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HEADACHE CURRENTS

Headache associated with COVID-19: Epidemiology, characteristics, pathophysiology, and management

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Abstract

Objective: To review data regarding the epidemiology, pathophysiology, characteristics, and management of COVID-19–associated headache. The persistence of headache after the acute phase of COVID-19 was also reviewed.

Background: Headache is a frequent symptom of COVID-19, and understanding its management is important for health-care professionals involved in treating the disease.

Method: This is a narrative review. A literature review was conducted in the PubMed database with the following terms: "headache" and "COVID-19." All articles written in English that were considered relevant were included.

Results: Half of the patients who have COVID-19 present with headache, which occurs more frequently in younger patients; in those with previous primary headache or with previous migraine; and in those who have concomitantly presented with anosmia, ageusia, and myalgia. The headache usually begins early in the symptomatic phase, is bilateral, moderate to severe, and has a similar pattern to tension-type headache. All studies found the migraine pattern and the tension-type headache pattern to be frequent patterns. The possible pathophysiological mechanisms include direct viral injury, the inflammatory process, hypoxemia, coagulopathy, and endothelial involvement. Common analgesics and nonsteroidal anti-inflammatory drugs are the most commonly used drugs for headache in the acute phase of COVID-19. The headache may persist beyond the acute phase, and in such cases, there is an improvement over time. However, not all patients' headaches improve. It seems to be a greater proportion of patients whose headache improves in the first 3 months after the acute phase of the disease than after this period. COVID-19 may trigger new daily persistent headache.

Conclusions: Headache is a clinically significant symptom of COVID-19. Although its characteristics in the acute phase of the disease are already well known, there is a need for studies on its management and persistence.

KEYWORDS
COVID-19, disease management, headache, headache disorders, secondary, physiopathology, post-acute COVID-19 syndrome

Abbreviations: COVID-19, coronavirus disease 2019; CI, confidence interval; CSF, cerebrospinal fluid; IL, interleukin; NSAIDs, nonsteroidal anti-inflammatory drugs.

INTRODUCTION

Neurological symptoms are frequent in coronavirus disease 2019 (COVID-19), the disease caused by the coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and affect 9% to 92% of hospitalized patients. This difference in frequencies is due to methodological differences between studies (e.g., data collection through patient interviews vs. a review of medical records) and patients with different disease severity included in them.[1–6] Although respiratory symptoms generally dominate the clinical aspects of the disease, 22% of patients with moderately severe COVID-19, who do not need to be admitted to the intensive care unit, report that neurological symptoms trouble them the most.[6] The most frequent neurological symptoms of the disease are headache, anosmia, ageusia, and myalgia.[1–3,6–10]

During the first half of 2020, studies that assessed the symptoms of COVID-19 considered headache an infrequent, minor symptom that affected 10% of patients.[11] Over time, studies have demonstrated a much higher frequency of headache and that headache may be a significant clinical problem in the treatment of these patients.[6,12–20] For 14% to 19% of patients who present with headache, this is the symptom that most troubles them.[6,16,19]

The aim of this article is to review the epidemiology, characteristics, secondary headache associated with complications of COVID-19, pathophysiology, and management of headache associated with COVID-19. The persistence of headache after the acute phase of COVID-19 was also reviewed.

METHODS

This is a narrative review. A literature review was conducted in the PubMed database with the following terms: (1) headache and (2) COVID-19. All articles written in English that were considered relevant were included. There was no limitation on the date of publication.

EPIDEMIOLOGY

Headache affects 47.1% (95% confidence interval [CI]: 35.8%–58.6%) of patients in the acute phase of COVID-19.[21] The frequency of headache varies according to the level of severity of the disease and is more frequent in outpatients than in hospitalized patients.[21] However, one cannot rule out the possibility that headaches were underreported by hospitalized patients.

The occurrence of headache is more frequent among younger people;[12,15,18,22] among those who have presented with previous primary headache[9,18,20] or previous migraine;[14,23] and those who have concomitantly presented with anosmia,[6,12,15,18] ageusia,[6,15,18] and myalgia[6,9,12] during the symptomatic phase of COVID-19. While some studies have reported that women have more headaches than men,[2,6,12,18,20,24] other studies have not.[13–15,17,22,25–27]

An association between fever and headache in COVID-19 has been reported by some[6,12,20] but not by all.[13,14,18,22,27] Although the presence of fever is considered important for the pathophysiology of headache associated with systemic viral infections,[28] to date, no studies have had the primary objective of assessing the association between headache and fever in COVID-19.

Controversy exists over whether headache is a good prognostic marker for patients with COVID-19. No association was observed between the presence of headache and the length of hospital stay in a case-control study conducted in Spain. However, those with headache had lower mortality than those without headache.[22]

In a Spanish retrospective cohort study, headache was associated with a lower mortality rate of patients hospitalized for COVID-19.[12] However, the presence of anosmia, which was associated with headache and the prognosis in other studies, was not controlled in the analysis.

No association was observed between the presence of headache and the length of hospital stay or mortality in a retrospective cohort study conducted in Brazil. This study aimed to assess whether neurological symptoms and complications were associated with the prognosis. Those with anosmia presented with a lower mortality rate and those with encephalopathy presented with a higher mortality rate.[29]

In a prospective cohort in Spain, patients with headache had a shorter illness compared to those without headache. There was no difference in mortality or length of hospital stay between those with or without headache.[18]

A prospective cohort study conducted in Iran that aimed to assess whether neurological symptoms were associated with the prognosis of COVID-19 reported that those with headache and those with anosmia presented with a less severe disease and a lower mortality rate.[25]

THE CHARACTERISTICS OF HEADACHE IN THE ACUTE PHASE OF COVID-19

Headache usually begins early in the symptomatic phase of COVID-19, [12,14,16,17,20,30] starting on the first day of illness in 39% to 55%,[6,9,12,15,16,19] and is the first symptom in 6% to 29% of patients (generally around 25%).[6,12,14,16–20,31] In some patients, headache may be the only symptom of COVID-19.[32]

For 47% to 80% of those with previous headache, the COVID-19 headache is described as being different from the previous pattern.[6,14,15,17,22,33] In general, the pain has an insidious onset,[17] is bilateral,[1,14–16,19,27,31] is of a moderate to strong intensity,[6,14–16,18–20,27,31] and presents a pressing or tightening quality.[14,16,18,19,27,30,31] Pain may be associated with photophobia (in 14% to 49%),[6,14–16,19,27,30] phonophobia (in 5% to 41%),[14–16,19,27,30] and nausea and/or vomiting (in 14% to 43%).[6,15,16,18,19,27,30] The most frequent pattern reported by most studies was a tension-type headache phenotype.[6,9,19,20,27] However, other studies have reported a migraine phenotype.[15,25,34] All studies found the

migraine pattern and the tension-type headache pattern as frequent phenotypes.[6,9,15,18–20,25,27,34]

The headache presented by patients admitted during the symptomatic phase of COVID-19 in a Spanish hospital met the criteria of the International Headache Society for headache attributed to systemic viral infection in 94.3% of cases.[19]

Although cough has been reported as a frequent symptom of COVID-19, a few studies have assessed the cough headache pattern (headache triggered by cough). These studies observed a frequency of 2%,[25] 10%[14] and 16%.[15]

Patients cite coughing (33% to 43%),[14,19] physical activity (10% to 53%),[14,15,18,19] moving the head (31%),[19] moving the eyes (19%),[19] and bending (7%)[19] as factors that aggravated the headache.

SECONDARY HEADACHE ASSOCIATED WITH COMPLICATIONS OF COVID-19

Several neurological complications for which a headache may be a symptom have also been linked to COVID-19. Among these, arterial and venous cerebrovascular diseases, encephalitis, and acute disseminated encephalomyelitis are the most outstanding.[35,36]

A systematic review reported an incidence of cerebral venous thrombosis of 0.8 cases per 1000 hospitalized patients. In 19% of cases, there were other risk factors for cerebral venous thrombosis in addition to COVID-19. In 7% of cases, symptoms of cerebral venous thrombosis preceded respiratory symptoms and in 1.8%, headache was the only symptom presented.[37]

A case series involving 25 patients with COVID-19 who underwent cerebrospinal fluid (CSF) examination for refractory headache drew attention to the possibility of the presence of intracranial hypertension. Five patients presented with a CSF opening pressure greater than 250 mm CSF; four of these were women and four had no papilledema. These patients presented no other CSF changes and their brain magnetic resonance imaging (MRI) had normal findings.[38]

We previously described a case of meningitis associated with SARS-CoV-2. The patient had a fever in the first 7 days of symptoms, but when the headache began, she no longer presented this symptom. She had no meningeal signs. She had a continuous headache that lasted 7 days.[39]

Patients with a COVID-19 headache present a high frequency of red-flag symptoms.[16,17] This is not surprising because a COVID-19–associated headache is a secondary headache. Among the traditional red flags, the most clinically significant are sudden headache, headache triggered by Valsalva maneuver, progressive headache, headache associated with abnormal neurological examination (except anosmia and myalgia), treatment-resistant headache, and headache associated with epileptic seizures. The ability of red flags to identify a complication of COVID-19 has yet to be assessed.

Thus, when there is a case of suspected neurological complications from COVID-19 based on the patient's history and physical examination, MRI of the brain, a cerebral magnetic resonance angiogram, and CSF examination should be requested.

PATHOPHYSIOLOGY

Possible mechanisms for the occurrence of headache in COVID-19 include direct viral injury, the inflammatory process, hypoxemia, coagulopathy, and endothelial involvement.[40] None of these mechanisms fully explain the occurrence of the headache. In this section, evidence on possible mechanisms will be discussed.

Direct viral injury, vascular injury, and local inflammatory process

There is an association between headache and anosmia and ageusia. These symptoms most often occur in clusters,[6] usually early in the symptomatic phase of COVID-19.[6,15] Those with anosmia/ageusia are more likely to present with headache.[6,12,14,15,41] It is possible that these symptoms partly share the same pathophysiological mechanisms.

A case series that assessed patients with persistent headache and anosmia with MRI reported microbleeds in the olfactory bulb. This study suggested that these changes were a consequence of direct viral injury or vascular injury.[42]

Those with symptoms of rhinosinusitis are more likely to present with headache.[27] Thus, the local inflammatory process may also be an important factor for the occurrence of headache.

In principle, both damage to the olfactory pathway and inflammation of the nasal cavity are capable of activating the trigeminal system and causing headache.[43] However, not everyone who has anosmia has headache, and not everyone who has headache has anosmia.[6,12,14,15,41] Likewise, not everyone who has rhinosinusitis has headaches and vice versa.[27] Thus, neither injury to the olfactory pathway nor local inflammation completely explains the genesis of headache.

Hypoxemia and dehydration

A study that compared hospitalized individuals with and without headache reported that those with headache presented with a greater need for high oxygen flow,[22] showing that hypoxia may be involved in the occurrence of the headache. Another study reported that the presence of dehydration was also associated with headache.[31]

Systemic inflammation

We recently observed that headache occurs in clusters with flu-like symptoms such as chills, fever, sore throat, fatigue, and myalgia.[6] Others have reported that 46% to 62% of individuals who had previously presented headache associated with systemic viral infection had assessed the COVID-19 acute-phase headache as being similar to that headache.[12,16] The systemic inflammatory response to

infection is considered important for the occurrence of headache associated with systemic viral infection.[28,40]

Bolay et al. compared patients with severe headache to those without headache among those who had been hospitalized with moderate COVID-19.[40] Those with headache presented statistically significantly higher levels of pro-inflammatory serum high mobility group box-1, nod-like receptor pyrin domain-containing 3 and interleukin (IL) 6, and angiotensin-converting enzyme 2. There was no difference in serum IL-10 and calcitonin gene-related peptide levels in the two groups.[44]

There is controversy about the role of interleukins in the occurrence of headache. The mean level of IL-6 was higher in the 13 patients with headache than in the 15 patients without headache in a Turkish study.[1] However, a Spanish study that compared 36 patients with headache and 24 patients without headache found the opposite result; IL-6 levels remained more stable over time in the headache group.[18]

Karadaş et al.[26] assessed 287 patients with moderate COVID-19 disease, 83 of whom presented with headache. There was no difference in the level of serum IL-6 between those with or without headache. However, there was a positive correlation between the levels of this interleukin and the intensity of headache.[26]

Trigo et al.[45] compared 45 serum interleukins and cytokines between 29 patients with headache and 75 without who were hospitalized for COVID-19. The amount of only IL-10, which is anti-inflammatory, was higher in those with headache. Levels of IL-23 ($p = 0.08$) and the placental growth factor ($p = 0.07$), which are pro-inflammatory, were higher in those with headache but were not statistically significant. There was no difference for IL-6. The authors hypothesized that those with headache would have had a greater inflammatory response, and that a greater level of IL-10 would be caused by a better homeostatic response.[45]

One of the difficulties in interpreting these studies is the lack of standardization for collecting samples of the levels of these substances.

MANAGEMENT

There are no clinical trials that assess the treatment of headache in the acute phase of COVID-19.

The effect of using corticosteroids on COVID-19 headache remains controversial. An Egyptian study assessed 172 hospitalized patients with COVID-19 and headache. As part of the hospital protocol, corticosteroids were used for moderate to severe cases of COVID-19, regardless of headache. No association was observed between using or not using corticosteroids with the frequency or intensity of headache. Fever and dehydration were associated with a more intense headache, drawing attention to the need to treat these conditions.[31] Another Egyptian study included 782 hospitalized patients with COVID-19. Corticosteroids were also used in moderate to severe cases. Eighty percent of patients with headache responded well to analgesics. There were statistically significantly fewer patients who had used corticosteroids in the poor responder group.[20]

A study conducted in a Spanish hospital reported that the most commonly used drugs for headache were acetaminophen (75%) and nonsteroidal anti-inflammatory drugs (NSAIDs), metamizole, triptans, or a combination of these (25%). A total of 26% reported complete pain relief, and 54% reported partial relief.[14] In another Spanish study, 95% of patients needed to use medications for headache, including acetaminophen (93%), ibuprofen (17%), and metamizole (12%).[16]

In a Turkish study, 59% of patients hospitalized for moderate COVID-19 reported an improvement in the headache after 1 g of intravenous paracetamol was administered. Those who did not improve with paracetamol underwent greater occipital nerve blocks using lidocaine, with an improvement in 85% of cases.[26]

A study that included 37 patients with headache that occurred during the acute phase of COVID-19 or that persisted after other symptoms resolved, assessed the use of oral indomethacin (50 mg twice daily for 5 days). Thirty-six patients reported that there was greater than 50% improvement in the headache.[46]

At the beginning of the COVID-19 pandemic, there was concern that the use of NSAIDs, especially ibuprofen, was associated with a worse prognosis of the disease and greater infectivity of SARS-CoV-2. However, this was not confirmed in later research. Thus, these drugs can be used safely.[47] The kidneys are one of the target organs in COVID-19, and it is necessary to monitor kidney function should the use of NSAIDs be necessary.[48,49]

A case series described six patients whose headache improved after sphenopalatine ganglion block. However, it is unclear whether the headache was acute or persistent, or for how long the patients were followed up.[50]

THE PERSISTENCE OF HEADACHE AFTER THE ACUTE PHASE OF COVID-19

For between 6% and 45% of those who complain of headache in the acute phase of COVID-19, the headache persists beyond the symptomatic phase.[6,13,16,18–20,25,34]

Caronna et al.[18] compared those who no longer presented with headache and those who still reported headache 6 weeks after the acute stage. The group with a persistent headache contained significantly more women, with more previous headaches, more persistent symptoms, more headache as a first symptom, and they were less responsive to acute pain management. In 61% of patients with persistent headache, the headache was daily and constant.[18]

A systematic review that included 36 articles on post-COVID symptoms observed that headache may persist for up to 60 days in 16.5%, for 90 days in 10.6%, and for more than 180 days from symptom onset to discharge in 8.4% of patients. Thus, there is a decrease in the prevalence of headache over time.[21]

A post hoc secondary analysis of six Spanish studies that included 905 adults with headache in the acute phase of COVID-19

also reported a decrease in the prevalence of headache over time (1 month: 31%; 3 months: 19%, 6 months: 16.8%, and 9 months: 16%). A more severe headache in the acute phase was associated with greater persistence of headache after 9 months of follow-up.[51]

In another study, which assessed patients who had been discharged from the hospital after a mean period of 7 months, the diagnosis of previous migraine was not associated with the persistence of headache.[52] However, previous primary headaches may become worse after COVID-19.[23,34]

Although it is already known that headaches may persist after the acute phase of COVID-19, little is known about the frequency of the attacks of this headache and its impact. Viral infections may be a trigger for developing new daily persistent headache (NDPH). Reports already exist of this type of headache after COVID-19.[53–55]

Secondary headaches should always be ruled out in those with NDPH. Treatment should consist of assessing the pattern of this headache (migraine phenotype vs. tension-type headache phenotype) and managing according to this pattern. In cases in which this headache is triggered by a viral infection, pulse corticosteroid therapy may also be used.[56,57]

We have previously described a case of NDPH with a migraine phenotype.[53] After the publication of that case, the patient was treated with venlafaxine with good results.

Caronna et al.[55] described three cases of NDPH with migraine features, two of which improved after using amitriptyline and onabotulinumtoxinA. The third patient did not improve after treatment. This patient had no previous primary headache, and his headache started late when respiratory symptoms were improving. In addition to the headache, the patient also had complaints of insomnia, fatigue, and cognitive and memory impairment, which are suggestive of the "post–COVID-19 syndrome." The authors suggested that the headache pathophysiology of this patient was different from the other two.[55]

Dono et al.[54] described a case of NDPH that improved after pulse methylprednisolone therapy (1 g intravenously per day for 3 days) followed by oral prednisone (25 mg for 7 days).[54]

CONCLUSIONS

Headache associated with COVID-19 is frequent, commonly with a similar pattern to tension-type headache or migraine phenotype, and is usually treated with common analgesics and NSAIDs. This type of headache may persist beyond the acute phase, and in these cases, improves over time. However, not all patients improve. There seems to be a greater proportion of patients who improve in the first 3 months after the acute phase of the disease than after this period. COVID-19 may trigger NDPH. Although the characteristics in the acute phase of the disease are already well known, there is a need for studies on its management and persistence.

CONFLICTS OF INTEREST

The author reports no relevant conflicts of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: Pedro Augusto Sampaio Rocha-Filho. *Acquisition of data*: Pedro Augusto Sampaio Rocha-Filho. *Analysis and interpretation of data*: Pedro Augusto Sampaio Rocha-Filho. *Drafting of the manuscript*: Pedro Augusto Sampaio Rocha-Filho. *Revising it for intellectual content*: Pedro Augusto Sampaio Rocha-Filho. *Final approval of the completed manuscript*: Pedro Augusto Sampaio Rocha-Filho.

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