that long COVID may have neurological manifestations that could be associated with structural and functional brain changes. To assess the effects of COVID-19 on the brain, a longitudinal project was conducted that had been studying brain structure and cognitive function over time in 785 participants prior to the pandemic onset. The study compared participants who tested positive for COVID-19 (n 01) with those who remained COVID-19 free (n 84) by analysing neuropsychological and MRI information. A second comprehensive evaluation,

including MRI, was conducted 38 months after the first one. The study has found that grey matter reduction was observed in patients with COVID-19, specifically in the parahippocampal gyrus (Douaud et al., 2022). Moreover, a higher cortical surface area and grey matter volume in orbitofrontal cortex was observed in a sample of patients with long COVID headache, but no differences were documented regarding cortical thickness, which could imply that some grey matter changes may be manifestation-specific (Planchuelo-Gómez et al., 2021). Most changes were observed in areas that were functionally connected with the primary olfactory cortex (Sollini et al., 2021) (Guedj et al., 2021). Resting-state functional connectivity has been compared between COVID-19 survivors and healthy controls, observing weakened functional connections between the cingulate, hippocampal gyri, parietal, temporal and frontal gyri and strengthened functional connectivity with occipital regions. Furthermore, white matter changes have been reported in COVID-19 survivors, compared with healthy controls, with higher axial diffusivity in corona radiata, and internal and external capsules (Planchuelo-Gómez et al., 2021). These findings suggest some degree of white matter axonal alterations, which could be involved in the persistence of headache. However, the specificity of these changes in regard to headache is still to be ascertained.

Regarding brain metabolism, there are no headache-specific studies, but the regions most frequently reported as hypometabolic include the right parahippocampal gyrus, the brainstem, thalamus, amygdala, orbital gyrus, olfactory gyrus, and temporal lobe. One study compared images from 18-fluor-deoxy-glucose PET and functional MRI imaging, showing an overlap between the areas where the connectivity was altered in the MRI and F-18 FDG PET changes (Kiatkittikul et al., 2022).

Overall, these findings suggest that long COVID may have neurological manifestations that could be associated with structural and functional brain changes. The specific mechanisms that cause these changes are still not fully understood. However, these findings can help in the development of better treatment and management strategies for patients experiencing long COVID symptoms.

## Conclusion

Headaches are a common and often severe symptom of COVID-19 and Long COVID, affecting a considerable proportion of patients during the acute phase and persisting afterward. While the exact cause of these headaches is not yet fully understood, medical professionals suggest that they may be attributed to the immune and inflammatory responses triggered by the viral infection. These persistent headaches can significantly impact a person's quality of life, making it difficult to carry out daily activities and leading to a decline in overall wellbeing. Therefore, it is crucial to seek medical attention for accurate diagnosis and management of these headaches. A healthcare provider can help determine the underlying cause of the headaches and recommend effective treatments to alleviate the symptoms.

Moreover, the observation of prolonged headaches post-infection highlights the need for more research into COVID-19's long-term neurological impacts. It is currently unclear whether these headaches are a result of direct damage to the nervous system or a secondary effect of the viral infection.

Understanding the pathophysiology behind these headaches is essential for developing effective treatments and managing long-term neurological complications. In conclusion, persistent headaches are a serious and common symptom of COVID-19 and long COVID. Seeking medical attention and conducting research to understand the underlying cause of these headaches is crucial for effective management and treatment.

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