

BRIEF COMMUNICATION

Protracted headache after COVID-19: A case series of 31 patients from a tertiary headache center

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Abstract

Background: Headache can be a prominent feature of Post-Acute Sequelae of SARS-Cov2 infection (PASC) and previous studies have centered around PASC headaches that have resolved within a month of infection.

Methods: We performed a retrospective chart review of 31 adults evaluated at the Stanford Headache Clinic between September 2020 and January 2022 who developed new or worsening headaches after COVID-19 infection that were unresolved at time of evaluation for demographics, medical history, and headache diagnosis.

Results: Headache had been present for a mean duration of 7.4 ± 4.8 months after infection. Notably, 25/31 (81%) had a previous history of headache. The specific features of the headache varied considerably, but 23/31 (74%) met International Classification of Headache Disorders, Third Edition (ICHD-3) criteria for migraine, with 20/31 (65%) meeting ICHD-3 criteria for chronic migraine, while only 5/31 (16%) met these criteria before COVID infection. Additionally, full-time employment decreased from 25/31 (81%) to 17/31 (55%). Prior to establishing care at our clinic, 13/18 (72%) of the patients who were started on preventive medications currently indicated for migraine management, reported a decrease in frequency and/or severity of headaches.

Conclusions: Our study presents a group of patients with protracted headache after COVID-19 infection that includes both patients with a previously lower headache burden who largely exhibited chronification from episodic to chronic migraine, as well as patients with no previous history of headache who meet ICHD-3 criteria for headache attributed to a systemic viral illness, mostly with a migrainous phenotype.

KEY WORDS

chronic migraine, COVID-19, headache, PASC, post-acute sequelae of severe acute respiratory syndrome coronavirus 2 infection, post-COVID headache

INTRODUCTION

Headache remains a common initial symptom of coronavirus disease 2019 (COVID-19) infection and is present in up to 49% of patients.¹ It typically presents on the first day of symptoms, can be the first sign of infection, and has a higher prevalence in persons with a previous history of migraine.²⁻⁴ These headaches are described as

holocephalic or bilateral, "oppressive" or pulsatile, and with migrainous features.² The presence of headaches has also been associated with less common COVID-19 symptoms including anosmia, ageusia, dizziness, and gastrointestinal complaints, but not with increased rates of pneumonia or hospitalization.^{2,5-7}

Headache after COVID-19 has been found to last a median of 14 days (6-39) and extends after 3 months in 19% and after

Abbreviations: COVID-19, coronavirus disease 2019; ICHD-3, International Classification of Headache Disorders, 3rd edition; IRB, institutional review board; PASC, post-acute sequelae of severe acute respiratory syndrome coronavirus 2 infection.

9 months in 16%.⁸ These persistent headaches are associated with a prior history of headache, female sex, and long-term symptoms such as fatigue.^{5,9} Previous studies noted a holocranial or bitemporal pain pattern and case reports indicate potential improvement with typical migraine therapies.^{1,5}

While previous studies have sought to characterize overall headache after COVID-19, we present a dedicated group of patients with unresolved, protracted headache after COVID-19 who mainly converted from episodic to chronic migraine, as well as a smaller subgroup who developed a new persistent headache.

METHODS

We conducted a retrospective chart review of 31 adults, approved by the Stanford Institutional Review Board (IRB), who were evaluated at the Stanford Headache Clinic between September 2020 and January 2022 and developed new or worsening headache after COVID-19 infection, for demographics, medical history, and headache diagnosis. COVID-19 diagnoses were made through positive laboratory testing available through the Stanford electronic health record (17/31), outside reported positive testing (8/31), or symptoms consistent with COVID-19 prior to widespread testing availability (6/31). Information for the individual medical charts was obtained by the individual headache attendings during new and follow-up patient visits from direct patient interview. Post-acute sequelae of severe acute respiratory syndrome coronavirus 2 infection (PASC) symptoms noted in this study were those collected at the time of the interview only. Written informed consent was waived by the IRB based on the exclusion of Health Insurance Portability and Accountability Act identifiers. Cases referred for review by the Stanford Headache Neurology group were uploaded via medical record number to the secure Stanford Research Repository Tools software and de-identified. The sample size was obtained from the number of referred patients who met criteria; all patients who were referred were included. Data were then evaluated in a secure de-identified Microsoft Excel spreadsheet. Inclusion required a prior diagnosis of COVID-19, age of at least 18, and onset of new or worsening headache starting within 1 month after the infection. This is the primary analysis of these data. Missing data were limited to one patient whose ethnicity was not reported.

Statistical analysis

Descriptive statistics were calculated within Microsoft Excel including frequency, percentage, mean, and standard deviation.

RESULTS

Our study population of 31 adults with new or worsening headache after COVID-19 had an average age of 41.3 ± 11.9 years and the

TABLE 1 Demographics

Age (Mean years \pm SD)	41.3 \pm 11.9	
Sex	N (31)	%
Male	11	36
Female	20	65
Ethnicity		
White	16	52
Hispanic/Latino	10	32
Black	2	7
Asian	2	7
Unknown	1	3
Employment at time of initial infection		
Full time	25	81
Part time	1	3
Unemployed	5	16
Employment at time of visit		
Full time	17	55
Part time	1	3
Unemployed	10	32
On disability	3	10

majority were female (20; 65%; [Table 1](#)). Sixteen (52%) were White, ten (32%) were Hispanic/Latino, two (7%) Black, two (7%) Asian, and one (5%) unknown. Of note, full-time employment showed a decrease from 25/31 (81%) at time of initial COVID-19 infection to 17/31 (55%) at time of evaluation.

Within our study population, 25/31 (81%) patients had a previous history of headache, with 18/25 (72%) of that subgroup meeting International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria for migraine; migraine on fewer than 15 days was present in 12/31 (48%) and 5/31 met ICHD-3 criteria for chronic migraine (20%). Obstructive sleep apnea was the most common comorbidity in 5/31 (16%) patients, followed by hypertension in 4/31 (13%). Three patients reported depression (3/31, 10%). An additional three patients (3/31, 10%) reported previous history of concussion but did not meet ICHD-3 criteria for headache attributed to trauma or injury to the head and/or neck.

Headache characteristics varied greatly ([Table 2](#)). Unilateral and bilateral pain occurred most frequently, in 14/31 (45%). More rarely, the headaches were holocephalic in 3/31 (10%), midline in 2/31 (7%), and side-locked in 1/31 (3%). The location of pain was highly variable with occipital pain being most common in 11/31 (36%) patients, followed by frontal in 9/31 (29%), and temporal or neck pain in 7/31 (23%) patients each. No patients reported mild pain; 18/31 (58%) patients reported severe pain and 12/31 (39%) noted moderate pain. The nature of the pain varied too, most commonly characterized as throbbing in 8/31 (26%), sharp in 7/31 (23%), and dull or pressure-like in 6 additional patients each (6/31, 19%). Migrainous features were common including nausea in 24/31 (77%), photophobia in 22/31 (71%), and phonophobia in 21/31 (68%). Aura was rare, occurring in only 4/31 (13%). Cranial autonomic features were present in 10/31 (32%) patients.

TABLE 2 Headache characteristics

Sidedness (could have multiple locations)	N (31)	%
Unilateral	14	45
Bilateral	14	45
Holocephalic	3	10
Midline	2	7
Side-locked	1	3
Location (could have multiple locations)		
Occipital	11	36
Frontal	9	29
Neck	7	23
Temporal	7	23
Face	4	13
Retroorbital	3	10
Vertex	3	10
Shoulders	2	7
Parietal	2	7
V2	2	7
Maxillary	1	3
Retroauricular	1	3
V2-V3	1	3
Severity		
Severe	18	58
Moderate	12	39
Unknown	1	3
Characteristic of the pain (could have multiple)		
Throbbing	8	26
Sharp	7	23
Dull	6	19
Pressure	6	19
Stabbing	4	13
Pulsatile	4	13
Burning	2	7
Additional features		
Nausea	24	77
Photophobia	22	71
Phonophobia	21	68
Autonomic symptoms	10	32
Aura	4	13
Duration (Mean hours \pm SD)	21.2 \pm 15.2	
Frequency (Mean days per month \pm SD)	23.1 \pm 8.7	

Headache occurred on a mean of 23.1 \pm 8.7 days per month and 16/31 (52%) patients reported headaches every day of the month. Nineteen patients (19/31, 61%) noted headaches lasting the entire day.

TABLE 3 Medication and response initiated prior to visit

Response to treatment prior to visit	N (31)	%
Started on any preventive medication	18	58
Any response		
Gabapentin	4	31
Topiramate	3	23
Nortriptyline/amitriptyline	2	15
OnabotulinumtoxinA	2	15
Verapamil	1	8
Sumatriptan	1	8
Nutraceuticals	1	8
Nature of response		
N (13)		
Decrease in frequency	5	39
Decrease in severity	6	46
Decrease in frequency and severity	2	15

At time of evaluation migraine was the predominant headache diagnosis by ICHD-3 criteria. The criteria for migraine were met by 23/31 (74%), with 20/31 (65%) meeting ICHD-3 criteria for chronic migraine. Additionally, four patients (4/31, 14%) met ICHD-3 criteria for medication-overuse headache. New cranial nerve neuralgias were diagnosed in 5/31 (16%). Both chronic tension-type headache and trigeminal autonomic cephalalgias were diagnosed by ICHD-3 criteria in two patients each (2/31, 7%).

Beyond headache, the most common additional patient-reported PASC were tinnitus in 12/31 (39%), fatigue in 11/31 (36%), and dizziness and cognitive difficulties in 6/31 (19%) each.

Of the 31 patients, 18 (58%) had been started on preventive medications either prior to seeing us, or at their initial appointments with a Stanford Headache Clinic attending with 13/18 (42%) reporting a decrease in their headache burden (Table 3). In this subset, anti-seizure medications (gabapentin and topiramate) were most commonly used in 7/18 (54%). Tricyclic antidepressants (nortriptyline and amitriptyline) and onabotulinumtoxinA were each used in 2/18 (15%) patients. In this 18-patient subgroup, those who responded to treatment primarily noted a decrease in severity in 6/18 (46%) or frequency in 5/18 (39%) and 2/18 (15%) noted both.

DISCUSSION

Our study population of 31 patients presented as two subtypes of protracted headache after infection with COVID-19: six patients (19%) with no previous history of headache who developed new onset headache, often with a migrainous phenotype, and 25 patients (81%) with a previous history of headache whose overall headache burden increased, including a marked conversion from episodic to chronic migraine. This predominance of patients with a history of headache who experienced an exacerbation after COVID-19 infection is consistent with previous literature, and significantly exceeds previously reported chronification rates of 2.5% yearly from episodic to chronic migraine among the general population.^{9,10} We observed a stark shift

in headache burden in those with a previous history of headache with an increase in the percentage of patients in our group who met ICHD-3 criteria for chronic migraine prior to COVID infection from 16% before to 65% after. Consistent with this higher burden of chronic migraine we observed a high frequency of headaches, as well as elevated pain ranking moderate to severe and a notable burden of other migrainous features including nausea, photophobia, and phonophobia. The much smaller group of six patients without a previous history of headache had phenotypically similar headaches to the group with previous headaches, and half (3/6) met the ICHD-3 criteria for chronic migraine. Beyond the increased burden of headache itself, protracted headaches after COVID often occur as part of a larger PASC picture and our study population had increased rates of typical PASC symptoms including severe fatigue, dizziness, and cognitive difficulties.

Given the shift toward chronic migraine and overall higher headache burden in this group, it is unsurprising that full-time employment dropped considerably from 81% to 55% and 10% of patients applied for and qualified for federal disability benefits. This compares to an about 14% decrease in employment and a 19% increase in unemployment when patients convert from episodic to chronic migraine.¹¹⁻¹³ This is likely exacerbated by delays in care and undertreatment of both headache and PASC symptoms; one study showed decrease in employment among persons with ongoing PASC symptoms, with 22% being unable to return to work and 45% needing to reduce their work schedule.¹⁴ Patients had an average of 7.4 ± 4.8 months from time of infection to evaluation in the headache clinic and 43% of patients had not been started on medication to prevent headaches. This delay in care represents a crucial missed opportunity when effective preventive medication could have decreased their headache burden, leading to improved quality of life and decreases in underemployment or unemployment.

In terms of treatments for protracted headache after COVID-19, 13 of the 18 persons (72%) started on preventive medication prior to first visit at our clinic or at our first visit noted a decrease in headache burden, with data missing for the remaining five patients due to lack of follow-up. While our study was not powered or designed to assess efficacy of medication, these results suggest that initiation of medications typically used for the prevention of migraine is a reasonable treatment plan for headache occurring after COVID-19 and has also been previously reported in other studies.^{1,5}

The generalizability of our study is limited by sample size and that participants were included solely from a tertiary headache center. It is quite plausible that patients with milder headaches and lower PASC burden did not seek treatment or require the services of a tertiary headache center; our study population may only reflect these more affected patients. Patients were also evaluated a mean of 7.4 months after initial infection so recall bias may have affected the answers given on evaluation. In addition, our study drew its patients from the entire duration of the pandemic and did not link symptoms and headache phenotypes to specific virus variants. Future studies will need to draw from not only headache specialists but primary care physicians as well and it will also be necessary to determine if different COVID-19 variants lead to different headache presentations.

CONCLUSION

Headache persisting beyond the acute COVID-19 infection requires close monitoring by providers. Our study demonstrates that patients with a history of migraine are at a notable risk of converting from episodic to chronic migraine. Recognition of this risk may fall to primary care providers to be cognizant of their patients with a previous history of infrequent headache who had COVID-19 and have had a worsening of their headaches. Larger studies of patients with a history of headache who experience COVID-19 are needed to further characterize this risk factor and its sequelae. Validation of the use of migraine preventive treatments in this patient group will also help guide future treatments for protracted headache after COVID-19 infection.

AUTHOR CONTRIBUTIONS

Study concept and design: Liza Smirnoff. *Acquisition of data:* Leon S. Moskatel, Liza Smirnoff. *Analysis and interpretation of data:* Leon S. Moskatel. *Drafting of the manuscript:* Leon S. Moskatel, Liza Smirnoff. *Revising it for intellectual content:* Leon S. Moskatel, Liza Smirnoff. *Final approval of the completed manuscript:* Leon S. Moskatel, Liza Smirnoff.

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CONFLICTS OF INTEREST

The authors declare no financial conflicts of interest.

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