



Headache as a Symptom of COVID-19: Narrative Review of 1-Year Research

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Abstract

Purpose of Review Headache is a common symptom of COVID-19 with emerging literature being published on the subject. Although it may seem unspecific, scientific evidence has allowed a better definition of this headache type, revealing relevant associations with other COVID-19 symptoms and prognoses. We therefore sought to highlight the most remarkable findings concerning headache secondary to COVID-19, specifically focusing on epidemiology, characteristics, pathophysiology, and treatments.

Recent Findings The real prevalence of headache as a symptom of COVID-19 is still unclear ranging from 10 to 70%. Headache mainly has a tension-type-like phenotype, although 25% of individuals present with migraine-like features that also occur in patients without personal migraine history. This finding suggests that a likely pathophysiological mechanism is the activation of the trigeminovascular system. SARS-CoV-2 neurotropism can occur by trans-synaptic invasion through the olfactory route from the nasal cavity, leading to anosmia which has been associated with headache. SARS-CoV-2 protein has been found not only in olfactory mucosa and bulbs but also in trigeminal branches and the trigeminal ganglion, supporting this hypothesis. However, other mechanisms such as brain vessels inflammation due to SARS-CoV-2 damage to the endothelium or systemic inflammation in the context of cytokine storm cannot be ruled out. Interestingly, headache has been associated with lower COVID-19 mortality. No specific treatment for COVID-19 headache is available at present.

Summary Studies show that investigating COVID-19 headache represents an opportunity not only to better understand COVID-19 in general but also to advance in the knowledge of both secondary and primary headaches. Future research is therefore warranted.

Keywords Headache; SARS-CoV-2 · COVID-19 · Migraine · Pathophysiology

Introduction

At the end of 2019, the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), emerged in the city of Wuhan, China [1], being responsible for severe forms of pneumonia. The SARS-CoV-2 infection was defined as

coronavirus disease 2019 (COVID-19). Coronaviruses have a zoonotic origin but can cause severe respiratory infections in humans, as demonstrated in 2002 and 2012, respectively, by the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [1]. However, due to its even higher pathogenicity and transmissibility, the SARS-CoV-2 has rapidly spread all over the world, causing millions of deaths and putting health systems at stake [2].

On March 11th, 2020, the WHO officially characterized the global COVID-19 outbreak as a pandemic [3], turning it into one of the main global health issues of our times. Nowadays, 1 year later, the world keeps struggling with COVID-19, and while some nations have been able to control it, others have faced different waves of the pandemic with an unstoppable increase in the numbers of COVID-19 cases [4]. Recently vaccines against SARS-CoV-2 have been

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developed and campaigns to achieve immunization have started globally as preventive measures [5]. Nevertheless, we will still be dealing with SARS-CoV-2 in the near future and, probably, with its consequences in long term. This fact makes it mandatory to further advance in the understanding of this virus and its pathophysiological mechanisms to keep ensuring effective healthcare measures on a global scale.

Since the beginning of the pandemic, a lot of research has been made and published on COVID-19.

COVID-19 is primarily recognized for involving the respiratory system, potentially leading to respiratory failure that requires urgent medical aid [1]. However, infected people may experience a variety of symptoms such as gastrointestinal, renal, and hematological that could range from mild to severe [1]. Among COVID-19 symptoms, the neurological ones have emerged as relevant clinical manifestations of the SARS-CoV-2 infection, involving either the central or the peripheral nervous system [6].

Headache is no exception. Specifically, as a symptom of COVID-19, it represented one of the major complaints expressed by SARS-CoV-2-infected patients, leading neurologists to analyze it in detail.

In this narrative review, we sought to highlight the most remarkable findings concerning headache secondary to COVID-19; this is a headache as a symptom of the SARS-CoV-2 infection. However, to fully clarify the advances made in the field of headaches secondary to viral infections, we should put studies into context by evaluating the similarities and differences with primary headache disorders and their role in COVID-19.

Headache as a Symptom of COVID-19

Definition

As SARS-CoV-2 is a new entity and headache in this setting has never been studied before, headache associated with COVID-19 lacks a specific definition and could be therefore considered as *9.2.2 headache attributed to systemic viral infection*, following the International Classification of Headache Disorders-3 (ICHD-3) [7]. This definition requires that headache is 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. Evidence of causation should be demonstrated by at least two of the following: (1) headache has developed in temporal relation to 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 improvement in or resolution of the systemic viral infection, and (4) headache has either or both of the following characteristics:

(a) diffuse pain and (b) moderate or severe intensity. Moreover, according to ICHD-3, it could be defined as acute if a headache has been present for < 3 months or chronic if present for > 3 months; the systemic viral infection still being active or has resolved within the last 3 months.

However, as we will discuss in this review, the amount of research done in this field has allowed us to better characterize headache associated with COVID-19 showing the limitation of the present classification of “headache attributed to a systemic viral infection.”

Epidemiology

According to the World Health Organization, headache is listed in the category of less common symptoms of COVID-19 [8]. Prevalence data on headache associated with COVID-19 mainly come from studies involving the inpatient population with the limitation of often excluding severe patients due to the difficulty in collecting headache characteristics. Different prevalence rates have been observed that seem to be related with study design showing retrospective studies around 10–20% prevalence of headache associated with COVID-19 [9–11, 12•], compared to > 50% in cross-sectional or prospective studies assessing headache face-to-face in the acute setting [13•, 14–17]. So, the real prevalence is still a matter of debate and differences may also be the result of the specific objective of the study (assessing specifically headache vs. COVID-19 symptoms in general) and the researchers involved (neurologists vs. non-neurologists).

Limited data are available on the outpatient population, however, headache seems to be a common symptom reaching 60% prevalence [18].

Characteristics/Phenotype

Several studies have focused on describing the characteristics of headache associated with COVID-19. Females and young people seem to be more likely to experience headache in the context of COVID-19, whereas patients without headache seem to be older and more frequently men [12•, 13•]. In this context, according to a web-based study, having male gender together with bilateral localization, duration over 72 h, and analgesic resistance were important variables to differentiate between COVID-19 positive patients from negative ones [19]. Headache is also more common in patients with primary headache disorders but not exclusive of this population [13•].

Concerning headache phenotypes, around a 25% experience a migraine-like headache [13•, 20], whereas the most common presentation is a tension-type-like headache. In one study, patients with severe headache had also more constant and difficult-to-treat pain and more frequently presented headache before any other COVID-19 symptom. Another

study that specifically investigated certain headache characteristics such as quality of pain and associated symptoms in COVID-19 patients suggests that individuals with history of migraine or other primary headaches presented headache in the setting of COVID-19 more compatible with their medical history, for example, showing more pulsating pain in the group with migraine history [21]. However, we should consider that (1) migraine-like features are expressed as well in patients without personal migraine history [13] and (2) COVID-19 patients with previous headache history may present with a different headache in the acute phase of the infection than their usual one, especially in terms of severity or duration [16, 22].

A very interesting finding that has been reported in several studies is that COVID-19 patients with headache more often associate anosmia and ageusia, linking together the two major neurological symptoms at a cranial level [12, 13, 15].

Prognosis

The presence of headache has been associated with better COVID-19 evolution in terms of 1-week shorter COVID-19 disease duration [13] and was inversely associated with worse outcomes in one study involving 1000 patients attended at the ER [23]. Two studies also observed that headache was associated with lower mortality [12], findings confirmed by a recent meta-analysis showing a significantly higher risk ratio of survival COVID-19 in patients with headache [24].

The better prognosis seems to be validated by findings on inflammatory biomarkers, showing lower C-reactive protein (CRP) [11, 16] and lower and more stable Interleukin-6 (IL-6) levels during hospitalization [13] in COVID-19 patients with headache compared to those without it. One study assessing inflammatory biomarkers in relation to COVID-19 headache phenotypes observed that tension-type-like headache was the one associated with lower CRP and procalcitonin, whereas the migraine-like phenotype showed more lymphopenia that may suggest worse disease outcomes in this specific subgroup [25].

Concerning specifically headache prognosis, limited data are available at present. A prospective study with a 6-week follow-up observed a mean headache duration of 2 weeks; however, 37.8% of COVID-19 patients had an ongoing headache at this timepoint [13]. Interestingly, 50% of them had no previous headache history. This study also observed that those patients with persisting headache had a higher proportion of headache starting as the first symptom, compared with patients that were not suffering from headache anymore, as well as higher proportions of previous headache history [13]. At longer terms, presence of headache has been scarcely investigated, and no study specifically focuses

on prevalence and characteristics of persisting headache. However, at present one study on multiple COVID-19 symptoms shows a prevalence of headache at 3 months of 38% [26], while another study around 2% at 6 months [27].

Pathophysiology

Headache pathophysiology in the setting of the acute phase of SARS-CoV-2 infection may be the result of different mechanisms both unspecific and specific. Among unspecific mechanisms that could be related to headache, fever is still a matter of debate and could be mediated by an increase of proinflammatory cytokines [28]. In two recent studies on COVID-19, headache seemed to be present independently from fever [13, 21], whereas another work observed higher odds of having headache in COVID-19 patients with fever [12]. Nevertheless, COVID-19 patients with headache had more frequent and severe headaches when associating fever and dehydration [14]. Another unspecific mechanism that is worth mentioning is hypoxia that can lead to cerebral vasodilation and therefore headache [11, 29].

However, SARS-CoV-2 itself may activate specific pathophysiological mechanisms leading to headache, that could potentially represent (1) a direct viral invasion of the nervous system or (2) systemic factors with indirect brain effects. The fact that headache attributed to COVID-19 could have migraine features even in individuals without a personal history of it point to the trigeminovascular system as one of the main targets of the virus, leading to headache.

The possibility of direct CNS invasion for SARS-CoV-2 has been suggested by the neurotropism showed by SARS-CoV-1 and MERS-CoV as well as by the ample spectrum of neurological complications associated with COVID-19 [30]. Although SARS-CoV-2 can infect neurons *in vitro* and cause neuronal death [31], data from CSF and autopsy have been controversial, showing limited evidence of direct CNS invasion [32, 33]. However, a recent study has helped demonstrating the existence of this phenomenon [34], which may occur through two main pathways: the olfactory route and the blood–brain barrier (BBB). The most interesting one is represented by the olfactory route as it could explain the association between headache and anosmia, the virus being able to invade peripheral nerve terminals and enter the central nervous system through trans-synaptic pathways. Similar to other coronaviruses, SARS-CoV-2 could be internalized in nerve terminals by endocytosis, transported retrogradely, and spread trans-synaptically to other brain regions [35] and use angiotensin-converting enzyme-2 (ACE2) as the main receptor to gain cell entry [36]. The ACE2 receptor is present in the nasal mucosa but on epithelial cells rather than olfactory neurons [37]. Nevertheless, SARS-CoV-2 RNA has been detected not only in olfactory mucosa but also in the olfactory bulb and different branches of the trigeminal nerve

(including conjunctiva, cornea, mucosa covering the uvula and the respective trigeminal ganglion [34•]). These data support a peripheral neurotropism that takes place inside the nasal cavity where the activation of the trigeminovascular system may be mediated by the pathogen itself on trigeminal branches present at this level or through olfactory-trigeminal interactions.

The other mentioned pathway could be explained by the fact that SARS-CoV-2 can reach the meninges through bloodstream dissemination. The presence of ACE2 in human brain vessels [38] and immunoreactivity to SARS-CoV-2 protein in cerebral and leptomeningeal endothelial cells [34•] seems to confirm the possibility for the virus to cross the intact BBB and invade the CNS. Virus entrance into endothelial cells of brain vasculature activates neutrophils and macrophages and complement pathways, promoting inflammation [34•]. Proinflammatory cytokines may lead to BBB instability, further damaging the brain, and may activate the trigeminovascular system, causing headache [39, 40]. Moreover, coagulopathy is a well known phenomenon associated with COVID-19 [41], and inflammation in the brain can potentially promote microthrombi deposition in brain vessels [34•], resulting as well in headache. However, SARS-CoV-2 may also enter the brain in regions with a leaky BBB due to fenestrated capillaries, such as the median eminence of the hypothalamus and other circumventricular organs [42, 43]. A dysfunction in these areas cannot be ruled out, with potential consequences on headache, as the hypothalamus is a well-known region in migraine pathophysiology [44].

Among systemic factors that could affect the brain leading to headache, it is important to point out that COVID-19 may trigger a hyperinflammatory state in some patients known as cytokine storm [45], with a prominent role of IL-6 [46, 47], whose levels seem to correlate with dysregulation of other coagulation and inflammatory biomarkers in a recent proteomic study [48]. The role of IL-6 has been also demonstrated in neuroinflammation [49] and specifically in migraine [50]. One study observed that COVID-19 patients with headache had lower and more stable IL-6 levels, finding that together with the better COVID-19 prognosis in this group may indicate that inflammation is kept to a more localized level [13•]. However, a cluster analysis on COVID-19 patients with headache observed higher levels of IL-6 in patients reporting more severe headache in the acute phase of COVID-19 [51].

Other molecules, such as calcitonin gene-related peptide (CGRP), may also be involved in headache in the setting of COVID-19. CGRP has several other functions in the human body [52]. For example, by producing vasodilation and modifying vascular permeability, it potentially allows the recruitment of inflammatory cells to the local area [53], being involved in tissue inflammation and sepsis. However,

CGRP, depending on the situation, may promote inflammation or protect from it [54]. Recently, there is growing evidence of a neuroimmune unit in the lungs able to regulate pulmonary inflammatory responses, through the vagus nerve and the activation of the TRPV1 channel that could lead to CGRP release [55]. Therefore, CGRP could be involved in the systemic inflammation produced by SARS-CoV-2 and acts as well in the brain. CGRP is elevated during migraine attacks [56] and headache during COVID-19 might represent an increase in CGRP levels as a host response. At present, one study has analyzed CGRP in COVID-19 patients, showing a surprisingly reduction in its levels [57], though it is still unclear whether this is pathological or compensatory. The existence of anti-CGRP medications for migraine treatment [58] makes the understanding of the CGRP pathway in COVID-19 valuable as available drugs could be repurposed to treat COVID-19. An anti-CGRP drug is currently under trial as a potential COVID-19 therapy [59], but results have not still been published.

Other factors could be related to COVID-19 headache pathophysiology according to the current knowledge on primary headache disorders. For example, ACE2, the receptor used by SARS-CoV-2, belongs to the renin-angiotensin system, which could be altered in migraine [60], and drugs that inhibit ACE1 or block angiotensin receptors are used in migraine prevention [61]. Another factor could be vitamin D deficiency which has been associated with COVID-19 mortality [62] and represent a possible migraine preventive treatment [63].

From a pathophysiological standpoint, other aspects to be analyzed are the mechanisms underlying persistent headache in the context of COVID-19, which could be different from the headache experienced in the acute phase. Although no data are available at present, persistent headache may reflect a sensitization of the trigeminovascular system that persists once the viral infection has resolved. The fact that a relevant proportion of patients without a personal history of headache had persistent headache [13•] may point to a post-infectious etiology for cases of new daily persistent headaches [7]. This sensitization may represent persistent inflammation due to activation of microglia and release of inflammatory mediators, such as glutamate, quinolinic acid, interleukins, complement proteins, and TNF- α .7 [64, 65]. Increased quinolinic acid can lead to higher glutamate and upregulation of NMDA receptors. Glutamate is reported to be involved in migraine pathophysiology and at present treatments to block the NMDA receptor, such as memantine, are used in migraine prevention [66].

Treatment

No specific acute treatment exists for headache related to COVID-19 and drugs can be chosen according to headache

phenotype. For migraine-like phenotypes triptans and, where available, lasmiditan and gepants may be an option, although it is important to consider all possible contraindications that could be related not only to patients' comorbidities but also to COVID-19 clinical stage and severity at the moment of the prescription. Although concerns had been raised in the use of nonsteroidal anti-inflammatory medications (NSAIDs) during the COVID-19 outbreak, due to the putative risk that they may upregulate ACE2 and therefore facilitates SARS-CoV-2 infection, there are no clear scientific data that preclude their use in the general population who may acquire COVID-19 or in those acutely infected with the virus [67, 68]. Corticosteroids, that represent an effective treatment in status migrainosus, seem to be beneficial in severe COVID-19 [69]. They therefore represent potentially safe medication to be used in patients with a prolonged headache that does not respond to other acute treatments [68]. Peripheral nerve blocks especially of the greater occipital nerve could be useful as well [51].

Prevention should be considered for persistent headache and the type of drugs prescribed can be based on (1) headache phenotype (migraine-like vs. tension-type-like), (2) patient's comorbidities, and (3) existence of other concomitant conditions that developed in the setting of COVID-19 and are frequently reported in the post-COVID phase (sleep disturbances, mood disorders, memory impairment, etc.). However, due to the lack of scientific data, studies evaluating specific preventive treatments and regimens are warranted to define the best therapeutic strategies for persistent headache. Two considerations should be done concerning specific headache preventive treatments. First, similar to NSAIDs, concerns on renin-angiotensin system (RAS) blockers had initially been raised for the potential ACE2 upregulation, although based on current evidence, there is no increased risk of COVID-19 in patients treated with these drugs [67, 70]. Therefore, they can still represent a therapeutic option in headache prevention. Second, as CGRP may promote or protect from inflammation, the safety of CGRP antagonism during the pandemic has been studied comparing migraine patients with and without anti-CGRP monoclonal antibodies [71]. Results showed that they seem to be safe as the number of COVID-19 cases and severity were similar between groups. However, as mentioned earlier in the review, CGRP antagonism could be even beneficial for COVID-19, but its efficacy in both SARS-CoV-2 infection and specifically in treating COVID-19 headache still has to be proven.

Future Implications

As headache represents a common and complex symptom of COVID-19 but is still scarcely understood, new research in the field is necessary. Specifically, the literature

available at present has raised several questions that should be addressed by future investigations to advance in defining and treating this headache type.

COVID-19 Headache vs. Headache Due to Other Viral Infections

The COVID-19 pandemic represented a unique scenario to study headache attributed to viral infection, as, due to the need of doctors, many neurologists attended COVID-19 patients as general clinicians in the acute setting. This was an opportunity to better observe the presence of neurological symptoms, such as headache otherwise not analyzed in detail. For this reason, it was possible to collect specific data on headache due to COVID-19, whereas literature regarding headache associated with other viruses is very limited. Headache characteristics, for example, have been only marginally studied in Dengue [72], Zika [73], and HIV [74], making it difficult to assess whether headache, as described in relation to COVID-19, is specific to this disease or not. A daily persistent headache is reported as a consequence of the 1890 Russian/Asiatic flu [75], which may suggest that at least certain headache-related pathophysiological mechanisms are similarly activated by a variety of viruses. However, the specific involvement of trans-synaptic pathways and therefore of trigeminal branches in SARS-CoV-2 infection may represent a rationale for separating headache attributed to SARS-CoV-2 from the general definition of 9.2.2 *headache attributed to systemic viral infection*, as it already happened, although for other scientific reasons, in ICHD3 for A9.3 *Headache attributed to human immunodeficiency virus (HIV) infection* [7].

Headache Evolution vs. COVID-19 Evolution

COVID-19 patients may experience different headache phenotypes, mainly migraine-like or tension-type-like, that suggest different pathophysiological mechanisms. These mechanisms could underlie not only different headache evolutions, but also different presentations of COVID-19 itself and different disease courses. For this reason, specific headache phenotypes may be related to a specific COVID-19 prognosis, and inversely, different degree of severity of COVID-19 may result in different headache characteristics and evolution. Considering the lack of data at present, more research should be conducted in characterizing headache phenotypes and evolution in mild, moderate, and severe COVID-19 patients, respectively, as a tool for clinicians to precisely define patients' prognosis.

Headache in the Acute Phase vs. Headache in the Post-COVID Setting

After 1 year from the pandemic outbreak, an emerging health issue is represented by the long-term sequelae of the SARS-CoV-2 infection, notably the so-called post-COVID-19 syndrome [76]. Persistent headache is one of the main symptoms that patients may experience [26] and will probably represent a common reason to seek specialized medical care in the future. Unfortunately, due to the lack of specific literature, it is not possible to define at present headache outside the acute phase. Future studies will have not only to characterize it but also to clarify the relationship between headache in the acute phase and the one following it, as the underlying mechanisms may be different and could impact treatment. Moreover, the link between headache and other post-COVID symptoms (memory loss, fatigue, etc.) should be investigated.

Primary Headache Disorders in the Context of COVID-19

As already mentioned, the fact that patients without previous migraine history can suffer from a migraine-like phenotype in the context of SARS-CoV-2 infection supports the idea of the activation of the trigeminovascular system. This perhaps is due to the existence of shared pathophysiological mechanisms between primary and secondary headache disorders. On this basis, a genetic predisposition to activate the trigeminovascular system is present in migraine, whereas an acquired activation of this system due to a viral infection or other noxae may lead to migraine-like secondary headaches [77].

Investigating primary headache disorders in the context of a viral infection will be even more relevant in the future, considering that COVID-19 studies have observed that headache as a symptom of the acute phase of the infection is associated with lower mortality. It is therefore logical to wonder whether primary headache disorders as well may be protective in viral infections [24]. In that case, questions may raise on whether they have emerged as adaptive responses in human evolution to enhance survival and consequently genetically selected in the population in response to certain stimuli such as viruses [24]. Genetic studies on COVID-19 will offer the opportunity to evaluate the risk and severity of the SARS-CoV-2 infection in specific populations such the ones with headache as a symptom of the disease or as a comorbid disorder, thus clarifying their mutual relationships.

Conclusions

Headache is a common symptom of COVID-19, resulting from mechanisms involving individual factors and SARS-CoV-2 characteristics such as its neuro-invasive potential

and ability to produce inflammation. Although several questions still need to be answered, studies on COVID-19 have helped to regain interest in *9.2.2 headache attributed to systemic viral infection*. However, COVID-19 headache research represents a unique opportunity to better understand COVID-19 in general and advance in the knowledge of both secondary and primary headaches.

Compliance with Ethical Standards

Conflict of Interest Dr Caronna has received honoraria from Novartis and Chiesi. Dr Pozzo-Rosich has received honoraria as a consultant and speaker for the following: Allergan-AbbVie, Almirall, Biohaven, Chiesi, Eli Lilly, Medscape, Neurodiem, Novartis, and Teva. Her research group has received research grants from Novartis and has received funding for clinical trials from Alder, Amgen, Electrocore, Eli Lilly, Novartis, Teva. She is a trustee member of the board of the International Headache Society and the Council of the European Headache Federation. She is on the editorial board of *Revista de Neurologia*. She is an editor for *Cephalalgia*, *Headache*, *Neurologia*, *Frontiers of Neurology*, and advisor for *The Journal of Headache and Pain*. She is a member of the Clinical Trials Guidelines Committee of the International Headache Society. She has edited the Guidelines for the Diagnosis and Treatment of Headache of the Spanish Neurological Society. She is the founder of www.midolordecabeza.org. PP-R does not own stocks from any pharmaceutical company. The authors declare no conflict of interest in regard to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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