

BRIEF COMMUNICATIONS

Toward a better understanding of persistent headache after mild COVID-19: Three migraine-like yet distinct scenarios

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Abstract

One year after the outbreak of coronavirus disease 2019 (COVID-19), referrals for persistent headache, often defined as “post-COVID headache,” have become increasingly common in outpatient headache clinics. However, it is important to take into consideration that this term may include a spectrum of clinically different headache types. We describe three cases of migraine-like headaches in individuals with a history of mild COVID-19 infection to demonstrate some of the different phenotypes of persistent headaches seen. These cases highlight the importance of a careful evaluation when assessing the complexities of “post-COVID headache” as well as the need to further investigate the different, underlying, pathophysiological mechanisms.

KEYWORDS

headache, migraine, post-COVID-19, SARS-CoV-2

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus, responsible for coronavirus disease 2019 (COVID-19),¹ that emerged in China at the end of 2019 causing the current global pandemic.² During the acute phase of infection,³ COVID-19 can trigger a headache that is phenotypically similar to migraine or tension-type headache,^{3,4} among other neurological symptoms.⁵

Some patients do not fully recover after the acute phase and experience persistent symptoms and/or delayed or long-term complications of COVID-19, generally referred to as “post-COVID syndrome.”⁶ These symptoms may include memory impairment, insomnia, fatigue, dizziness, etc.^{7,8} Headache is also a post-COVID symptom⁹ in some patients and consultations for persistent headache attributed to COVID-19, often referred to as “post-COVID headache,” are presumably being seen more often in clinical practice.

Although data on persistent headache attributed to COVID-19 are still lacking, clinical observation by neurologists during their daily

practice appears to indicate the presence of many different headache types. This would imply that the term “post-COVID headache” may be too broad to describe the complex spectrum seen. Different types of headaches may be a result of different pathophysiological mechanisms, even if they display similar characteristics, such as migraine-like features. Consequently, they may have different prognoses and responses to treatment.

Here, we describe the cases of three different patients, evaluated in our headache clinic, with “post-COVID headache.” We focus on patients with a history of mild COVID-19 infection and migraine-like features to stress the existence of a complex scenario even within a group of patients with similar characteristics. We discuss our main findings and their implications below.

PATIENT 1: MIGRAINE CHRONIFICATION

A 56-year-old woman with a history of low-frequency episodic migraine (<1 day/month) and the absence of other comorbidities, who

TABLE 1 Main features of the three patients presented

	Patient 1	Patient 2	Patient 3
Demographics			
Age, years	56	55	44
Menopause	Yes	Yes	N/A
Sex	Female	Female	Male
Family migraine history	Yes	No	No
Personal migraine history	Yes	No	No
COVID-19 and headache characteristics			
COVID-19 severity	Mild	Mild	Mild
Headache in the acute phase	Yes	Yes	No
Anosmia/ageusia	Yes	Yes	No
Migraine-like features	Yes	Yes	Yes
Concomitant "post-COVID" symptoms	Fatigue, insomnia	Hyposmia, fatigue, insomnia	Fatigue, insomnia, mood disorder, loss of memory, dizziness
Treatment response			
Response to triptans	Yes	Yes	No
Response to preventive medications (AMT+BTX)	Yes	Yes	No

Abbreviations: AMT, amitriptyline; BTX, onabotulinumtoxinA; N/A, not applicable.

had menopause at the age of 49, had a mild COVID-19 infection. The patient exhibited symptoms of headache, anosmia/ageusia, and malaise at the end of May 2020. The presence of COVID-19 was confirmed using a positive real-time reverse transcriptase polymerase-chain reaction (RT-PCR) assay test. Headache was the first symptom of infection, starting a couple of days prior to the other symptoms. The patient's headache was characterized as being: frontally located, throbbing in quality, with a moderate–severe pain intensity, and associated with nausea, photophobia, and phonophobia. She reported that it differed from her usual migraine in that the pain since onset was constant. This constant pain was most likely the reason why the patient started overusing acute medication (paracetamol and nonsteroidal anti-inflammatory drugs) during the first 2 months, although later the lack of pain relief made her reduce her analgesic intake. The patient also started noticing allodynia while combing her hair.

The patient first visited our headache clinic at the end of October 2020 to discuss persistent headache. She also reported fatigue and insomnia. Results from a CT scan with contrast, lab work, and a neurological examination were within the norm and did not suggest the presence of secondary causes. The patient did not have hypertension or any new onset comorbidity. The patient was instructed on lifestyle changes and, given the disabling nature of her headaches and other symptomology, was offered combined preventive treatment with amitriptyline 25 mg QD, also beneficial in treating her insomnia, and onabotulinumtoxinA (BTX) 195U based on her chronic migraine-like phenotype. Because of the patient's initial reluctance toward BTX, we began with amitriptyline only. After 4 weeks, the patient's sleep quality had improved; however, she continued to experience headache almost daily, although with a reduction in intensity. We

then added BTX to her treatment and after 3 months, the patient experienced a reduction in headache frequency to around 8–10 days/month and a return in character to her usual migraine. The patient's allodynia also disappeared. Her symptoms remained stable throughout the second cycle of BTX.

PATIENT 2: LONG-LASTING COVID HEADACHE

A 55-year-old woman, with no personal or family history of a primary headache disorder and no other comorbidities, who underwent menopause at age 51, had a mild COVID-19 infection. She exhibited symptoms of headache, anosmia/ageusia, cough, shortness of breath, malaise, and diarrhea at the end of March 2020. The presence of COVID-19 was confirmed by a positive RT-PCR. Pneumonia was ruled out with a chest X-ray. The patient's headache started a few days after the appearance of her other symptoms. Headache characteristics included holocranial location, moderate severity, and tightness/pressure in terms of type of pain although the patient also reported moments of more severe, throbbing pain. Headache was accompanied by photophobia, phonophobia, and nausea. The patient was unable to engage in her usual physical exercise due to worsening of pain with movement. She had constant pain following headache onset and was taking paracetamol daily.

The patient first visited our headache clinic at the beginning of July 2020 because of the presence of persistent headache. Furthermore, she was still experiencing hyposmia, fatigue, and insomnia. An MRI of the brain with MR angiography, blood tests, as well as a neurological examination were performed but did not yield any secondary causes. We discussed lifestyle changes with the

patient and, based on the same rationale as in Patient 1, a combined preventive treatment plan of amitriptyline 25 mg QD coupled with BTX 195U were initiated immediately. Three months later, the patient's sleep quality had improved alongside an important reduction in both headache frequency (1-2 headache days/week) and severity (50%-75% reduction). On headache days with migraine features, the patient displayed a good response to almotriptan 12.5 mg. The patient remained clinically stable with two subsequent BTX administrations, although she did report the effects of the treatment "wearing off" prior to each injection.

PATIENT 3: DELAYED-ONSET-COVID HEADACHE

A 44-year-old man with asthma and no personal or family history of a primary headache disorder had a mild COVID-19 infection. He exhibited symptoms including cough, shortness of breath, and malaise at the end of March 2020. The presence of COVID-19 was confirmed by a positive RT-PCR. Pneumonia was ruled out by a chest X-ray. The patient did not experience loss of smell/taste or headache in the acute phase of infection. In May 2020, when his respiratory symptoms began to improve, he started to report the presence of headaches with holocranial localization, throbbing pain, photophobia, phonophobia, nausea, and worsening of pain with movement. Over the course of the following weeks, his headaches increased to a constant, daily frequency although he could still distinguish severe migraine-like days from milder ones. He was not overusing acute medication given he did not experience any kind of pain relief from analgesic use. An MRI of the brain with MR angiography, blood tests, and neurological examinations were performed in that period and were not suggestive of secondary causes.

The patient first visited our headache clinic in mid-July 2020 because of the presence of persistent headache. He complained of fatigue and insomnia and was found to be newly hypertensive at 140/90 mm Hg. First, we attempted to address other possible factors related to headache through the use of a combined preventive treatment plan of amitriptyline 25 mg QD for insomnia and candesartan 16 mg QD for hypertension. The patient was also instructed to undertake changes in lifestyle. Five weeks later, hypertension was controlled, sleep quality had partially improved, but the patient did not report any significant clinical changes in his persistent headaches. BTX 195U was added to the patient's treatment plan but was discontinued after two cycles due to a lack of improvement. Rizatriptan 10 mg was ineffective in treating migraine-like days. During the follow-up, the patient started reporting other symptoms such as cognitive impairment, memory loss, heart palpitations, and dizziness, for which he had scheduled a visit at a memory unit and a cardiology clinic, respectively. On the patient's last visit in April 2021, escitalopram 10 mg QD was started due to changes in mood. He was still experiencing disabling, daily, and constant headache and had not returned to work or his usual activities.

DISCUSSION

Although we are aware of a potentially wide spectrum of persistent post-COVID headaches, we report these three cases as they (1) demonstrate the existence of phenotypically similar (i.e., all of these cases had migraine-like features and were found in patients having undergone a mild COVID-19 infection) but considerably different headache subtypes and (2) represent some of the patients we have observed in clinical practice (Table 1). Moreover, in light of the emerging complications post-COVID-19, they raise several questions of scientific and clinical interest in headache, based on the following aspects:

First, Patient 1 seems to suggest SARS-CoV-2 as a risk factor for the sudden worsening of a previous headache disorder, such as migraine, potentially leading to its chronification. Worsening of headache following acute SARS-CoV-2 infection has been reported by several patients with migraine.¹⁰ Thus, the lingering headache observed, despite COVID-19 resolution, may reflect persistent changes in migraine characteristics as a result of COVID-19, rather than a new type of headache. Considering the high frequency of migraine in the general population, Patient 1 is a potential representation of one of the most common displays of post-COVID headache.

Second, migraine-like features are present in patients without a personal migraine history, as shown in Patients 2 and 3, pointing to an acquired activation of the trigeminovascular system by the SARS-CoV-2 infection.³ In support of this hypothesis, a recent study has found SARS-CoV-2 proteins in trigeminal branches and the trigeminal ganglion.¹¹ The detection of these migraine characteristics may guide acute and preventive therapeutic strategies, although the response to specific migraine treatments may not be always effective (i.e., Patient 3) as a result of other concomitant factors or mechanisms.

Third, persistent headache attributed to COVID-19 may emerge despite not having experienced headache in the acute infection phase, as observed in Patient 3. Therefore, headache as a long-lasting symptom following the acute phase of COVID-19 infection may be pathophysiologically different from headache appearing as a delayed symptom when the infection is about to resolve. For example, factors such as altered levels of glutamate and hypoxic injury are believed to play a more prominent role in the post-COVID-19 phase.¹² This suggests that new daily persistent headache (Patients 2 and 3) may, in reality, harbor different subtypes with different clinical courses.

Fourth, headache can be associated with many other symptoms (insomnia, memory loss, dizziness, fatigue, etc.) that identify "post-COVID-19 syndrome," as seen in Patient 3. The presence of these comorbid conditions could (1) point to the involvement of different pathophysiological pathways (e.g., brainstem in insomnia,¹³ neurotransmitter depletion in neuropsychiatric symptoms¹²) all leading to headache and (2) directly affect headache prognosis.^{14,15}

Thus, future research studies should focus on studying how these aspects (i.e., migraine history, migraine-like features, headache in the acute phase, headache onset post-COVID, presence of associated symptoms) interact in determining specific clinical

phenotypes, to better understand their mechanisms and define the best therapeutic strategies.

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CONFLICT OF INTEREST

Dr. Caronna has received honoraria from Lundbeck, Novartis, and Chiesi. Dr. Alpuente has received honoraria from Allergan plc, Novartis, and Chiesi. Dr. Torres-Ferrus has received honoraria from Allergan plc, Novartis, and Chiesi. Dr. Pozo-Rosich has received honoraria as a consultant and speaker for: Allergan-AbbVie, Almirall, Biohaven, Chiesi, Eli Lilly, Medscape, Neurodiem, Novartis, and Teva. Her research group has received research grants from Novartis and funding for clinical trials from Alder, Amgen, Electrocore, Eli Lilly, Novartis, and Teva. She is an Elected Trustee of the board for the International Headache Society and a member of the Council for the European Headache Federation. She is a member of the editorial board for *Revista de Neurologia*. She is an editor for *Cephalalgia*, *Headache*, *Neurologia*, *Frontiers of Neurology* and an advisor for *The Journal of Headache and Pain*. She is a member of the Clinical Trials Standing Committee for the International Headache Society. She has edited the *Guidelines for the Diagnosis and Treatment of Headache* for the Spanish Society of Neurology. She is the founder of www.midolordecabeza.org. P.P.-R. does not own stocks from any pharmaceutical company. There are no conflicts of interest with regard to this manuscript.

AUTHOR CONTRIBUTIONS

Study concept and design: Edoardo Caronna, Patricia Pozo-Rosich. *Acquisition of data:* Edoardo Caronna. *Analysis and interpretation of data:* Edoardo Caronna, Patricia Pozo-Rosich. *Drafting of the manuscript:* Edoardo Caronna, Patricia Pozo-Rosich. *Revising it for intellectual content:* Edoardo Caronna, Alicia Alpuente, Marta Torres-Ferrus, Patricia Pozo-Rosich. *Final approval of the completed manuscript:* Edoardo Caronna, Alicia Alpuente, Marta Torres-Ferrus, Patricia Pozo-Rosich.

PATIENT CONSENT

All patients provided fully informed, voluntary and written consent to publish.

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