Post-COVID Headache: A Literature Review

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Abstract

Purpose of Review Post-COVID headache may be unique in presentation and mechanism, often presenting as a new phenotype in patients with a history of a primary headache disorder or resulting in a new headache syndrome in those without history of headache. This review presents a description of the literature published focused on post-COVID headache. Additionally, we discuss potential mechanisms and considerations for treatment of post-COVID headache.

Recent Findings Headache is one of the most common symptoms of COVID. Common characteristics are revealed when reviewing the phenotypes of headaches that have been described in patients with COVID-19, with most headache phenotypes resembling migraine and new persistent daily headache. Post-COVID headaches are often described as moderate to severe, persistent, and treatment refractory.

Summary This review highlights the diversity of presentation of headaches that present as a complication of COVID-19. Treatment of post-COVID headache is challenging, especially in the setting of a pandemic where resources are limited.

Clinical Case A 42-year-old woman with a history of episodic migraine without aura presents over video visit with a new headache type. Her typical headaches are predominantly left sided, throbbing in nature, and associated with photophobia and phonophobia. They are fully relieved by oral sumatriptan 2 h after treatment. She describes this new headache as a constant, pulsating, holocephalic pain with no other migrainous features that have been ongoing for 6 weeks. She notes that the headache has been persistent since that time. She has tried over-the-counter acetaminophen and ibuprofen and her typical migraine abortive therapy without relief. She is debilitated and wonders if there is anything that will take the pain away. She shares that she tested positive for COVID-19 about 2 days prior to headache onset and has associated rhinorrhea, anosmia, and ageusia.

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Introduction

Headache in association with viral infection, either in accompaniment with or post-infectious, is a well-documented phenomenon that is acknowledged by the International Classification of Headache Disorders, 3rd edition (ICHD-3), and may be a result of neuroinvasive disease or systemic infection [1]. Historically, headache has been observed as a complication of many viral epidemics, including Spanish influenza in 1918 and the Russian or Asiatic flu in 1890 [2, 3]. This has also been seen more recently in 2009 during the H1N1 pandemic, in which the most frequent neurological sign reported was headache [4]. In the current coronavirus disease 2019 (COVID-19) pandemic, headache has been found to be one of the most common neurological symptoms of SARS-CoV-2 infection and has even been included as one of the presenting cardinal

symptoms [5–7]. In this review, we will provide an update on headache post virus, with an emphasis on reports published within the last 3 years. As our literature search revealed that the bulk of original research centers on our understanding of headache after COVID-19, we have centered our review on this specific topic.

Prevalence

Reported rates of headache in the setting of COVID-19 are variable, ranging from 6.5 to 71% in various studies [8, 9]. It should be noted that studies that cite higher frequency of headache are often using healthcare professionals as their population, and therefore these individuals may be better able to recognize their symptoms. Davidescu et al. described in their retrospective cohort study that the most frequent neurological manifestation of COVID-19 in younger patients was headache, in contrast to stroke and confusion in older adults [10].

Current literature suggests that headache associated with COVID-19 may be unique, often presenting as a new pheno-type in patients with a history of a primary headache disorder or resulting in a new headache syndrome in those without history of headache. Although the literature describes many types of headaches occurring in the setting of COVID-19, common features include a moderate to severe persistent headache that is often refractory to treatment [11–13]. It is also becoming apparent that patients with long-term effects from COVID-19, so-called COVID long haulers, experience headache as one of the most common persistent symptoms [14, 15]. Given the extent of impact headache has on patients who have had SARS-CoV-2 infection, the need for timely diagnosis of associated headache disorders, investigation of underlying mechanisms, and ultimately optimization of treatment is prudent [16].

Mechanism

Respiratory viral infections are associated with headache even without direct CNS infection, and although the exact mechanism has yet to be elucidated, this is likely a result of fever and activation of inflammatory cytokines and cytokine release storm [4, 17, 18]. Support for an underlying cytokine-driven mechanism is reinforced by the findings of increased levels of IL-10 in patients with headache, along with the trend towards elevation of other interleukins (including IL-23 and PIGF1) in an exploratory study comparing cytokine profiles in patients with and without headache in SARS-CoV-2 infection [19]. Interleukin-6 (IL-6), a proinflammatory cytokine which also has been implicated in migraine, has also been studied in the COVID-infected population retrospectively with some

associations found with pain in frontal regions, though another study noted that levels were found to be lower in a headache group presenting for emergency care [20]. Headaches may also occur as a result of complications of viral infection, such as hypoxia and dehydration [17].

However, there have been many hypothesized mechanisms describing the ability of SARS-CoV-2 to invade the central nervous system, and therefore headache due to direct CNS invasion may be the causal mechanism in some patients [21]. It has been demonstrated that the binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) receptors results in cellular invasion, and the ACE2 receptors are located on cells of the CNS including neurons and glia of various structures including olfactory groove and trigeminal ganglia [8, 22–24]. Another possible mechanism of neuroinvasion includes the entry of SARS-CoV-2 via the endothelial cells of the blood brain barrier in the setting of viremia, which has been demonstrated with other viruses [25]. Furthermore, many viruses, including human coronaviruses, use retrograde axonal transport to allow CNS invasion via peripheral nerves [26]. Additionally, neuroinvasion of SARS-CoV-2 via the olfactory nerve has been demonstrated in the animal model [27], which is supported by the characteristic symptom of anosmia commonly suffered by patients with COVID-19 [28]. Meinhardt et al. recently described the discovery of SARS-CoV-2 protein in the trigeminal branches and the trigeminal ganglion, suggesting that this may lead to activation of the trigeminovascular system, which is an established mechanism of headache causality [29].

Clearly, there are many hypothesized mechanisms of how the SARS-CoV-2 virus may lead to headache. It is often difficult to determine whether a patient's headache is a result of systemic infection or direct neuroinvasion. Bobker and Robbins propose that presentation of headache early in the course of COVID-19 is more likely due to systemic infection, as it often correlates with fever and other upper respiratory symptoms. In contrast, headache which presents later in the course of COVID-19 infection may be attributed to neuroinvasion and cytokine release storm [17].

Many of the mechanisms described above have only been elucidated or investigated at the cellular or animal model level. Therefore, further research needs to be done to determine what mechanisms may play a role in headache in humans. Likely, it will be a complex interaction of many mechanisms and may vary by individual and headache phenotype.

New Headache Phenotypes in Patients with Pre-existing Primary Headache Disorder

Given the high prevalence of primary headache disorders such as migraine in the general population, it is expected that new or worsening headache is a common symptom in

those with previously diagnosed primary headache disorders in the setting of COVID-19 infection [30]. As seen in clinical practice, people with primary headache disorders often have exacerbation of their typical headaches in the setting of systemic pathology such as viral infection. However, it is often difficult to discern if the headache these patients are experiencing is truly an exacerbation of their known headache disorder, a novel headache syndrome in the setting of infection, or a new secondary headache. A careful history, which should include ascertainment of possible red flag signs, and a detailed neurologic exam can help clarify this. García-Azorín et al. evaluated the frequency of red flags in patients with COVID-19 and headache and concluded that there was no universal red flag, although fever was the most common and was to be expected in the setting of known infection (89.4%) [31]. Therefore, it is recommended to screen patients for all red flags. If patients with pre-existing headache conditions develop signs and symptoms consistent with red flags, then secondary headaches must be considered and further investigated with neuroimaging and/or lumbar puncture (LP) depending on the clinical context.

The impact of COVID-19 on individuals with migraine has been evaluated by multiple studies which all demonstrate that there is a reported increase in migraine frequency and intensity, as well as increased use of acute migraine treatments even if not infected with COVID-19, likely as a result of psychosocial stressors related to the pandemic [32, 33]. Therefore, it is reasonable to assume that those who have a history of headache may have more problems with COVID-related headache when compared to those without a prior headache history. Literature from Magdy et al. supports this, as their study investigating predictors of headache frequency and intensity in patients with COVID-19 demonstrated that patients with pre-existing primary headache had significantly more frequent COVID-19-related headache than those without (52.9% vs 47.1%) [13]. The negative impact of the pandemic in general has also been demonstrated in patients with medication overuse headache (MOH). For example, Li et al. demonstrated that patients with MOH experienced worse relief of headache symptoms and drug withdrawal during the pandemic compared to the pre-pandemic period, likely as a result of greater comorbid psychological distress and lack of close follow up with their headache clinician [34]. Overall, it is likely that patients with pre-existing headache disorders will be more disabled from COVID-19 infections when compared to age-matched controls [35, 36]. Additionally, Bhasker describes that patients with chronic neurological disease were more likely to experience worsening despair or depression in the setting of COVID-19, resulting in non-adherence, potential relapse, and overall worsening of their pre-existing headache condition [37].

Porta-Etessam et al. investigated the characteristics of headache associated with COVID-19 infection in healthcare professionals, finding that history of migraine was present in 17.9% of this population and was associated with higher frequency of pulsating headache. It is unclear if these individuals with migraine had pulsating headaches as a feature of their typical migraine phenotype [38].

Singh and Ali described 2 patients with a history of migraine who had headache as the presenting symptom of COVID-19. The first patient was described as a 31-year-old woman who had developed a new moderate to severe headache that was pounding, continuous, and distinct from her typical episodic migraine. Her headache was refractory to her typical abortive medications, and did not respond to multiple other abortive therapies including naproxen, acetaminophen, and tizanidine. Her headache resolved 4 days after the COVID-19 diagnosis. The second case describes a 32-year-old woman who developed a severe, intractable headache that was unresponsive to her typical abortive therapy of sumatriptan. Ultimately, pain relief was achieved by adding topiramate and tizanidine and switching to rizatriptan [35]. Similarly, Rocha-Filho and Voss described the case of a 40-year-old woman with migraine with and without aura who developed a continuous, severe, pulsating, bilateral headache associated with photophobia and phonophobia. Although it was acknowledged that this headache had many migrainous features, its phenotype was different from her typical migraine and was considered the most disturbing symptom of her COVID-19 illness. Her headache was refractory to her typical abortive therapies, and she was reportedly continuing to experience the headache 85 days after the onset of her COVID-19 infection. Of note, MRI brain imaging was negative, and LP was not performed. Therefore, meningitis cannot be definitively excluded as the cause of her headache, although the authors note that lack of fever, meningeal signs, and focal neurologic deficits made meningitis overall less likely [39]. Given its persistence, this patient will likely ultimately be diagnosed with new persistent daily headache (NDPH), an uncommon headache disorder which can be triggered by a viral infection as one potential etiology [1].

Headache Attributed to Systemic COVID Infection Without Known Meningitis or Encephalitis

As seen in clinical practice and highlighted through literature in the following section, headache may manifest because of systemic COVID-19 infection, even without evidence of primary CNS infection. The ICHD-3 does include criteria for headache attributed to a systemic viral infection, without meningitis or encephalitis [1].

Toptan et al. discuss a case series of 13 patients who presented with a chief complaint of headache and

otherwise mild COVID-19. Of note, this case series excluded patients with symptoms suggestive of viral meningoencephalitis. It was notable that only 7/13 patients had no previous history of headache. All of these patients noticed the current headache associated with COVID-19 was moderate to severe and incapacitating. Common aggravating factors included bending over and routine movement. 9/13 patients reported only partial or temporary responses to analgesics including paracetamol or NSAIDs. The most common associated symptoms were photophobia and phonophobia in 9/13 of patients. Interestingly, 3/12 of these patients had headaches as the lone symptom of COVID-19. In 70% of patients, headache resolved within 3 days of COVID-19 diagnosis; however, this means that 30% of patients had some persistent headache symptoms beyond the day 3 time point. The authors noted that the headaches described in this case series do have migrainous features, but they describe that this was often either a new phenotype in patients with previous migraine history or a new headache syndrome in those without migraine history. Additionally, given that these patients had headache as a presenting symptom and otherwise mild COVID-19 infection, they suggested that headache does not correlate with disease severity [40]. Bolay et al. support these findings as in their experience, COVID-19 patients developed new-onset moderate to severe bilateral headaches that were aggravated by bending over [8]. They also describe that a striking feature of these headaches was a resistance to analgesics, a common theme seen in much of the literature.

NDPH is a known primary headache disorder, thought to be triggered by viral infection in a subset of patients [41], such as COVID-19. As described by Rozen, NDPH may have been a sequela of prior viral epidemics and therefore may be seen as a neurologic sequelae of the SARS-CoV-2 infection [2]. Supporting this is literature from Dono et al. who report 2 cases of patients who presented with moderate-to-severe, unremitting headache, and no other features that would classify them under another primary headache phenotype [42]. Both patients remembered the exact time of onset of the headache. Both patients had treatment refractory headaches, and because they were not followed to 90 days, a diagnosis of probable NDPH was made. The first patient was treated with steroids with good relief, and the other patient refused treatment with steroids due to a history of side effects to steroids [42].

Interestingly, when investigating headache as a predictor of COVID-19 clinical evolution, Caronna et al. demonstrated that headache predicted a shorter COVID-19 clinical course. However, several of these patients reported persistent headache even when other COVID-19 symptoms resolved. Specifically, at 6 weeks, of the followed-up patients with headache, 37.8% had ongoing headache. Of these, 50% (14/28) had no previous headache history [15].

Some literature has also attempted to uncover predictors of developing headache with increased intensity and frequency in those with COVID-19. There are reports that patients with comorbidities have significantly worse headaches than people who do not have comorbidities. These comorbidities included hypertension, diabetes, hypothyroidism, ischemic heart disease, and epilepsy. Additionally, dehydrated patients were found to have higher headache frequency, and fever predicted both higher frequency and intensity of headache related to COVID-19 [13].

Notably, the studies described in this section include a majority of patients with no previous headache history. Interestingly, the features of the headaches described are similar to the patients with pre-existing primary headache disorders (i.e., moderate to severe, persistent, treatment refractory), suggesting a possible common pathophysiology unique from primary headache disorders in patients affected by COVID-19 headache.

Headache Attributed to Meningitis or Encephalitis Due to COVID-19

Patients with neuroinvasive complications of COVID-19 disease have typically had nonspecific cerebrospinal fluid (CSF) abnormalities, with limited evidence of SARS-CoV-2 viral RNA detection [43, 44]. Even a large systematic screening of CSF samples for SARS-CoV-2 were very low (2/578 samples screened were slightly positive using a reportedly high-sensitive RT-PCR assay) [45]. Another multicenter analysis that undertook the systematic review of CSF profiles in COVID-19 disease reported that half of samples (58/116) demonstrated some evidence of blood-CSF barrier dysfunction as the most common finding (elevated CSF/serum albumin ratio); total protein was elevated in 54/118, and pleocytosis was noted in 14/128. Two of 19 were observed to have elevated SARS-CoV-2 IgG antibody index both in association with significant elevation in white blood cell count [46].

Additionally, given that viral meningitis and encephalitis are generally treated supportively (with notable exceptions including certain herpes virus infections), we may take into consideration that performing an invasive and non-emergent testing such as an LP in the setting of the COVID-19 pandemic where resources and personal protective equipment were limited may not have been practical for all suspected cases of neuroinvasive disease. However, it is important to note that headache attributed to viral meningitis or encephalitis should be considered when headache is associated with fever, neck stiffness, nausea, photophobia, and phonophobia according to the ICHD-3 [1]. Herpesvirus reactivation has been observed in the setting of COVID-19 disease including cases of HSV-1 and VZV meningitis/meningoencephalitis and thus should also be a consideration [46].

Moriguchi et al. describe a 24-year-old man who presented with generalized convulsions and neck stiffness who was found to have SARS-CoV-2 RNA in the CSF. Interestingly, nasopharyngeal swab testing did not return positive for SARS-CoV-2 RNA. MRI brain demonstrated hyperintensity of the right lateral ventricle and right mesial temporal lobe and hippocampus, suggesting SARS-CoV-2 meningitis. Of note, the authors note that this patient's preceding symptoms prior to hospitalization included worsening, persistent, severe headache with no other upper respiratory symptoms that were suggestive of COVID-19 infection [47]. Further details of the headache are not provided in this case.

Arca and Starling also describe a case of a 58-year-old woman with history of previously well-controlled chronic migraine and current COVID-19 pneumonia for whom neurology was consulted due to headache, neck stiffness, and behavioral abnormalities. This patient was ultimately suspected to have COVID-19 meningoencephalitis rather than exacerbation of her known migraine given differences in current headache features of neck stiffness and associated transient psychological symptoms inclusive of auditory and visual hallucinations. The patient's headache was refractory to her typical abortive therapies and resistant to many of the medications used for headache in the inpatient setting, including IV acetaminophen and IV anti-emetics such as prochlorperazine, promethazine, and ondansetron. The patient had a robust initial response to IV lacosamide, but this was not sustained. Ultimately, rapid uptitration of her existing migraine preventatives (topiramate and gabapentin) and early administration of fremanezumab, in combination with initiation of oral lacosamide, helped improve headache severity. One week after discharge, the patient's headache was resolved. This case highlights the importance of differentiating secondary headache from exacerbation of primary headache in patients with pre-existing headache disorders. However, it should be noted that there was no LP performed in this case due to limited resources in the setting of the pandemic, and therefore, it is unclear if the patient truly had COVID-19 meningoencephalitis. This case does highlight the clinical circumstances and diagnostic challenges many neurologists had to face when resources were limited [48].

Treatment

Given that headache associated with COVID-19 is a novel syndrome with unknown mechanisms and pathophysiology, optimal treatment is unclear.

As described here, treatment of headache associated with COVID-19 is often composed initially of abortive analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs. However, these are often ineffective or result in only temporary, partial relief. Second-line therapy has been suggested to focus on treatment of the headache according to its most similar phenotype. For example, one of the most common phenotypes related to COVID-19 headache described in the literature is that of migraine [35, 40]. Therefore, the second-line therapies may consist of IV migraine medications while in the hospital such as prochlorperazine, metoclopramide, and subcutaneous sumatriptan (assuming no contraindications). However, we note that multiple case reports have described these rescue therapies to be ineffective. Another option includes rapid uptitration of preventative therapies [35, 48]. Arca and Starling described the successful use of antiseizure medications such as lacosamide, which may be useful given their limited side effect profile [48]. As with any headache treatment, comorbidities must be taken into consideration when selecting treatment. Dono et al. describe the successful use of steroids in a patient with probable NPDH in the setting of COVID-19 [42].

It should be noted that although initial speculation suggested that NSAIDs may be associated with a worse COVID-19 clinical course, no such objective evidence has been demonstrated, and NSAIDS can be continued in patients who previously benefited from them or trialed in patients who may benefit from them [49, 50].

Similar to other novel headache disorders which lack a clearly recognized or specific treatment, headache secondary to COVID-19 and post-viral headaches are treated based on phenotype. For this reason, obtaining a careful history and teasing out the details of the patient's symptoms, as well as all other relevant history as it pertains to their other medical conditions, complete list of current medications, allergies, etc., is important, as these points will help in shared decision-making when it comes to selecting a medication for treating this headache. Patients should be given appropriate counseling on the medication that will be trialed, including not only potential side effects, but also the titration plan, and what length of time constitutes an appropriate trial. A review of these details helps to set the patient up for success. Ultimately, the goal will be to understand the unique pathophysiology involved in COVID-19-related headaches and adjust to targeted treatment.

Application of Telemedicine in the COVID-19 Pandemic

Given the importance of social distancing in the COVID-19 pandemic, many of the usual in-person visits with patients were either rescheduled or converted to telemedicine if deemed non-urgent [17, 51]. Pre-pandemic literature described that headache management via telemedicine is efficient and as safe as traditional in-person consultation in a randomized controlled trial [52]. This was supported by another randomized controlled trial of patients with severe

migraine-related disability, which demonstrated that telemedicine was feasible and effective when compared to in-office visits [53]. A patient survey study from the American Migraine Foundation also found that telemedicine helped to facilitate care for people who have migraine. Not only were survey respondents satisfied with their experience, but many were interested in continuing with this option even post-pandemic [54].

López et al. conducted a cross-sectional study with a survey to headache neurologists in Spain with the goal of investigating the impact of COVID-19 on headache management and found that 95.8% of all centers were limiting face-to-face contact, with the majority being converted to telephone consultation [51]. Interestingly, this same study found that 86% of headache neurologists intended to increase the use of telemedicine in the future [51]. This highlights that the future of headache medicine may rely more heavily on telemedicine given its ease of use and convenience for the patient.

In the world of headache medicine, procedures such as cranial nerve blocks and onabotulinumtoxinA injections were either delayed or canceled, likely resulting in breakthrough migraine attacks and worsening of symptom burden for patients who depend on these procedures for their headache control. Kristoffersen et al. investigated the impact on headache care in the COVID-19 pandemic and demonstrated that only 36% of neurology departments administered onabotulinumtoxinA [55]. Ali also describes 3 similar patient scenarios, wherein onabotulinumtoxinA was delayed due to restrictions in procedures and face-to-face visits, and highlights the importance of flexibility and creativity for the headache medicine neurologist. One recommendation was that video visits could be completed in place of onabotulinumtoxinA administration to discuss temporizing alternative therapy options that did not require in-person office appointments, such as new oral or self-administered abortive or preventive therapy, with these patients who are often reliant on timely administration of their injections [56].

There has also been literature to support the adaptation of telemedicine in behavioral programs for medication overuse headache in those with known chronic migraine. Grazzi et al. demonstrated that implementation of a mindfulness program by smartphone combined with video calls resulted in similar positive outcomes when compared to previous studies relying on in-clinic treatment alone [57].

Neurological care is necessary during the pandemic given the various neurological complications of COVID-19, and the use of teleneurology is supported by the literature to protect the patient and consultant from unnecessary exposures when necessary [58, 59]. Ultimately, although the COVID-19 pandemic proposed difficulties with providing medical care, important lessons have been learned which will help future practice if social distancing is reinforced.

There has also been literature to support the adaptation of telemedicine in behavioral programs for MOH in those with known chronic migraine. Grazzi et al. demonstrated implementation of a mindfulness program by smartphone combined with video calls demonstrated similar positive outcomes when compared to previous studies relying on in-clinic treatment alone [57].

Neurological care is necessary during the pandemic given the various neurological complications of COVID-19, and the use of teleneurology is supported by the literature to protect the patient and consultant from unnecessary exposures [58, 59]. Ultimately, although the COVID-19 pandemic proposed difficulties with providing medical care, important lessons have been learned which will help future practice if social distancing is reinforced.

Conclusion and Future Directions

This review highlights the diversity of presentation of headaches that present as a complication of COVID-19. We see that headaches can be a symptom associated with COVID-19 in both patients without any history of a headache disorder, as well as present as a new emerging phenotype in patients with a history of headaches. Additionally, we see that headache may be a result of systemic infection or possibly due to direct neuroinvasion and should be evaluated by a thorough history and physical exam to discern this, as it may change diagnostic work up, although may not change management given treatment of viral meningitis and encephalitis is often supportive. It is notable that common characteristics are revealed when reviewing the phenotypes of headaches that have been described in patients with COVID-19, particularly characteristics similar to migraine and NPDH in phenotype. Across all of the subgroups discussed above, headaches are often described as moderate to severe, persistent, and treatment refractory. Future directions include further investigations of mechanisms underlying COVID-19 headache in human models which will help optimize treatment moving forward.

Case Revisited

You obtain a detailed history and ask for any additional red flag signs, which is unrevealing for another cause of this new headache phenotype. Neuroimaging is unrevealing for a secondary cause of headache. You suspect that this may be a post-viral headache associated with her preceding COVID infection. You confirm that she is now fully recovered from her COVID infection. You treat her with oral steroids and start her on a headache preventative agent which helps reduce the intensity and frequency of this headache

over time. She continues to have episodic migraine without aura similar to her previous phenotype which continues to be readily aborted with oral sumatriptan.

Compliance with Ethical Standards

Ethical Standard All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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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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