Review Article

Headache in Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A Narrative Review

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Objective.—To summarize available literature regarding headache as a manifestation of coronaviruses and to describe potential underlying mechanisms.

Review Methods.—References for this review were identified by searches within PubMed without any date restrictions. The search terms used were coronavirus disease 2019 (COVID-19) clinical manifestation, COVID-19 epidemiology, neurologic findings in COVID-19, headache in COVID-19, neurologic manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and headache in SARS-CoV-2.

Results.—Headache is one of the most common neurologic complaints in patients with SARS-CoV-2. While the pathophysiological connection between headache and SARS-CoV-2 is unclear, inflammatory mechanisms may play a key role. One of the mechanisms cited in the literature of migraine and other headache disorders is the activation of nociceptive sensory neurons by cytokines and chemokines. A similar mechanism has been reported in SARS-CoV-2 with the release of cytokines and chemokines by macrophages throughout the course of infection. Other mechanisms for headache in SARS-CoV-2 include (1) viral neuroinvasion as seen with viral encephalitis; (2) hypoxemia due to the well-described pulmonary manifestations of the disease; and (3) thrombosis secondary to COVID-19 induced hypercoagulable states.

Conclusion.—According to the Centers for Disease Control, common symptoms of human coronavirus include fever, cough, runny nose, sore throat, and headache. In the case of SARS-CoV-2, there are limited reports about headaches, one of the most common clinical manifestations. There are currently no studies that focus specifically on headache among patients with SARS-CoV-2 infection.

Key words: coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, headache, migraine

INTRODUCTION

Coronaviruses are positive-sense ribonucleic acid (RNA) viruses that have been shown to invade the respiratory system, gastrointestinal (GI) system, and the central nervous system (CNS). At the end of 2019, scientists identified a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the city of Wuhan, China.[1] In February of 2020, the World Health Organization named the infection, "COVID-19" and characterized it as a pandemic on March 11, 2020.[1,2]

Coronaviruses are 100 nm on average with a crown-like shape due to their membrane glycoproteins spikes.[3] Previously identified viruses in the same family of betacoronaviruses, (but with different clades), include the Middle East respiratory syndrome virus

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and severe acute respiratory syndrome (SARS-CoV-1) virus.[4-6] Both SARS-CoV-2 and SARS-CoV-1 attach to the angiotensin-converting enzyme 2 (ACE2) for cell entry.[4,5] ACE2 is expressed in neurons, astrocytes, oligodendrocytes, substantia nigra, ventricles, middle temporal gyrus, posterior cingulate cortex, and olfactory bulb.[7] In China, a phylogenetic analysis of 103 strains identified 2 types of SARS-CoV-2 virus (L type [70%] and S type [30%]). There was no significant difference reported in clinical manifestations of these 2 subtypes.[6] According to several reports, the incubation period is predominantly between 2 days and 2 weeks after exposure. Most patients develop symptoms of SARS-CoV-2 infection within the first 4-5 days after exposure.[8,9]

The aim of the present narrative review was to qualitatively summarize data from published literature on headache as a manifestation of SARS-CoV-2 and to discuss the potential underlying mechanisms of headache in adults affected by SARS-CoV-2.

METHODS

Search Strategy.—For this narrative review, sources were identified by specific keywords within PubMed without any date restrictions. The search terms used were coronavirus disease 2019 (COVID-19) clinical manifestations, neurological manifestations of COVID-19, headache in COVID-19, neurologic manifestations of SARS-CoV-2, and headache in SARS-CoV-2. There were no language restrictions. Studies that did not discuss headache or the clinical manifestations of COVID-19 were excluded. Screening was completed by 2 expert reviewers (AT and VC). The screening process was supervised by (DK and NZ). Two hundred and thirty-eight studies resulted from the search using the keyword "COVID-19 clinical manifestation," 102 studies with "neurological manifestations of COVID-19," 64 studies with the keyword "neurologic findings in COVID-19," 45 studies using the keyword "headache in SARS-CoV-2," and 53 studies using the keyword "headache in COVID-19."

Data Extraction.—Studies were included if they focused on headache diagnosis, headache descriptive factors, headache prevalence or possible pathophysiologic mechanisms of headache in COVID-19 patients. Studies were excluded if they were unrelated to the topic.

This search resulted in 20 studies. These studies included 9 retrospective observational studies, 3 retrospective epidemiological studies, 4 case reports/case series, 3 meta-analyses, and 1 cross-sectional study.

RESULTS

Non-Neurological Manifestations.—SARS-CoV-2 can present with several symptoms. In a case series of 138 hospitalized patients with confirmed SARS-CoV-2 pneumonia in Wuhan, Wang and colleagues reported fever as the most common symptom (99%), followed by fatigue (70%), dry cough (59%), anorexia (40%), myalgia (35%), dyspnea (31%), and sputum production (27%).[10] Elevated lactate dehydrogenase (LDH), leukocytosis (>10,000/μL), and leukopenia (<4000/μL) are commonly seen among patients.[10] Serum procalcitonin levels could vary from normal to high. However, patients under serious condition usually have elevated levels of procalcitonin.[10] Laboratory features such as elevated LDH, c-reactive protein, troponin, D-Dimer, creatine phosphokinase, and ferritin are suggestive of a worse outcome.[9-14]

The clinical presentation of SARS-CoV-2 varies from having no symptoms to multi-organ failure and death. In a study from March 2020, 17% (619 people) of passengers on a cruise ship were confirmed to have SARS-CoV-2 infection, and approximately 50% of those were asymptomatic.[15] In another study by Wang et al, of 138 hospitalized SARS-CoV-2 patients with pneumonia, about 20% developed acute respiratory distress syndrome (ARDS). A median of 8 days following the onset of symptoms. Of these patients with ARDS, 12.3% of those patients required mechanical ventilation.[10]

Imaging findings on chest radiograph may vary from normal to consolidation and ground-glass opacities, with bilateral, peripheral, and lower lung zone distributions.[16] Chest computed tomography (CT) seems to have a higher sensitivity to detect lung involvement. Ground-glass opacification with or without consolidative abnormalities is most frequently seen on chest CT.[17]

Neurological Manifestations.—While pneumonia appears to be the most common serious manifestation of this infection, various neurologic manifestations may develop in patients with SARS-CoV-2 infection.[11,18] In a retrospective observational case series, Mao and

colleagues described neurologic manifestations among 214 hospitalized patients with a confirmed diagnosis of SARS-CoV-2; 36 patients (16.8%) reported dizziness, 15 patients (7.5%) developed altered mental status, and 6 patients (2.8%) developed acute cerebrovascular disease. Interestingly, 12 patients (5.6%) had dysgeusia, 11 patients (5.1%) had anosmia, and 3 patients (1.4%) developed vision changes.[18] In another retrospective case series of 219 admitted SARS-CoV-2 patients by Li and colleagues, 10 patients (5%) developed acute ischemic stroke, and 1 patient (0.5%) developed cerebral venous sinus thrombosis and cerebral hemorrhage.[19]

Headache in SARS-COV-2.—Headache is one of the most common neurologic presentations in patients with SARS-CoV-2 with a wide-ranging prevalence of 6-71%. In a study of 214 hospitalized patients with SARS-CoV-2, a variety of neurological manifestations were reported. Thirteen patients (10.3%) had non-severe headaches, while 15 patients (17%) suffered from severe headaches.[18]

In February 2020, Huang and colleagues reported headache in 3 out of 38 (8%) patients with confirmed COVID-19 infection.[11] Chen and colleagues also analyzed clinical manifestations of 99 hospitalized COVID-19 patients in February 2020. Of those, 8 patients (8%) had headache.[20] Jin and colleagues evaluated the clinical characteristics of patients with COVID-19 infection in 74 patients. Sixteen patients (21.62%) with GI symptoms developed headaches during the disease.[21]

In a retrospective study performed by Yang and colleagues on critically ill patients with SARS-CoV-2 pneumonia who were admitted to the ICU, 3 out of 52 patients (6%) reported headache.[22] In another retrospective study on 1099 patients, 150 patients (13.6%) reported headache as one of the neurologic manifestations of SARS-CoV-2.[23] The prevalence of headache was 53.33% (16 of 30 patients) and 71.1% (64 of 90 patients) in 2 separate retrospective studies on health care workers diagnosed with SARS-CoV-2 in China and Netherlands, respectively.[24,25]

In a case series of 13 patients, 3 patients (23.1%) with SARS-CoV-2 had headache.[26] In another retrospective case series, 9 out of 138 patients (6.5%) reported headache.[10] Borges do Nascimento conducted a meta-analysis of 61 studies; headache prevalence was reported in 12% in patients with SARS-CoV-2.[27]

In 2 retrospective case series on 262 and 21 patients, headache prevalence was 6.5% (17 patients) and 13.6%, respectively.[28,29] One meta-analysis found that 12.1% of patients with SARS-CoV-2 reported headache or dizziness.[30] In another meta-analysis of 38 studies on patients with SARS-CoV-2 infection, headache prevalence was reported in 15.4% of all SARS-CoV-2 patients.[31]

While studies have looked at the prevalence of headache among patients with COVID-19 infection, limited data regarding the specific features of headache are available. In a cross-sectional study of 112 healthcare professionals with confirmed diagnosis of SARS-CoV-2 and headache, 52 patients (46%) had hemicranial pain, 48 patients (42.5%) had holocranial pain, and 20 patients (17.7%) reported occipital headache. Headache described as a pressing quality was the most commonly reported headache, which was reported by 90 patients (80.4%), followed by stabbing pain in 12 patients (10.7%) and pulsating pain in 8 patients (7.1%).[32]

DISCUSSION

It is known that various groups of viruses have the capability of causing damage to the nervous system which can lead to the development of headaches. Encephalitis due to direct invasion of a viral agent to the brain tissue, toxic metabolic encephalopathy, post-viral demyelinating disease, and infection of immune-functioning macrophages, microglia, and astrocytes are potential triggers of headache in viral syndromes.[3,33,34] Various mechanisms have been proposed as possible etiologies of headache in SARS-CoV-2.

Infection of the Central Nervous System.—Headache can be a sign of aseptic meningitis due to SARS-CoV-2. In a study in 1995, headache characteristics of 41 patients with aseptic meningitis were described. Thirty-nine patients complained of severe headaches and 2 reported mild headaches. Among all cases, 6 patients had an abrupt onset of headaches. Thirty-nine patients reported bilateral headaches and 2 had unilateral headaches.[35] Moriguchi and colleagues reported findings in a 24-year-old man with SARS-CoV-2 meningitis. Surprisingly, the specific SARS-CoV-2 RNA was detected in the cerebrospinal fluid (CSF), while the nasopharyngeal swab remained negative.[36]

In a study in 2007 by Rozen, CSF TNF α was elevated in 19 out of 20 patients with new daily persistent headache.[37]

Neuroinflammation Secondary to Cytokine Storm.—Cytokine storm related to SARS-CoV-2 has been widely reported.[38,39] Liu and colleagues analyzed the lymphocyte responses and cytokine profiles among 40 patients with SARS-CoV-2 in China. Twenty-seven patients developed severe disease and 13 patients had mild symptoms of SARS-CoV-2. Severe cases had a reduction in $CD8^+$ T cells and an increase in neutrophils compared with milder cases. Plasma levels of IFN-γ, IL-2, IL-6, and IL-10 were reported higher among patients with severe disease as well.[39] A rise in Inflammatory markers in patients with SARS-CoV-2 infection indicates potential inflammation and infection of the CNS which can manifest with headache.

In a case report by Belvis, he reported different types of headaches during his SARS-CoV-2 infection course. He experienced episodes of moderate diffuse pain as well as cough-induced headaches which occurred on the posterior and bilateral areas of the head during the first 3 days of the disease. After day 3, while his systemic symptoms subsided temporarily, tension-type headache-like pain started as a bilateral mild pain with cervical and trapezius muscle tenderness.[40] A potential underlying etiology for the headache relapse after day 3 could be attributed to cytokine release. It has been shown that cytokine storm in SARS-CoV-2 usually occurs a few days after the initial symptoms start.[40] The underlying mechanism of the temporal relationship between viral respiratory infections and headache is not yet well understood but is possibly related to inflammatory mediators and cytokine storm.

Coagulopathy.—A cytokine storm seems to facilitate ischemic events and coagulopathy among patients with SARS-CoV-2. In a retrospective study on 214 hospitalized patients with SARS-CoV-2 infection, 5 patients (5.7%) with severe disease developed ischemic stroke.[18] In another study, among 219 hospitalized patients with SARS-CoV-2, 10 patients (4.6%) developed acute ischemic stroke.[19] Elevation in fibrin/fibrinogen degradation products and D-dimer are known as early coagulopathic manifestations in SARS-CoV-2.[41] These ischemic events can also trigger headaches in patients with SARS-CoV-2.

SARS-CoV-2 has a strong affinity to the ACE2 which is considered as a protective enzyme in cerebrovascular and cardiac cells. The inactivation of ACE-2 receptors caused by SARS-CoV-2 is a potential mechanism for high blood pressure, damage to the blood-brain barrier, and subsequent headache in affected patients.[3]

Hypoxemia.—Alveolar damage and edema secondary to viral infections may lead to reduced tissue oxygenation in the CNS. An acidic environment due to anaerobic metabolism in the setting of CNS hypoxia can lead to the development of cerebral vasodilation, interstitial edema, and headache.[3]

All mechanisms discussed above are potential causes of headache among patients with SARS-CoV-2. However, to date, the exact mechanism of headache in SARS-CoV-2 is not well understood.

Headache Prevalence in SARS-CoV-2.—Headache is a common neurological presentation in patients with SARS-CoV-2 (Table 1), but there are limited studies that focus on headache characteristics and associated features among SARS-CoV-2 patients. Existing studies report a very wide range of prevalence of headache in these patients. While most studies report the headache prevalence to be between 6 and 21%, 1 study from China reported a prevalence of headaches at 53.33% among 30 health-care workers (64 of 90 patients). In another retrospective study in medical professionals diagnosed with SARS-CoV-2 in the Netherlands, 64 of 90 patients (71.1%) reported headache during the disease.[24,25] The vast differences in prevalence could be due to inconsistent or inaccurate reporting of symptoms among patients and inconsistent or inaccurate data collection on the part of health care workers in the setting of an overwhelmed health-care system.

Headache is also a common neurological manifestation of upper respiratory tract infections. There are some clear differences when we compare the prevalence of headache in SARS-CoV2 patients and the prevalence of headache in influenza A and B patients. In a study on 240 hospitalized patients with influenza, headache/myalgia was reported in 90 patients (38%), with a higher prevalence in patients with influenza A (54%) compared to influenza B (34%).[43] In another clinical trial conducted by Eccles and colleagues on

Table 1.—Headache Prevalence in Patients With Confirmed SARS-CoV-2

Authors	Study Design	Headache Prevalence	Limitation
Mao et al[18]	Retrospective, observational case series of 214 patients	Non-severe 10.3% (13/126) Severe 17% (15/88)	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Huang et al[11]	Prospective cohort study on 41 patients	8% (3/38)	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Chen et al[20]	Retrospective single center on 99 patients	8% (8/99)	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Jin et al[21]	Retrospective study on 74 COVID-19 patients with GI symptoms	21.62% with GI symptoms (16/74) 8.84% without GI symptoms (51/557)	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Xiaobo et al[22]	Retrospective study on 52 critically ill patients	6% (3/52)	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Liu et al[24]	Retrospective study on 30 medical workers with new coronavirus pneumonia	53.33% (16/30)	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Li et al[30]	Retrospective, case series of 1995 cases	12.1% (242/1994)	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Guan et al[23]	Retrospective, case series of 1099 cases	13.6% (150/1099)	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Chang et al[26]	Retrospective, case series of 13 cases	23.1% (3/13)	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Wang et al[42]	Retrospective, case series of 138 cases	6.5% (9/138)	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Kui et al[27]	Retrospective, case series of 137 cases	9.5% (13/137)	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Borges do Nascimento et al[28]	Meta-analysis of 61 studies (59,254 patients)	12%	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Tian et al[25]	Retrospective, case series of 262 cases	6.5% (17/262)	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Tostmann et al[31]	Prospective cohort study in 803 healthcare workers	71.1% (64/90)	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Zhu et al[29]	Meta-analysis of 38 studies (3,062 patients)	15.4%	Lack of headache characteristics and accompanying symptoms description, no CSF analysis
Gupta et al[7]	Retrospective, case series with 21 cases	13.6% (3/21)	Lack of headache characteristics and accompanying symptoms description, no CSF analysis

272 patients with acute upper respiratory tract infection, 68% of patients reported headache.[44] The existing data on headache in patients with SARS-CoV-2 show a prevalence of 6-71% (Table 1). At this point, the literature demonstrates a broad range of headache prevalence in patients who have SARS-CoV2. There it is difficult to compare headache prevalence in SARS-CoV2 with headache prevalence in other viral illnesses.

Diagnostic and Therapeutic Approach to Headache in Patients With SARS-COV-2.—Further evaluations should be considered to exclude secondary etiologies of headache in patients with SARS-CoV-2.[45]

Brain magnetic resonance imaging with and without gadolinium should be considered as the imaging modality of choice to evaluate secondary causes of headache including structural abnormalities, meningitis, encephalitis, malignancies, and intracranial pressure changes. If further information is needed, then a lumbar puncture can measure opening pressure and be analyzed for inflammatory markers as well as infectious etiologies including SARS-CoV-2 RNA in CSF. Symptomatic management of headache is the next step once secondary etiologies are ruled out. Appropriate treatment should be considered according to the phenotype of headaches. Acetaminophen appears to be a safe agent to use in patients with COVID-19. Nonsteroidal anti-inflammatory medications (NSAIDs) may play a role in increasing ACE-2 levels.[46] However, no robust data indicate that NSAIDs facilitate SARS-CoV-2 infection.[46]

For headaches with a migraine phenotype, 5-HT1B/1D receptor agonists (triptans), 5 HT1F receptor agonists (Lasmiditan), as well the calcitonin gene-related peptide receptors antagonists (gepants) can be considered for abortive therapy after considering possible contraindications based on the patient's comorbid medical conditions. Intravenous agents, such as magnesium and dopamine receptor antagonists and peripheral nerve blocks (occipital, auriculotemporal, supraorbital, supratrochlear), are other potential therapeutic approaches in patients with a prolonged headache that is not responding to oral migraine medications.

CONCLUSION

Infection with SARS-CoV-2 may lead to various neurologic presentations. Headache is one of the most common neurologic manifestations in patients with SARS-CoV-2. While the exact mechanism of headache in SARS-CoV-2 is not clear, inflammatory mechanisms, hypoxemia, and hypercoagulable states can play an important role. Secondary etiologies of headache should be excluded before proceeding with symptomatic management that is based on headache phenotype.

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