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Original

Headache changes in individuals with migraine post-Covid-19: general characteristics of the acute phase and worsening of the migraine pattern

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Abstract

Introduction
The aim of this study was to investigate how infection with SARS-CoV-2 affected headache in individuals with migraine, and to identify characteristics associated with a worsening of the migraine post COVID-19.

Methods
Observational study composed of 157 individuals with migraine and who had been infected with the SARS-CoV-2 virus. They were recruited from the database of the headache research group at the Pontifical Catholic University of Paraná. The participants responded online to questions about their anthropometric data, history of infection with SARS-CoV-2, presence and characteristics of the headache in the acute phase, perception of a worsening of the migraine after infection, use of analgesics and prophylactic migraine medication. Validated digital questionnaires were used: Migraine Disability Assessment (MIDAS), Beck Depression Inventory (BDI) and Allodynia Symptom Checklist (ASC-12). The results of these questionnaires were compared to values previously recorded in the database, this information having been obtained prior to the infection with COVID-19.

Results
The first symptom of infection was respiratory for 76/157 (48.7%) individuals, followed by headache with 18 (11.5%). Headache was present in the acute phase of COVID-19 in 142 (90.4%) participants. A worsening of the migraine pattern post-COVID-19 occurred in 48 (30.6%) participants and they mostly suffered from presence of headache [48/48 (100.0%) vs. 94/109 (86.2%); p=0.006], throbbing headache [46/48 (95.8%) vs. 63/109(57.8%); p<0.001] and which lasted longer (5 vs. 3 days; p=0.001). Prior to contracting COVID-19, these patients already were presenting with greater MIDAS score (31 vs. 13; p=0.001), ASC-12 score (8 vs. 4; p=0.004) and BDI score (14 vs. 10; p=0.033). After infection with COVID-19, those who suffered a worsening of the migraine pattern increased their use of analgesics [41/48 (85.4%) vs. 29/109 (26.6%); p<0.001], needed to adjust or substitute their prophylactic medication [30/48 (62.5%) vs. 37/109 (33.9%); p=0.004] and continued to be more severe with regard to the MIDAS scores (34 vs. 12; p=0.001) and BDI score (16 vs. 9; p=0.008).

Conclusion
Individuals who notice a worsening in migraine post-COVID-19 have a more severe migraine condition prior to infection, have more prominent headache during the acute phase and, subsequently, present with greater disability.

Keywords:
Headache
Migraine
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Introduction

The last three years went by with an additional note of chaos caused by the COVID-19 pandemic, which brought much uncertainty and left many survivors living with sequelae of various degrees of severity. The main symptom of the infection caused by the SARS-CoV-2 virus was respiratory in origin, however, headache figures among the five principal symptoms persisting after the acute phase has passed, referred to as long COVID.[1] Although the majority of cases have a favorable outcome, as many as 19% of individuals may continue to experience headache three months after COVID-19.[2] This fact could be even more worrying considering the occurrence of infection with SARS-CoV-2 in individuals previously diagnosed with migraine, which affects over 1 billion people worldwide, equivalent to 14.4% of the global population.[3]

Migraine is a genetically determined neurological disease that predisposes individuals to repeated episodes of headache with a combination of specific characteristics such as high intensity, unilateral, throbbing headache accompanied by phonophobia, photophobia, nausea or vomiting.[4]

The occurrence of infection with the SARS-CoV-2 virus in people with migraine has been linked to an increase in the intensity and frequency of headache[1], but the true impact of the infection on migraine has not been particularly well explored. This study aims to investigate how infection with SARS-CoV-2 has affected headaches in individuals with migraine and to identify characteristics associated with an exacerbation of the migraine pattern post COVID-19.

Methods

Design and population

Observational study developed electronically via email, the WhatsApp® digital messaging application and through a form available in Google Forms®. Participants were recruited from the database of the Headache Research Group at the Londrina campus of the Pontifical Catholic University of Paraná. This database comprised 1,601 individuals with a diagnosis of migraine who took part in different stages of the study developed by the group. The diagnosis of migraine was made in accordance with the diagnostic criteria of the 3rd Edition of the International Classification of Headache Disorders (ICHD-III beta).[5]

The participants responded digitally to questions concerning their personal and anthropometric data from May to October 2022. The diagnosis of COVID-19 was reported by the participant and data were obtained of their history of infection as the diagnostic method, acute phase symptoms, need for hospital treatment, presence of headache and the characteristics of the headache. There were also questions about their perception of a worsening of their migraine after infection, the use of analgesics and of prophylactic medication for migraine. Participants were deemed to have made use of prophylactic medication if they used topiramate, valproic acid, propranolol, atenolol, metoprolol, bisoprolol, amitryptiline, nortryptiline, clomipramine, venlafaxine or flunarizine.

Validated digital questionnaires were used to evaluate migraine disability (Migraine Disability Assessment - MIDAS)[6]; depressive symptoms (Beck Depression Inventory - BDI)7 and allodynia (Allodynia Symptom Checklist - ASC-12).[8] The results of these questionnaires were compared to values previously recorded in the database, information which was input prior to infection with COVID-19.

Statistical analysis

The categorical data were displayed as an absolute number and percentage and evaluated through the Fisher's exact or chi-square tests, as appropriate. Numeric variables were expressed as the median and interquartile range, and were analyzed through the Mann-Whitney or Wilcoxon tests in non-paired and paired analyses, respectively. Any difference was considered statistically significant difference where $P<0.05$. The analyses were conducted using version 21.0 of the SPSS statistical software application.

Ethical Aspects

The participants digitally signed a free and informed consent form and confirmed their participation by ticking the box "yes, I understand and agree". The project was designed in accordance with National Health Council Resolution 466/2012. This project was approved by the Research Ethics Committee at the Pontifical Catholic University of Paraná, under opinion no. 98316718.7.0000.0020.

Results

Contact was made with 1,061 patients, of whom 189 answered the form. A total of 157 individuals with migraine and who had been infected with the SARS-CoV-2 virus took part. The remaining 32 participants were excluded as they had not received a diagnosis of infection with SARS-CoV-2.

The majority of participants were female [142/157 (90.4%)], young (a median age of 30 years) and Caucasian [140/157 (89.2%)]. Migraine manifested without aura in 63/154 (59.1%) of cases and 90/156 (57.7%) of the participants did not use prophylactic medication for migraine. The participants answered the research study form 6 to 17 months after the acute infection with COVID-19 (Table 1).

Table 1. Distribution of general characteristics of the study population.

		N	(%)
Sex	Female	142	(90.4)
	Male	15	(9.6)
Age (years)		30	(24-41)
BMI (Kg/m2)		24	(22-28)
Ethnicity	Caucasian	140	(89.2)
	Non-Caucasian	17	(10.8)
Tobacco use	Present	11	(7.0)
	Absent	146	(93.0)
Type of Migraine	With Aura	63	(40.9)
	Without Aura	91	(59.1)
Prophylactic Treatment	Present	66	(42.3)
	Absent	90	(57.7)

Categorical variables were shown as an absolute number (n) and percentage (%), and continuous variables were shown as median and interquartile range (25-75).

For 93 participants (59.2%), COVID-19 was diagnosed using the rapid nasal swab test while the RT-PCR test was used for 64 (40.8%) individuals. Five patients reported having been diagnosed through serology against Sars-CoV2. The first symptom of infection was respiratory in 76 (48.7%) individuals, followed by headache in 18 (11.5%), myalgia in 11 (7.1%), fever in 9 (5.8%) and anosmia/hyposmia in 8 (5.1%). Symptoms such as mood swings, anosmia/hyposmia and ageusia were present in 58 (37.2%), 79 (50.6%) and 79 (50.6%) individuals, respectively. Only 2 (1.3%) patients required hospital treatment and there were no indications of intubation or being admitted to the ICU.

Headache was present in the acute phase of COVID-19 in 142 (90.4%) participants, and lasted 2 to 6 days. The pain was bilateral in 101 (65.2%) while 109 (69.4%) individuals reported a throbbing pain. Worsening of the migraine pattern post-COVID-19 occurred in 48 (30.6%) participants, while 70 (44.6%) felt it necessary to increase the use of analgesics, and 67 (42.7%) increased or substituted their prophylactic migraine medication.

Table 2 displays the characteristics of those individuals who experienced a worsening of the migraine pattern after infection with COVID-19. In the acute phase, these individuals most frequently experienced mood swings [27/47(57.5%) vs. 31/109 (28.4%); p=0.001], headache [48/48 (100%) vs. 94/109 (86.2%); p=0.006], throbbing headache [46/48 (95.8%) vs. 63/109 (57.8%); p<0.001] and suffered for longer (5 vs. 3 days; p=0.001). Prior to the COVID-19 condition, these patients had already presented with greater migraine-related disability (MIDAS: 31 vs. 13; p=0.001), higher intensity of allodynia (ASC-12: 8 vs. 4; p=0.004) and higher scores for depression (14 vs. 10; p=0.033). After infection with COVID-19, those who experienced a worsening of the migraine pattern increased their use of analgesics (85.4% vs. 26.6%; p<0.001), needed to adjust or substitute their prophylactic medication (62.5% vs. 33.9%; p=0.004) and continued to receive more severe scores for disability (34 vs. 12; p=0.001) and depression (16 vs. 9; p=0.008). In a comparison of the scores for disability, allodynia and depression, there was no difference between the evaluations prior to and subsequent to COVID-19 (p>0.05).

Table 2. Characteristics of individuals with migraine who experienced a worsening of the disease after infection with COVID-19, compared to those who did not experience a worsening of the migraine pattern.

		Worsening of migraine pattern Post-COVID-19		No change in migraine pattern post-COVID-19		p
		n	(%)	n	(%)	
Clinical Characteristics						
Sex	Female	45	(93.8)	97	(89.0)	
	Male	3	(6.3)	12	(11.0)	0.556
Age (years)		31	(25-38)	29	(23-42)	0.759
BMI (kg/m2)		24	(22-29)	24	(22-28)	0.672
Ethnicity	Caucasian	43	(89.6)	97	(89.0)	0.912
	Non-Caucasian	5	(10.4)	12	(11.0)	
Tobacco usage	yes	3	(6.3)	8	(7.3)	1.000
	no	45	(93.8)	101	(92.7)	
Type of Migraine	With aura	24	(51.1)	39	(36.4)	0.089
	Without Aura	23	(48.9)	68	(63.6)	
Prophylactic Treatment	yes	25	(52.1)	41	(38.0)	0.099
	no	23	(47.9)	67	(62.0)	
Infection with COVID-19						
Hyposmia/ Anosmia	yes	25	(53.2)	54	(49.5)	0.676
	no	22	(46.8)	55	(50.5)	
Ageusia	yes	28	(59.6)	51	(46.8)	0.143
	no	19	(40.4)	58	(53.2)	
Mood Swings	yes	27	(57.4)	31	(28.4)	0.001
	no	20	(42.6)	78	(71.6)	
Headache in acute phase	yes	48	(100.0)	94	(86.2)	0.006
	no	0	(0.0)	15	(13.8))	
No. days with headache related to the acute phase	5	(3-10)	3	(2-5)	0.001	
	no	0	(0.0)	15	(13.8)	
Unilateral Headache	yes	17	(35.4)	37	(34.6)	0.919
	no	31	(64.6)	70	(65.4)	
Throbbing Headache	yes	46	(95.8)	63	(57.8)	<0.001
	no	2	(4.2)	46	(42.2)	
Validated Scales prior to infection with COVID-19						
MIDAS		31	(19-51)	13	(5-32)	0.001
BDI		14	(6-24)	10	(5-15)	0.033
ASC-12		8	(4-9)	4	(3-8)	0.004
Validated Scales subsequent to infection with COVID-19						
MIDAS		34	(20-64)	12	(4-29)	<0.001
BDI		16	(8-26)	9	(3-14)	0.008
ASC-12		7	(4-10)	6	(3-9)	0.073

BMI (Body Mass Index), MIDAS (Migraine Disability Assessment), BDI (Beck Depression Inventory), ASC-12 (Allodynia Symptom Checklist). Categorical variables were expressed as absolute numbers and percentages, and continuous variable as median and interquartile range (25-75).

Discussion

Although the most common clinical condition of COVID-19 involves respiratory symptoms, headache is described as a common symptom, as observed in this study[2,9], despite not having been reported as a primary symptom as frequently as in some other studies.[9-11] It is more commonly seen in patients who did not require hospitalization and, generally speaking, in younger people with a history of primary headache, data which were also observed in this study, considering that none of the cases studied required intensive care.[12]

Headache is a common symptom of viral infections and is a common, secondary cause of headache.[11,10] In our study, 142/157 (90.4%) of participants presented with headache in the acute phase of COVID-19 and all those who experienced a worsening of the headache pattern also had headache in the acute phase of the infection [48/48 (100%) vs. 94/109(86.2%); p=0.006]. Specifically with regard to COVID-19, the headache may materialize during the acute phase with two more common phenotypes: one with characteristics of migraine and the other with characteristics of tension-type headache.[11,12]

The characteristics of migraine include unilateral, throbbing pain accompanied by photo- or phonophobia, while the characteristic of a tension-type headache is compressive, holocranial pain.[5] In the present study, although reported headache is bilateral in 101/155 (65.2%) of cases, it involves a throbbing sensation in 109/157 (69.4%) of cases, presenting with characteristics of both phenotypes, which is also a common finding in up to one third of patients, according to studies[11] and, as the migraine phenotype is very common, it is possible that the physiological mechanisms are similar to one another.[11,10] It should be stressed that the throbbing nature of headache in the acute phase of infection occurred most frequently in those individuals who experienced a worsening of the migraine pattern [46/48 (95.8%) vs. 63/109 (57.8%); p<0.001].

Studies have shown three main phenotypes for long COVID-related headache: one phenotype considered to be more rare, related to persistent headache on a daily basis ever since the onset, in previously healthy patients[13,14]; and two more common migraine-related phenotypes: the second would be the development of migraine in patients who had not previously presented with primary headache, and the third, which is the most relevant to this study, related to a worsening of the migraine pattern in patients already previously diagnosed.[15]

According to the literature, there is a strong association between hyposmia/anosmia and COVID-19 related headache, though this was not identified in the present study, although the sample in the present study did observe a percentage of anosmia/hyposmia similar to that expected.[10]

The worsening of the headache pattern post-COVID-19, in individuals with migraine, is a common complaint heard in the neurologist's office and it has become important to identify the characteristics of these individuals as it may be possible to intervene in unfavorable conditions. When individuals with migraine are compared to controls without the disease, migraine was not found to be associated with a higher chance of persistent post-COVID-19 headache.[16] In our study, we identified that several factors in the acute phase of infection were associated with a higher chance of a worsening migraine pattern, namely mood swings and the presence of throbbing headache for longer periods of time. On the other hand, factors existing prior to the COVID-19 infection were also associated with a worsening of the pain pattern, such as greater migraine disability, higher intensity of allodynia and depressive symptoms.

Lastly, as a consequence of the condition of COVID-19 superimposed on migraine, these patients with a worsening pattern of pain increased their use of analgesics and found it necessary to adjust their prophylactic treatment, and also achieved worse disability scores for migraine and depressive symptoms.

Garcia-Azorín et al.[2] evaluated patients, with or without primary headache, who presented with headache post-COVID-19, both persistent and non-persistent. They found that those individuals who still suffered from headache 9 months after infection were of a higher median age, were predominantly female and experienced throbbing pain. In our study, there were no differences between the groups in terms of age and sex, either with or without a worsening of the migraine pattern, however, in harmony with the findings of these authors, patients with a worsening migraine pattern had more frequent throbbing pain, a typical characteristic of migraine-related headache.[2]

Neuropsychiatric symptoms are common comorbidities of migraine and, in our study, we found that people with a worsening migraine pattern post-COVID-19 were the most susceptible to depressive symptoms, both before and after the acute phase of COVID-19, and also demonstrated a higher frequency of mood swings during the acute phase of the infection. Magdy et al.[17] observed that people with migraine, compared to the controls without migraine, had

a higher frequency of neuropsychiatric symptoms such as fatigue, depression, anxiety and insomnia.

This study has a number of limitations such as the wide variability in the interval between COVID-19 and answering the form, with the participants demonstrating a possible memory recall bias. The post-COVID-19 worsening of the headache pattern was subjectively assessed according to the perception of the patient. Prophylactic migraine treatment was also not uniform in nature among the participants. On the other hand, they are real-life data and, despite being subjective, the individual's perception regarding his/her disease is of extreme importance in the context of migraine, a disease with no biomarkers for estimating severity.

In conclusion, individuals with a perception of a worsening in the migraine pattern post-COVID-19 were those who, prior to infection, had a more severe migraine condition. In the acute phase, they had more prominent symptoms of migraine, and post-COVID-19 they developed greater disability. These patients had the most severe symptoms and continued to have them post-COVID-19. Therefore, these are individuals who require medical intervention, regardless of their previous or current history of COVID-19.

Authors' contribution:
AVS, VAB, RCP, conception, design of the work; AVS, analysis; MKP, APF, acquisition; AVS, MKP, APF, VAB, RCP, drafting the work, revising it critically for important intellectual content; and final approval of the version to be published.

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References

1. Tana C, Bentivegna E, Cho S-J, Harriott AM, García-Azorín D, Labastida-Ramirez A, . . . Martelletti P. **Long COVID headache.** *Journal Headache Pain* 2022;23(1):93 Doi:10.1186/s10194-022-01450-8
2. Garcia-Azorin D, Layos-Romero A, Porta-Etessam J, Membrilla JA, Caronna E, Gonzalez-Martinez A, . . . Pozo-Rosich P. **Post-COVID-19 persistent headache: A multicentric 9-months follow-up study of 905 patients.** *Cephalalgia* 2022;42(8):804-809 Doi:10.1177/03331024211068074
3. Stovner LJ, Nichols E, Steiner TJ, Abd-Allah F, Abdelalim A, Al-Raddadi RM, . . . Murray CJL. **Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016.** *The Lancet Neurol* 2018;17(11):954-976 Doi:10.1016/s1474-4422(18)30322-3
4. Charles A. **The pathophysiology of migraine: implications for clinical management.** *The Lancet Neurol* 2018;17(2):174-182 Doi:10.1016/s1474-4422(17)30435-0
5. **The International Classification of Headache Disorders, 3rd edition (beta version).** *Cephalalgia* 2013;33(9):629-808 Doi:10.1177/0333102413485658
6. Fragoso YD. **MIDAS (Migraine Disability Assessment): a valuable tool for work-site identification of migraine in workers in Brazil.** *Sao Paulo Med J* 2002;120(4):118-121 Doi:10.1590/s1516-31802002000400006
7. Gomes-Oliveira MH, Gorenstein C, Neto FL, Andrade LH and Wang YP. **Validation of the Brazilian Portuguese Version of the Beck Depression Inventory-II in a community sample.** *Rev Bras Psiquiatr* 2012;34(4):389-394 Doi:10.1016/j.rbp.2012.03.005
8. Florencio LL, Chaves TC, Branisso LB, Gonçalves MC, Dach F, Speciali JG, . . . Bevilaqua-Grossi D. **12 item Allodynia Symptom Checklist/Brasil: cross-cultural adaptation, internal consistency and reproducibility.** *Arq Neuro-Psiquiatr* 2012;70(11):852-856 Doi:10.1590/s0004-282x2012001100006
9. Sampaio Rocha-Filho PA, Albuquerque PM, Carvalho LCLS, Dandara Pereira Gama M and Magalhães JE. **Headache, anosmia, ageusia and other neurological symptoms in COVID-19: a cross-sectional study.** *The J Headache Pain* 2022;23(1):2 Doi:10.1186/s10194-021-01367-8
10. Sampaio Rocha-Filho PA and Magalhães JE. **Headache associated with COVID-19: Frequency, characteristics and association with anosmia and ageusia.** *Cephalalgia* 2020;40(13):1443-1451 Doi:10.1177/0333102420966770
11. Trigo López J, García-Azorín D, Planchuelo-Gómez Á, García-Iglesias C, Dueñas-Gutiérrez C and Guerrero ÁL. **Phenotypic characterization of acute headache attributed to SARS-CoV-2: An ICHD-3 validation study on 106 hospitalized patients.** *Cephalalgia* 2020;40(13):1432-1442

Doi:10.1177/0333102420965146

12. Sampaio Rocha-Filho PA. **Headache associated with COVID-19: Epidemiology, characteristics, pathophysiology, and management.** *Headache: The J Head Face Pain* 2022;62(6):650-656 Doi:10.1111/head.14319
13. Fernández-de-las-Peñas C, Gómez-Mayordomo V, Cuadrado ML, Palacios-Ceña D, Florencio LL, Guerrero AL, . . . Arendt-Nielsen L. **The presence of headache at onset in SARS-CoV-2 infection is associated with long-term post-COVID headache and fatigue: A case-control study.** *Cephalalgia* 2021;41(13):1332-1341 Doi:10.1177/03331024211020404
14. Dono F, Consoli S, Evangelista G, D'Apolito M, Russo M, Carrarini C, . . . Bonanni L. **New daily persistent headache after SARS-CoV-2 infection: a report of two cases.** *Neurological Sciences* 2021;42(10):3965-3968 Doi:10.1007/s10072-021-05444-3
15. Caronna E, Alpuente A, Torres-Ferrus M and Pozo-Rosich P. **Toward a better understanding of persistent headache after mild COVID-19: Three migraine-like yet distinct scenarios.** *Headache: The J Head Face Pain* 2021;61(8):1277-1280 Doi:10.1111/head.14197
16. Magdy R, Hussein M, Ragaie C, Abdel-Hamid HM, Khallaf A, Rizk HI and Dahshan A. **Characteristics of headache attributed to COVID-19 infection and predictors of its frequency and intensity: A cross sectional study.** *Cephalalgia* 2020;40(13):1422-1431 Doi:10.1177/0333102420965140
17. Magdy R, Elmazny A, Soliman SH, Elsebaie EH, Ali SH, Abdel Fattah AM, . . . Hussein M. **Post-COVID-19 neuropsychiatric manifestations among COVID-19 survivors suffering from migraine: a case–control study.** *The J Head Pain* 2022;23(1):101 Doi:10.1186/s10194-022-01468-y