Long COVID and especially headache syndromes

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Purpose of review
This is an expert overview on recent literature about the complex relationship between coronavirus disease 2019 (COVID-19) and headache.

Recent findings
Long COVID is a clinical syndrome characterized by the presence of persistent symptoms following the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Headache is one of the most common symptoms and is described most often as throbbing pain, associated with photo and phonofobia and worsening with physical exercise. In acute COVID-19, headache is usually described as moderate or severe, diffuse and oppressive although sometimes it has been described with a migraine-like phenotype, especially in patients with a previous history of migraine. Headache intensity during acute phase seems to be the most important predictor of duration of headache over time. Some COVID-19 cases can be associated with cerebrovascular complications, and red flags of secondary headaches (e.g. new worsening or unresponsive headache, or new onset of neurological focal signs) should be urgently investigated with imaging. Treatment goals are the reduction of number and intensity of headache crises, and the prevention of chronic forms.

Summary
This review can help clinicians to approach patients with headache and infection from SARS-CoV-2, with particular attention to persistent headache in long COVID.

Keywords
coronavirus disease 2019, headache, inflammation, migraine, pandemic

INTRODUCTION

The pandemic from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel enveloped, positive-strand ribonucleic acid virus has significantly engaged the global healthcare system in the last years [1]. The exceptional severity correlated with a systemic hyperimmune response and significant pulmonary damage associated with the infection have no precedents in the recent history [2]. The introduction of an effective group of vaccines has reduced significantly the rate of hospitalization and mortality from the novel coronavirus disease 2019 (COVID-19) [3▪]. Moreover, the use of booster doses has resulted in protection also against variants, although the protection seems to wane over time and the long-term immune effects are still unknown [4].

Headache is a common symptom of COVID-19 and can manifest early in the acute phase of the disease, associated with or without other constitutional symptoms, or can manifest weeks or months after the time of infection [5]. The persistence of long-lasting symptoms after an apparently harmless infection from SARS-CoV-2 is an emerging problem. There is no unique term for this condition, but long COVID or post-COVID-19 syndrome have been largely accepted by the majority of healthcare organizations [6]. Headache can be really disabling and a difficult-to-treat COVID-19 symptom, or a distinctive clinical exacerbation in patients with a previous history of primary headache, such as migraine [7▪▪].

An overview on recent literature about the complex relationship between COVID-19 and headache can help neurologists, or headache clinicians in general, to approach patients with headache and infection from SARS-CoV-2, with particular attention to persistent headache in long COVID.

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KEY POINTS

- Headache is a common symptom during the SARS-CoV-2 infection.
- Long COVID can manifest with a distinct clinical phenotype of headache.
- Patients with clinical red flags of secondary headaches (new worsening or unresponsive headache, or new onset of neurological focal signs) should be urgently investigated with imaging.

HEADACHE AS A SYMPTOM OF ACUTE CORONAVIRUS DISEASE 2019

Headache is a common symptom during the acute phase of the SARS-CoV-2 infection. It has been reported in up to 47% of patients, and the first manifestation in 25% of cases [8]. It fulfills the 9.2.2.1 criteria of the International Classification of Headache Disorders, 3rd edition, and is classified actually as an Acute Headache Attributed to Systemic Viral Infection [9▪]. Acute phase of COVID-19 can be characterized by a constellation of clinical manifestations such as fatigue, malaise, fever, cough, and sore throat. Symptoms prevalence, characteristics and severity of disease seem to vary according to the type of SARS-CoV-2 variant. It has been documented indeed that Omicron infection is less severe than previous variants such as Alpha and Delta, and a significantly lower rate of respiratory tract infections is reported. In additon, there is less need for intensive care, hospital admission and, importantly, the death toll is decreased [10▪▪]. Symptoms such as loss of smell and taste, persistent cough, and fever were more prevalent in individuals affected with Delta variant while other symptoms such as sore throat and hoarse voice were more prevalent in individuals with Omicron variant [11▪]. The prevalence of central nervous system (CNS) symptoms vary across the studies. Early data have shown that headache was commonly found in Omicron variant [12], while recent data from the ZOE COVID study report a higher prevalence of dizzy or light headed, headache and brain fog in Delta versus Omicron variant [11▪].

Headache is usually described as moderate or severe, diffuse and oppressive (75% of cases described as tension-type headache (TTH)-like) although sometimes it has been described with migraine-like characteristics such as throbbing pain that gets worse with movement, nausea, vomiting and photo or phonophobia, especially in patients with a previous history of migraine [13,14].

Additional data that emerge from the ZOE COVID study showed that omicron has a shorter duration of acute symptoms and infectivity than delta variant, and interestingly this data seems to be more marked in individuals receiving a triple vaccine dose (delta mean duration 7·71 days, 7·26–8·15; omicron mean duration 4·40 days 3·98–4·82, IQR 2·00–5·00; $P < 0·0001$) [11▪].

Red flags such as new worsening or unresponsive headache, change in clinical features or onset of neurological focal signs should be investigated to exclude secondary headaches such as those from ischemic or hemorragic strokes, tumors, or other focal injury. It should be considered that some COVID-19 cases can be associated with cerebrovascular complications. Patients with these symptoms should be urgently sent for the appropriate neuroimaging studies [15▪].

HEADACHE AS A COMPONENT OF LONG COVID

Persistent symptoms following the infection from SARS-CoV-2 are an issue of emerging interest. There is no consensus about the timeline that defines the persistence or chronicity of symptoms [16▪▪]. Frames between 4 and 12 weeks and more than 12 weeks have been used to define the persistent (postacute) disease and long COVID, respectively [17]. The prevalence of persistent symptoms, especially headache, after SARS-CoV-2 infection has been addressed in a recent meta-analysis of 28 peer reviewed studies enrolling 28,438 COVID-19 survivors, of which 12,307 females with a mean age of 46.61 years (SD: 17.45). These investigators found a prevalence of post-COVID-19 headache ranging from 8% to 15% during the first six months after the acute infection [18]. Patients with persistent headache after COVID-19 seemed to have a low incidence of pneumonia during the acute phase of the disease, and whether the patients was hospitalized was not a risk factor for chronicity of symptom. Adult age (52 years) and female sex have been found more frequently in patients with persistent headache at 9 months. Only headache intensity during the acute phase, however, seemed to be the most important predictor of duration of headache over time. Headache is described more often as throbbing pain, associated with photo and phonofobia and worsening with physical exercise, disclosing a migraine like-pattern. These data could support the basis of similar pathogenetic mechanisms between the two disorders (see below) [19▪].

PATHOPHYSIOLOGY OF HEADACHE ASSOCIATED WITH SARS-CoV-2

The mechanisms underlying the association between COVID-19 and headache are unknown. Neurological manifestations, especially headache, may result from the host membrane angiotensin-converting enzyme 2 (ACE2) receptor binding from SARS-CoV-2.

There are two local and systemic renin-angiotensin system (RAS) pathways with counterbalancing effects, ACE and ACE2. The classic ACE pathway is composed of ACE, angiotensin (Ang) II, and the angiotensin type 1 receptor, and the activation is associated with aldosterone and antidiuretic hormone release, vasoconstriction, inflammation, reactive oxygen species production and fibrosis.

The alternative (ACE2) axis acts as a counterbalance and is responsible for the Ang II to Ang-(1–7) conversion and activation of Mas receptor. The opposing antioxidant and anti-inflammatory activity on brain, cell signal transmission and survival and synaptic remodeling may well results in cognition improvement. Since ACE2 binding from SARS-CoV-2 is associated with enzyme internalization and degradation, the subsequent activity reduction and alteration of the local and systemic RAS homeostasis, favor inflammatory headache after SARS-CoV-2 infection [20]. Direct virus invasion of neuronal tissue, hypoxia and hypercapnia are other mechanisms which have been hypothesized, but the actual evidence argues more for the pathogenic role of CNS inflammation and hypoxic-ischemic damage, those mechanisms being more frequent in patients with neurological symptoms. For exampl, e one recent study reported hypoxic-ischemic lesions and inflammatory infiltrates in 40.8% and 44.0% of cases, respectively, and neurological symptoms were most frequently found in older patients. Other common neuropathological findings were microgliosis and astrogliosis [21▪].

Long COVID headache may activate different mechanisms from those that act in the acute phase of disease, namely persistent CNS inflammation such as unresolved brain or meninges inflammation, neuronal damage, persistent cytokine release and immune activation. It has been hypothesized that mechanisms such as high glutamate levels and N-methyl-D-aspartate receptors upregulation can account for symptoms such as brain fog, light headed and cognitive dysfunction [5,22].

The finding of high serum levels of interleukin 6 and 10 (IL-6, IL-10) and inflammosome components such as high mobility group box 1 and nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 argue in favor of a role of sustained inflammation and hyperimmune activity in long COVID headache [23]. Recently, it has been found that neuropsychiatric symptoms in some severe COVID-19 cases can derive from the development of antibodies directed against the NMDA receptors. The clinical picture seems to respond well to high-dose steroids and immunoglobulins [24].

Persistent headache may result also from the trigeminovascular system activation, a hypothesis which seems to be more likely in patients with a preexisting migraine pattern or in those with genetic predisposition to migraine [16▪▪]. Figure 1 shows the main mechanisms which can be involved in headache pathophysiology in COVID-19.

HEADACHE AND CORONAVIRUS DISEASE 2019 VACCINATION

Headache has been described among the main side effects of SARS-CoV-2 vaccination. A recent systematic review and meta-analysis of 12 articles including reports of adverse events (AEs) for a total of 45,380 subjects, found that headache was reported in up to 36.5 of vaccine vs 18.4% of placebo recipients, respectively ($P < .001$, 95% confidence interval CI −0.46 (−0.64 to −0.28), with the highest incidence reported after the second dose (43%). Other systemic AEs were fever, chills, fatigue and malaise while local pain, redness, swelling and tenderness have been described in the site of injection [25▪▪].

Headache is usually bilateral, moderate and transitory, lasting a few hours or weeks, and has pressing quality, less often presents with throbbing characteristics. Women with a previous history of migraine or headache during COVID-19 seem to experience more frequently headache after vaccination [26]. The frontal region has been described as site of pain for both ChAdOx1 nCov-19 (Oxford-AstraZeneca) and micro RNA (mRNA) BNT162b2 (Comirnaty, and Pfizer & BioNTech) vaccination, albeit the bitemporal zone has been indicated as another affected site for mRNA BNT162b2 vaccine [27].

A recent systematic review and meta-analysis has found that the risk of headache is doubled within 7 days from vaccination, and within 24 h in only one third of cases [28].

The association between a robust immune response and the highest incidence of headache after a second vaccine dose argues in favor of a complex immune activity as leading mechanism involved in headache after vaccination. CD4+ T-cell activity and Th1 cytokine expression such as tumor necrosis factor-alpha and IL-2 have been described as one of the putative pathophysiological

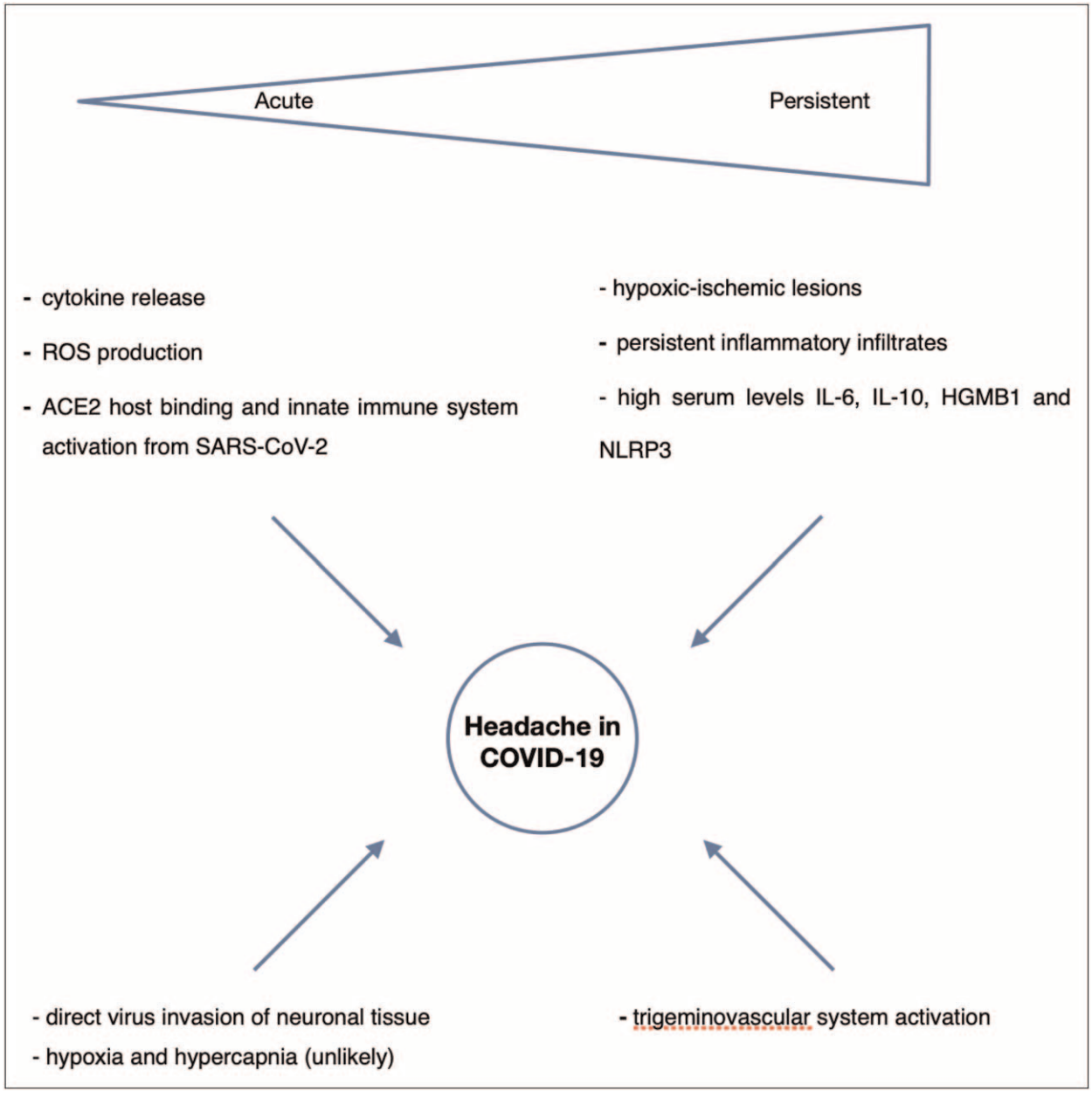

FIGURE 1. Main mechanisms which have been hypothesized to underlie headache in COVID-19 patients. ACE2, angiotensin-converting enzyme 2; HGMB1, High mobility group box 1; IL, interleukin; NLRP3, nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3; ROS, reactive oxygen species.

models. However, the full immune cascade underlying the association between headache and vaccination and also the other involved mechanisms are still largely unknown [29].

A severe immune-mediated thrombotic thrombocytopenia syndrome has been described rarely as a cause of headache or thrombotic manifestations after adenoviral vector vaccines administration such as ChAdOx1 nCov-19 and Ad26.COV2.S (Janssen/Johnson & Johnson). Arterial stroke, cerebral venous thrombosis or intracerebral hemorrhage have been reported as some of harmful clinical manifestations in a distinct category of at-risk patients, mainly young females [30].

A recent study has found that the presence of an onset of headache after three days after vaccination could be an accurate marker for concomitant cerebrovascular events, requiring an urgent imaging investigation [31].

Concerns were raised also about the occurrence of venous thromboembolic events (VTE) in young women with VTE risk factors such as obesity,

hyperhomocysteinemia, estroprogestinic therapy, history of chronic venous disease, presence of prothrombin G20210A or V Leiden heterozygous [32]. A recent study has found, however, that the incidence of thromboembolic events remains higher in patients with positive SARS-CoV-2 test versus those with vaccination and SARS-CoV-2 negative [33].

Cardiac complication such as myocarditis and pericarditis have been found in a disproportionate number of cases of male adolescents after dose 2 and first boosters [34]. A special attention therefore should be given therefore to such at-risk categories (young females with VTE risk factors and male adolescents) before the vaccine administration.

Vaccination benefits, however, outweigh risks in protecting against COVID-19. Specific indications and precautions have been given therefore for the use of these vaccines and they are constantly updated [35].

GUIDELINES OF TREATMENT

There are no specific studies aimed at investigating the effectiveness of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids on reducing frequency and intensity of headache in COVID-19 patients, and treatment recommendations are based on the current management of headaches. Treatment goals are the reduction of number and intensity of headache crises, and the prevention of chronic forms, especially in patients with predisposition to headache [36,37].

At the start of the pandemic, concerns were raised about the negative impact of NSAIDs, especially ibuprofen on the clinical outcome in COVID-19 patients. Previous studies had shown harmful effects of ibuprofen in COVID-19 patients in terms of more severe illness and complications. These negative effects were not confirmed by recent studies, and a recent systematic review and meta-analysis has excluded the presence of a significant increase of mortality, severe disease or hospital admission in patients who relied on NSAIDs, and NSAIDs are useful and safe to manage COVID-19 symptoms [38]. Acetaminophen has been reported to be the most common drug used to control headache in the acute phase of the disease, being taken by over 90% of the patients in one study. In acute disease, pressing quality of pain is reported more frequently, and this drug could be effective to control mainly the TTH-like phenotype [39]. Acetaminophen (1000 mg intravenous) was indeed effective in reducing headache in 59% of the cases in one study. Eighty-five percentage of the paracetamol unresponsive headaches were improved instead by greater occipital nerve blocks [40].

Patients with refractory forms, especially those with migraine-like phenotype could benefit more from drugs such as indomethacin, which has been effective to relieve headache in more than 50% of refractory cases, also to triptans. However, recommendation for indomethacin use should be taken with caution due to the small size of the study, and attention to kidney function and gastrointestinal symptoms should be always given before using this drug, which can be associated with severe adverse effects, especially if abused [41].

There is little evidence about the efficacy of corticosteroids in treating headache from COVID-19. Some recent data reporta small percentage of pain improvement in moderate to severe COVID-19 patients who were treated with corticosteroids regardless of the presence of headache. However, the cost-benefit ratio should be carefully analyzed before using this drug because of adverse effects, and should be reserved to refractory patients where other treatments are not effective [42].

About long COVID headache, there is evidence about the efficacy of amitriptyline as prophylactic drug to control the recurrence of headache crises. In a recent study, the authors found a 9-day median reduction of days of headache per month three months after starting the therapy. A standard and optimal response was observed in 44% and 21% of patients, respectively. The study was limited by factors such as the small sample size, retrospective design and absence of control group; however it was the first to assess the real-world effectiveness of amitriptyline in controlling the recurrence of post-COVID-19 headache [43▪▪]. Growing interest has emerged from reports about the effectiveness of ganglion sphenopalatine block on persistent headache following SARS-CoV-2 infection [44]. The only recorded placebo-controlled trial assessing pain intensity through visual analogue scale in standing position 30 min after the ganglion sphenopalatine block has been closed early for recruitment failure [45]. The main strategies of treatment of headache associated with COVID-19 are reported in Table 1.

CONCLUSION

Increased interest about long COVID has raised several questions about the aggressive management of headache as an acute symptom, as well as the chronic persisting condition associated with the disease.

Headache from SARS-CoV-2 infection should be considered as a distinct disorder and the International Classification of Headache Disorders classification should be updated accordingly.

Table 1. Main strategies of treatment of COVID-19 related headache. W&W, Watch and Wait.

	Acute disease (< 4 weeks)	Persistent headache (4--12 weeks)	Long COVID headache (>12 weeks)
Symptomatic drugs	Yes	Yes, consider triptans for migraine-like phenotype	Yes, consider triptans for migraine-like phenotype
Prophylaxis therapy	No, W&W strategy	Consider a short course of prophylaxis therapy	Yes, refer to a headache specialist
Red flags (eg. new worsening or unresponsive headache, or new onset of neurological focal signs)	Consider further investigation (e.g., imaging) before any drug treatment		

NSAIDs and acetaminophen are the mainstay of treatment for reducing acute symptoms from COVID-19. More studies should assess the specific effectiveness of NSAIDs, acetaminophen, triptans and corticosteroids in reducing headache in COVID-19 patients. Regarding the persistent headache in long COVID, specific placebo-controlled trials should be designed to confirm the efficacy of amitriptyline in headache prevention. Also the efficacy of other preventive drugs in reducing headache frequency and intensity is urgently needed given the widespread diffusion of persistent forms of COVID-19.

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Conflicts of interest

There is no conflict of interest about this paper. Dr Claudio Tana is serving as Section Editor for the journal Annals of Medicine.

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