

Brief Communications

Headache as the Presenting Symptom in 2 Patients With COVID-19 and a History of Migraine: 2 Case Reports

Jyotika Singh, DO ; Ashhar Ali, DO

The coronavirus disease 2019 (COVID-19) pandemic has now affected more than 5 million people globally. Typical symptoms include fever, cough, and shortness of breath. Patients with underlying medical comorbidities such as cardiovascular disease and diabetes are more likely to become severely ill. To date there is limited information on how COVID-19 affects patients with a history migraine. Here, we present the cases of 2 women with a history of migraine whose first symptom of COVID-19 was a severe persistent headache.

Key words: coronavirus disease 2019, migraine, headache, neurologic, symptoms

Abbreviations: COVID-19 coronavirus disease 2019, NSAIDS non-steroid anti-inflammatory drugs, WHO World Health Organization

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BACKGROUND

Coronavirus disease 2019 (COVID-19), which emerged in Wuhan, China in December, 2019, is now a global pandemic. It is a part of the coronavirus family, and uses the angiotensin-converting enzyme 2 (ACE-2) receptor to enter cells and can cause severe acute respiratory syndrome.¹ The median incubation period before one shows typical symptoms is estimated to be 5.1 days, but one may not show symptoms for up to 14 days.² While the most common symptoms of COVID-19 are fever, cough, and shortness of breath, neurological symptoms including headache have been reported. In 1 study, headache was noted in 12% of confirmed cases and was the most common neurological

symptom.³ In another study, from Wuhan, the epicenter of the outbreak, headache was reported as the second most common neurologic symptom after dizziness and was present in 13% of patients.⁴ Other less common neurological manifestations included anosmia, ageusia, ischemic infarct, and impaired consciousness.⁴

The mechanism by which COVID-19 causes headache remains unclear. One may postulate that its mechanism is like other respiratory viruses such as influenza A and B, in which headache often accompanies fever and fatigue.⁵ There are also reports that COVID-19 has neuroinvasive potential via various pathways.¹ The ACE-2 receptor, through which COVID-19 appears to cause infection, is primarily present in epithelium of the lungs; however, it is also found in the brain, particularly the brainstem.⁶ Another postulated mechanism of entry into the brain may be through the olfactory bulb via trans-synaptic route.⁶ It has been noted that patients with more severe disease are more likely to have

From the Department of Neurology, Henry Ford Health System, Detroit, MI, USA (J. Singh and A. Ali).

Address all correspondence to J. Singh, Department of Neurology, Henry Ford Health System, Detroit, MI, USA, email: Jyotikasinh21@gmail.com

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CNS involvement.⁷ Interestingly, couple recent studies have demonstrated changes in magnetic resonance imaging of the brain in patients with COVID-19 infection admitted to the ICU. Noted were cortical signal abnormalities on FLAIR imaging, cortical diffusion restriction, bilateral frontotemporal hypoperfusion, leptomeningeal enhancement, and cortical blooming artifact. It remains unclear if these findings are due to neuro-invasion with COVID-19 itself or as a secondary effect of systemic infection with COVID-19.^{8,9}

Given its prevalence, many patients with migraine have and will be infected with COVID-19. Their experience with the disease has not yet been reported. Here, we illustrate the cases of 2 patients – 1 with episodic migraine and 1 with chronic migraine – whom developed severe headache whilst infected with COVID-19. Of note, in both cases, the patients developed daily headache several days prior to the onset of typical symptoms of COVID-19.

CASE 1

A 31-year-old female has a history of episodic migraine since age 5. Her migraine attacks occur once to twice per month, are unilateral, throbbing in quality, moderate to severe in intensity, and are associated with photophonophobia and nausea. They typically last 2-8 hours with treatment. She developed a moderate to severe daily headache which she described as distinct from her usual migraine. It was a continuous, pounding, bilateral frontotemporal headache that was moderate to severe in intensity. She did not have photophonophobia or nausea. The headache would briefly improve with ibuprofen 400 mg, but would recur the following day. One week later, she developed fever, cough, severe myalgias, dyspnea, and diarrhea. She tested positive for COVID-19 via nasopharyngeal swab PCR. Once diagnosed, out of fear that her COVID-19 would be exacerbated by the use of non-steroid anti-inflammatory drugs (NSAIDs), she switched to acetaminophen without improvement. After consulting with a headache specialist, she was advised to take naproxen 440 mg twice daily as needed as well as tizanidine 4 mg every 8 hours as needed. The patient opted not to take tizanidine and only took 2 doses of naproxen, with which she saw no improvement and discontinued the use due to the apprehension of worsening infection. Both her classical symptoms of

COVID-19 and headache resolved 4 days after diagnosis and she did not undergo repeat testing for COVID-19.

CASE 2

A 32-year-old female has a history of chronic migraine and is currently on topiramate 50 mg nightly for prophylaxis and sumatriptan 50 mg for abortive therapy. Her migraine attacks occur 2-3 times per week and are bifrontal, throbbing in quality, severe in intensity, and associated with photophonophobia and nausea. Her migraine attacks typically last >24 hours if untreated. She developed a severe intractable headache 1 week prior to the onset of typical COVID-19 symptoms. The headache was different than her usual migraine. It was more intense, persistent, and not responsive to abortive therapy. She took acetaminophen daily without relief. Sumatriptan, her usual abortive treatment, was also not effective. One week later, she developed typical COVID-19 symptoms which consisted of low-grade fever, myalgias, nasal congestion, anosmia, and diarrhea. She tested positive for COVID-19 via nasopharyngeal swab PCR. After 2 to 3 days, these symptoms resolved, but her headache persisted. She was seen by a headache specialist via a telemedicine video visit 2 weeks after onset of her severe headache and 1 week after the onset of typical COVID-19 symptoms. Her topiramate was increased to 100 mg nightly, her sumatriptan was switched to rizatriptan, and she was started on tizanidine 4 mg every 8 hours as needed for breakthrough pain. Two days after starting this regimen, the patient's headache resolved. Repeat COVID-19 testing via nasopharyngeal swab was performed and was negative, 5 weeks after she initially tested positive.

DISCUSSION

The above 2 cases demonstrate headache as the first symptom of COVID-19 infection in patients with a history of migraine. Interestingly, the phenomenon of headache as an early symptom of COVID-19 infection was also noted by Mao et al. The authors describe patients who had symptoms of fever and headache. They were initially considered negative for COVID-19 infection through normal bloodwork and negative lung computed tomography (CT). However, several days later, they developed typical COVID-19 symptoms,

low lymphocyte count, and typical findings associated with COVID-19 on lung CT; the patients ultimately tested positive for COVID-19 via PCR. It is unclear, however, if these patients had a history of migraine.⁴ At this time, while we lack sufficient data to conclude that headache is an early symptom of COVID-19 infection, we recommend that in areas where COVID-19 is endemic, patients with a new type of headache take additional precautions.

In our patients, the headache preceding typical COVID-19 symptoms was distinct from the patients' usual migraine, alluding to the possibility that headache related to COVID-19 is mechanistically different than migraine. These headaches were described as more severe, unrelenting, and not as responsive to the patients' usual abortive treatments. It is possible that headache is a manifestation of COVID-19 CNS invasion or cytokine storm, though further data are needed.⁶

There were some differences between these 2 patients. Notably, the first patient's headache resolved with the resolution of other COVID-19 symptoms, while the second patient continued to have headaches for 2 weeks after the resolution of typical COVID-19 symptoms. Furthermore, our first patient did not have migrainous features with her continuous headache, but our second patient did.

Many patients infected with COVID-19 have underlying medical conditions. Often highlighted in the medical literature and mainstream media are the co-morbidities that are associated with increased mortality, such as cardiovascular disease, obesity, and diabetes.¹⁰ However, with the high prevalence of migraine in the general population, and as it is a leading cause of disability, it too is an underlying medical condition that warrants academic and clinical attention.¹¹ This includes a better understanding of the headache that occurs with COVID-19 – its qualities, characteristics, and true incidence. It also includes the need for larger retrospective studies evaluating the experience of COVID-19 in patients with a history of a primary headache disorder. Our experience with the above 2 cases suggests that migraine patients, particularly young healthy women wherein migraine is most prevalent, may be more disabled by COVID-19 infection compared with age-matched

cohorts, most of whom will only experience mild symptoms.¹²

Further investigation and discussion are also needed on the safety of commonly used headache treatments. There has been concern regarding the use of NSAIDs, due to anecdotal evidence citing worsening of COVID-19 symptoms in young patients who received treatment with NSAIDs early in the disease.¹³ However, there is no clinical or population-data that corroborates this risk, and hence, both the European Medicines Agency and World Health Organization (WHO) have not recommended that NSAIDs be avoided.^{14,15} Despite this recommendation, as a precautionary measure many providers have opted to avoid NSAIDs in patients with COVID-19. This carries several implications for the headache population. Our first patient self-discontinued her abortive therapy, ibuprofen, out of caution, and also chose to limit naproxen intake. Anecdotally, many non-infected patients at our headache center have expressed concern over continuing their NSAID abortive therapy during the pandemic. One patient on indomethacin for paroxysmal hemicrania raised concern about its continuation. As more data are collected, we will be better able to assess the risks. Nonetheless, in a recent article about migraine care in the era of COVID-19, Dr. Szperka et al recommend continued the use of certain NSAIDs (Indomethacin, ketorolac, naproxen, nabumetone, diclofenac, and mefenamic acid) as abortive treatment for migraine.¹⁶ In our practice, the decision to continue or stop NSAIDs in patients with COVID-19 is made in collaboration between the treating physician and the patient, after a brief discussion on the limited available evidence. Most patients tend to err on the side of caution. More data are needed, however, before broad recommendations are made.

Other considerations that affect our migraine population include limited access to care, be it in-person office visits, intravenous infusions, procedures such as nerve blocks or onabotulinumtoxinA injections. We have shared our experience in delaying certain in-person care in a recent publication.¹⁷

CONCLUSION

Further studies are needed to better understand the implications of headache in COVID-19 patients.

The above 2 cases demonstrate that patients with a history migraine may experience headache as their first symptom, and due to severe headache, may be more disabled by the infection compared with age-matched cohorts. Until we have more data, healthcare providers caring for these patients should prepare treatment plans to optimally manage headache during COVID-19 infection. This is of particular importance given the limited access to in-person evaluations and concerns by both providers and patients alike regarding the safety of NSAIDs.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design

Jyotika Singh

(b) Acquisition of Data

Jyotika Singh, Ashhar Ali

(c) Analysis and Interpretation of Data

Jyotika Singh, Ashhar Ali

Category 2

(a) Drafting the Manuscript

Jyotika Singh

(b) Revising It for Intellectual Content

Jyotika Singh, Ashhar Ali

Category 3

(a) Final Approval of the Completed Manuscript

Jyotika Singh

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