Neurology Perspectives 1 (2021) S31–S36

NEUROLOGY PERSPECTIVES

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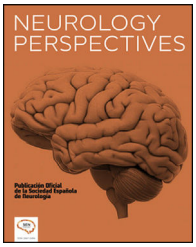

REVIEW

Persistent headache after COVID-19: Pathophysioloy, clinic and treatment

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Received 1 August 2021; accepted 12 October 2021

KEYWORDS
Headache;
SARS-COV-2;
COVID-19;
Long COVID;
New daily persistent headache

Abstract SARS-CoV-2 is the virus responsible for the COVID-19 pandemic. The acute infection is characterised not only by respiratory symptoms, but also by multiple systemic manifestations, including neurological symptoms. Among these, headache is a frequent complaint. As the pandemic progresses and the population of patients recovering from COVID-19 grows, it is becoming apparent that the headache present in the acute stage of the infection may persist for an indeterminate period, becoming a major problem for the patient and potentially leading to disability. In this review we describe the pathophysiological and clinical aspects of persistent headache after COVID-19 based on the information currently available in the literature and the authors' clinical experience.

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https://doi.org/10.1016/j.neurop.2021.10.003

PALABRAS CLAVE
Cefalea;
SARS-COV-2;
COVID-19;
Post-COVID;
COVID persistente;
Cefalea diaria persistente de novo

Cefalea persistente tras el COVID-19: Fisiopatología, clínica y tratamiento

Resumen El SARS-CoV-2 (Síndrome Respiratorio Agudo Grave – Coronavirus 2) es el virus responsable de la pandemia por la Enfermedad por el Coronavirus de 2019 (COVID-19). La fase aguda de la enfermedad se caracteriza no sólo por síntomas respiratorios, sino que el cuadro clínico puede estar acompañado de múltiples síntomas sistémicos, incluyendo los neurológicos. Entre ellos, la cefalea es una queja frecuente. A medida que avanza la pandemia y crece la población de pacientes que se recuperan del COVID-19, se está observando que la cefalea presente en la fase aguda de la infección puede persistir durante un periodo de tiempo indeterminado, convirtiéndose un problema capital para el paciente y llegando a condicionar discapacidad. En esta revisión proporcionamos información acerca de los aspectos fisiopatológicos y clínicos de la cefalea persistente tras el COVID-19 en base a la información disponible en la literatura actual y la experiencia clínica de los autores.

Concept of persistent headache following COVID-19: Disease mechanisms

SARS-CoV-2 is a novel coronavirus that appeared in China in late 2019, and causes the disease COVID-19. COVID-19 is characterised by respiratory symptoms, including respiratory insufficiency requiring invasive ventilatory support. However, since the beginning of the pandemic in early 2020, other symptoms have been described during the acute stage of infection; these include neurological, gastrointestinal, kidney, and haematological manifestations, among others.[1] Among neurological symptoms, headache is a common complaint.[2–5]

Since early in the pandemic, persistent symptoms and/or late-onset complications have been reported in some patients after the acute stage of COVID-19. The most frequent symptoms are headache, cognitive alterations, insomnia, fatigue, and dizziness[6,7]; this phenomenon has been referred to as "post-COVID syndrome." Although we currently lack epidemiological data on post-COVID syndrome, its high prevalence and the significant degree of disability it seems to be able to cause suggest that it may become a global healthcare issue in the immediate future. Among the associated symptoms, persistent headache is becoming an increasingly common reason for consultation at headache units. The objective of this study is to review the pathophysiology and clinical manifestations of persistent headache after SARS-CoV-2 infection and to provide recommendations on the management of these patients.

Several hypotheses have been proposed on the pathophysiology of headache in the context of acute COVID-19. Some of these mechanisms, both non-specific and specific to SARS-CoV-2, may be involved in the persistence of headache after resolution of the acute stage of the disease. However, due to the current lack of conclusive data, many of these hypotheses remain controversial.

Non-specific mechanisms include systemic inflammation, which during acute COVID-19 can be so severe that it has been described as a "cytokine storm."[8] It has been suggested that, during the acute stage, headache may be caused by circulating inflammatory mediators activating the trigeminovascular system at the meninges. We cannot rule out the possibility that this inflammatory response may be sustained after infection in some patients, which may play a role in the persistence of such post-COVID symptoms as headache. A recent study reported higher levels of proinflammatory cytokines between 3 and 9 months after hospital discharge in patients presenting persistent symptoms after COVID-19 than in healthy controls.[9] These findings have not been confirmed by other authors.[10,11] Another possibility is that more severe inflammation during the acute stage may cause persistent activation of the trigeminovascular system. However, this hypothesis would not explain the fact that post-COVID headache frequently appears in patients who presented milder disease in the acute stage. Therefore, the role of systemic inflammation in post-COVID headache remains controversial; clarifying this aspect of the pathophysiology of post-COVID syndrome is particularly relevant as inflammation reflects the activation of specific immune mechanisms. In this context, some authors have suggested that the persistence of symptoms after the acute stage may be related to constant immune activation.[12] We cannot rule out the hypothesis that this phenomenon may be promoted by the persistent presence of SARS-CoV-2 antigens in some tissues, despite no longer being detectable in nasopharyngeal exudate.[13] Other authors suggest that autoimmune mechanisms targeting host epitopes are generated during acute infection.[14] However, we currently have insufficient information on the relationship between immunity and these symptoms, including headache.

We must also consider the role of local inflammatory mechanisms in post-COVID headache. Specifically, a degree of localised inflammation in the nervous system may persist as a sequela of direct mechanisms of viral damage occurring during the acute stage. In the case of headache, trigeminovascular damage may occur through several mechanisms. SARS-CoV-2 appears to be neurotropic, invading the nervous system through the trans-synaptic pathway.[15,16] Another possibility is that the virus reaches the meninges via the blood, which would facilitate local inflammation of the endothelium (endotheliitis) and blood-brain barrier disruption,[17] with potential to activate the trigeminovascular system. Both mechanisms require prior viral invasion of the respiratory epithelium via angiotensin-converting enzyme 2 (ACE2), which acts as a receptor.[18] This enzyme is expressed

in the epithelial cells of the nasal mucosa, although it is not present in the nerve endings of the first cranial nerve.[19] However, recent studies have detected SARS-CoV-2 RNA not only in the olfactory mucosa, but also in the olfactory bulb and trigeminal nerve (including nerve endings in the conjunctiva, cornea, and the mucosa of the uvula, as well as the gasserian ganglion).[20] This finding supports the idea that this mechanism acts as an activation pathway of the trigeminovascular system due to direct involvement of branches of the trigeminal nerve. The presence of ACE2 in cerebral blood vessels[21] and the immunoreactivity of the cells of the cerebral endothelium and leptomeninges to SARS-CoV-2 proteins[20] also support the hypothesis of damage to the meningeal endothelium. Therefore, this damage during the acute stage would lead to the activation of local inflammatory mechanisms, particularly those involving the microglia; this would facilitate the continuous release in the brain of such mediators as glutamate, quinolinic acid, interleukins, complement proteins, and tumour necrosis factor α.[22,23] These mediators may perpetuate activation of the trigeminovascular system, playing a role in headache persistence.

Finally, we should mention the possible role of calcitonin gene-related peptide (CGRP). This protein is released by pulmonary nerve endings during viral infection, and participates in regulating the immunoinflammatory response.[24] CGRP levels are elevated in patients with migraine,[25] and infusion of the molecule can cause migraine attacks in patients with the condition.[26] Elevated circulating CGRP levels may cause headache in predisposed individuals in the context of acute COVID-19. Sustained activation of the trigeminovascular system during the acute stage may lead to central sensitisation of second-order neurons; this may play a role in the persistence of headache after infection, similarly to the mechanism by which episodic migraine transforms to the chronic form.[27] However, to date, only one study has attempted to analyse CGRP levels in patients with and without headache in the acute stage of COVID-19, finding no significant differences between groups[28]; another study observed lower CGRP levels in patients with COVID-19 than in controls.[29] Therefore, further research is needed to confirm these findings and to ascertain whether CGRP plays a role in headache associated with COVID-19.

These observations seem to indicate that persistent headache after COVID-19 may involve several complex processes.

Clinical phenotype

Both in clinical and in research settings, the terms "post-COVID headache" and "persistent headache after COVID-19" tend to be used to describe any chronic headache whose onset or worsening appears to present a temporal relationship with confirmed SARS-CoV-2 infection. However, several clinical patterns have been defined according to the specific moment of headache onset and its relationship with the patient's personal history (presence or absence of primary headache prior to COVID-19).[30]

The first pattern is persistence of headache with onset during the acute infection, despite the resolution of the remaining symptoms of COVID-19.[30] The prevalence of headache during acute COVID-19 ranges from 13.0% to 74.6%.[2–4,31,32] Studies that only analyse data on patients hospitalised due to COVID-19 tend to report lower prevalence (13.0%–22.6%)[4,31] than those including patients eligible for outpatient treatment (59.0%–74.6%).[2,3,32] Headache begins at onset of COVID-19 symptoms in 81.8% of patients[3]; it is usually bilateral frontal (34.0%–38.1%) or holocranial (34.0%–38.8%), and mainly presents in the form of oppressive pain (70.1%–73.7%). More than half of patients report moderate or severe pain (60.6%–75.3%). Headache episodes frequently last longer than 24 hours, with nearly half of patients reporting constant pain. In half of cases, pain follows a circadian rhythm, usually worsening in the evening (24.2%). Pain is often exacerbated by exercise (12.37%–45.5%) and coughing but not by other Valsalva manoeuvres (43.4%). Headache is often associated with photophobia (10.3%–29.3%) and phonophobia (10.3%–27.3%). Trigeminal autonomic symptoms are rare (1.0%), but have been reported to present ipsilaterally to unilateral headache.

Personal history of migraine influences the form of presentation in the acute stage and the possibility of persistence. The second pattern of persistent headache after COVID-19 is characterised by the worsening and chronic transformation of pain in a patient who had migraine prior to COVID-19.[30] The third pattern is daily persistent headache in patients with no personal history of primary headache, with pain beginning after resolution of acute COVID-19 (and no headache during the acute infection).

According to the criteria of the International Classification of Headache Disorders, third edition (ICHD-3) (Table 1), the first pattern may correspond to the diagnosis of chronic headache attributed to systemic viral infection (code 9.2.2.2). The second may correspond to chronic migraine (code 1.3), with SARS-CoV-2 infection serving as a transformation factor. The third pattern (new daily persistent headache in the absence of personal history of migraine or headache during acute COVID-19) cannot be diagnosed as headache attributed to systemic viral infection due to the lack of a temporal association between headache onset and onset of infectious symptoms, and the absence of improvement or exacerbation of pain in parallel with the progression of COVID-19. This headache may better fit the diagnosis of new daily persistent headache (NDPH; code 4.10).

While the true prevalence of this symptom is unclear, the literature includes cases of patients meeting diagnostic criteria for NDPH after resolution of acute COVID-19.[33] The main series of NDPH published before the COVID-19 pandemic described infections (mainly systemic viral infections associated with respiratory symptoms, such as influenza) as one of the main trigger factors (14%–43% of cases).[34] Likewise, daily persistent headache was reported as a sequela after resolution of acute infection during the "Asiatic flu" or "Russian flu" pandemic of 1890.[35] However, NDPH is classified in the ICHD-3 as a primary headache; therefore, if onset presents a clear temporal association with viral infection, whether due to SARS-CoV-2 or any other virus, it may be more appropriate to classify this symptom as chronic headache attributed to systemic viral infection. As mentioned above, diagnosis of NDPH would only be applicable when headache onset and progression do not coincide with the course of the systemic infection.

Prognosis: Duration and factors influencing persistence

The duration of persistent headache after SARS-CoV-2 infection remains unclear; there is a need for further studies with longer follow-up periods to clarify the prognosis of the condition. The current literature on the subject is limited to follow-up studies of patients with post-COVID symptoms evaluated at different time points. Some recent studies have evaluated the prevalence of various post-COVID symptoms in a first phase, 1.5-3 months after acute infection, and in a second phase, at 6-9 months.[36–38] With respect to headache, these studies did not find a decrease in prevalence between the 2 time points; at 6–9 months, headache persisted in 10%–37% of patients. However, the prevalence of most of the remaining post-COVID symptoms slightly decreased between the 2 evaluations. This suggests that persistent headache may also gradually decrease and resolve with the passage of time, although new studies with long-term follow-up are needed in order to determine its duration.

Regarding predictive factors, most of the studies published to date have focused on analysing post-COVID syndrome as a whole. Among the scarce studies analysing specific predictors of persistent headache after COVID-19, key findings include a significant association between presence of headache during the acute infection and headache persistence (de novo persistent headache rarely presents after COVID-19 in patients not presenting headache during the acute stage); history of migraine was not associated with greater prevalence of persistent headache.[39,40]

According to the ICHD-3, the clinical course of late-onset persistent headache meeting diagnostic criteria for NDPH after acute infection may present two different types of clinical course: a self-limited form, which resolves within months, and a chronic, treatment-resistant form.[41] In the observational studies published to date, the prevalence of both subtypes and total pain duration in the self-limited form are highly variable (66%–78% of patients diagnosed with NDPH are pain-free at 24 months of follow-up).[34]

Indication of complementary tests (warning signs and secondary headaches after COVID-19)

Imaging studies should be indicated to rule out secondary headache if warning signs are identified in a detailed clinical history interview and complete neurological examination performed in the event of headache with atypical characteristics of "red flags."[42] One of the tools created to increase suspicion of secondary headache is the SNNOOP10 list, applied in cases of new-onset headache.[43] In a study including 104 patients with headache hospitalised due to COVID-19, directly assessing the presence of warning signs, 79 patients (76%) presented red flags, with the most frequent being age over 50 years, fever, exacerbation with coughing, and elevated C-reactive protein levels.[31] Table 2 presents the main SNNOOP10 warning signs reported in patients with COVID-19. To date, no study has evaluated the frequency of warning signs in patients with headache after resolution of acute COVID-19.

In patients with persistent headache after COVID-19 who present warning signs, the specific study selected is determined by diagnostic suspicion and the equipment available at the centre; brain MRI is the technique of choice for non-acute headache (grade of recommendation B, class III).[41] To date, no study has described the incidence of specific neuroimaging abnormalities in patients with COVID-19 and headache. Lumbar puncture should be performed if there is suspicion of central nervous system infection or headache attributed to changes in intracranial pressure and space-occupying lesions have been ruled out.

Several cases have been published in which neuroimaging and/or cerebrospinal fluid analysis led to the diagnosis of secondary headache in patients with acute SARS-CoV-2 infection (Table 3). To date, no cases have been published of onset of secondary headache after resolution of the acute infection.

Symptomatic and preventive treatment

Little evidence is currently available on which are the most appropriate therapeutic options. However, we propose some measures that, according to the clinical experience of the authors, may be useful.

In patients with pre-existing primary headache and in whom COVID-19 represents an exacerbating factor, we propose using symptomatic and preventive treatment according to the individual characteristics of the patient and their headache, in accordance with the official guidelines.[44] The therapeutic approach in patients meeting diagnostic criteria for NDPH or chronic headache attributed to systemic infection is more challenging. In these cases, the selection of a preventive treatment will depend on whether the clinical phenotype bears a greater resemblance to migraine or tension-type headache. Thus, amitriptyline should be the treatment of first choice in patients with tension-type headache; venlafaxine and mirtazapine are other alternatives. Patients presenting headache with migraine-like characteristics may benefit from such classical oral treatments as beta-blockers, neuromodulators, antidepressants, calcium channel blockers, or ACE inhibitors/angiotensin II receptor blockers. In this patient group, we should be particularly alert to mood alterations and sleep disorders: in some cases, these are exacerbated by stress due to family, work, and socioeconomic difficulties related to the pandemic and may worsen the experience of pain (flunarizine and beta-blockers have been associated with the appearance or exacerbation of depressive syndromes). Furthermore, we must be aware that some drugs, such as topiramate, may cause cognitive secondary effects, which may be more significant in patients with subjective memory complaints or mild cognitive impairment following COVID-19. Therefore, taking into account the diverse comorbidities frequently observed in these patients, the use of onabotulinumtoxinA (155-195 units, administered according to the PREEMPT protocol[45]) may be a particularly beneficial treatment option due to its excellent safety and tolerability profile. Anaesthetic block of pericranial nerves may also be an interesting adjuvant therapy. If these procedures are used, we must guarantee patients' safety by ensuring asepsis, cleaning surfaces, and observing physical distancing and official

recommendations on the use of personal protective equipment by patient and physician.[46] General recommendations such as maintaining a regular lifestyle, exercising, and avoiding prolonged fasting continue to be relevant for patients with persistent headache after COVID-19. We recommend maintaining preventive treatment for at least 4–6 weeks before establishing lack of response and assessing other drug classes. If treatment is effective, we propose maintaining the therapy for 3–6 months.

Finally, this patient group presents high risk of medication-overuse headache[44]; therefore, patients should be properly informed about this condition and how to prevent it. Non-steroidal anti-inflammatory drugs, such as ibuprofen, may be safely used to treat mild attacks,[47] despite early reports questioning their safety due to their potential role in ACE2 overexpression. Triptans should be considered for the usual indications.

When the role of ACE2 in the invasion of human cells by SARS-CoV-2 was described, it was suggested that ACE2 inhibitors or angiotensin receptor II blockers may promote viral invasion. This phenomenon has not been demonstrated, and major scientific organisations recommend maintaining these treatments if they have previously been effective in preventing migraine.[47]

Conclusions

The mechanisms causing persistent headache after SARS-CoV-2 infection remain unclear. Clinically, headache during the acute stage usually presents as holocranial or bilateral frontal headache with moderate-severe pressing pain, frequently presenting migraine-like characteristics. The predictive factors of persistent headache after acute infection are unknown. Some patients with persistent headache after COVID-19 may meet diagnostic criteria for NDPH. Complementary tests must be performed if secondary headache is suspected after the clinical history interview and physical examination. While we currently lack data on the most appropriate treatment for these patients, in general terms, we recommend indicating treatment according to the clinical phenotype.

Funding

The authors have received no specific support for this research from public sector agencies, commercial or non-profit organizations.

Acknowledgements

To the researchers, clinicians and other health professionals working to overcome COVID-19 and its consequences.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2021.10.003.

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