Clinical Research Article

Persistent headache and chronic daily headache after COVID-19: a prospective cohort study

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Background: Little is known about the frequency and impact of the persistent headache and about the incidence of chronic daily headache (CDH) after coronavirus disease 2019 (COVID-19). The aim of this prospective cohort study was to assess the incidence, risk factors, characteristics, and impact of CDH in patients with COVID-19.

Methods: In the first stage, 288 patients were interviewed by telephone after the acute phase of COVID-19. Subsequently, 199 patients who presented headache were reinterviewed at least one year after COVID-19. Headaches that persisted beyond the acute phase of COVID-19 for three or more months and presented frequency \geq 45 days over the first three months were considered to be CDH.

Results: One hundred and twenty-three patients were included, 56% were females; median age: 50 years (25th and 75th percentile: 41;58). The headache persisted beyond the acute phase of COVID-19 in 52%, and 20.3% had CDH (95% confidence interval: 13.6–28.2). Individuals who previously had headaches and who had headaches of greater intensity during the acute phase were at higher risk of developing CDH. The group with CDH included more females, greater impact of headache, more persistence of headache beyond the 120th day of COVID-19 and less throbbing headache than did the other individuals whose headache persisted.

Conclusions: Patients who had COVID-19 had a high incidence of CDH. Previous headache and greater intensity of headache were associated with higher risk of CDH.

Keywords: COVID-19; Headache; Headache Disorders, Secondary; New Daily Persistent Headache; Pain; Post-Acute COVID-19 Syndrome; Prospective Studies; Risk Factors.

INTRODUCTION

Although most patients with coronavirus disease 2019 (COVID-19) recover completely within the first weeks after the start of the infection, 13 to 80% of the individuals affected may have symptoms that persist beyond the

acute phase. These may last for some weeks to months [1–5]. These individuals' condition has been defined as post-COVID syndrome/long COVID when the signs and symptoms developed during or after an infection consistent with COVID-19 persist for more than 12 weeks [6].

Headache is a frequent symptom during the acute

Received February 13, 2024; Revised April 4, 2024; Accepted April 5, 2024

Handling Editor: Woo Seog Sim

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phase of COVID-19 [7,8]. It occurs in around 47.1% of the patients [9–12]. Between 7 and 26% of individuals who have had COVID-19 develop persistent headache [2,12–16], which is the most common neurological manifestation in these patients [1,3,17,18]. The prevalence of headache seems to decline over time after the acute phase [12,19].

Although it is already known that headache may persist for a long period after the acute phase of COVID-19, little is known about the impact of such headaches. The aim of the present study was to assess the incidence, risk factors, characteristics, and impact of chronic daily headache (CDH) in patients with COVID-19. The authors also sought to compare the characteristics of patients with CDH with others whose headache persisted beyond the acute phase of COVID-19 but did not fulfill the criteria for CDH.

MATERIALS AND METHODS

This was a prospective cohort study. It was conducted in the Oswaldo Cruz University Hospital, in the city of Recife, capital of the state of Pernambuco, Brazil. This hospital is linked to the University of Pernambuco and is a reference center within the public healthcare system for treatment of infectious diseases in the state of Pernambuco.

All the patients provided oral consent for their inclusion in this study, and the study was approved by the Research Ethics Board of the Oswaldo Cruz University Hospital (CAAE: 56594622.8.0000.519; Approval Number: 5.381.694).

The aim of the first stage of this investigation was to evaluate the neurological symptoms that patients presented during the acute phase of COVID-19 and associations among these symptoms. Patients who became ill during the first wave of COVID-19 were included. Details of this stage of the investigation and its results were described previously [20]. Briefly, 288 patients who presented with COVID-19 that had been confirmed through reverse transcription polymerase chain reaction (RT-PCR) were interviewed by telephone (median time between the symptomatic phase and the interview: 111.5 days; range: 86-141.5). These interviews were conducted between June and November 2020. The questionnaire used sought to obtain information about the presence of previous primary headache and the symptoms presented, and about the presence and characteristics of headache presented during the acute phase of COVID-19 (pattern, intensity, and duration). To classify the phenotype of the headache which presented during COVID-19, the authors used the Portuguese version of ID-Migraine. Those who obtained a score greater than or equal to 2 were considered as presenting "phenotypic migraine-like features" [21].

In this second stage of the investigation, the patients who had presented with headache during the acute phase of COVID-19 were reinterviewed by telephone at least one year after the acute phase. These interviews were conducted between March and November 2022 by a medical resident in neurology and a medical student, who had been trained to conduct these interviews. If a patient could not be found even after three attempts to contact the person by telephone, this patient was considered to have been lost.

The interviews were conducted using a semi-structured questionnaire through which the following information was sought: sociodemographic data; whether hospitalization during the acute phase of COVID-19 had been necessary; whether the headache had persisted beyond the acute phase of COVID-19; the characteristics of this persistent headache; the frequency of the headache during the first three months after the acute phase of the disease and how long they continued to have headaches ("In the first 3 months after COVID-19, how many headache days did you have?"; "If you no longer have the headache you had when you had COVID-19, how long did you have this pain after COVID-19?"); the temporal evolution of the headache; and factors that made the headache better or worse. The Brazilian version of Headache Impact Test (HIT-6) was used to assess the impact of headache on the individual's daily activities [22]. The higher the score, the greater the impact.

Patients whose headaches persisted beyond the acute phase for three or more months and who presented with headache with a frequency greater than or equal to 45 days over the first three months after the acute phase of COVID-19 were classified as having CDH.

The statistical analyses were performed using STAT 13.0 for Windows. Quantitative data were presented as medians and interquartile range (percentiles 25–75) since all distribution was non-normal according to the Kolmogorov-Smirnov test. The percentage distribution of the categorical variables was compared between the groups by means of the Chi-square test or Fisher's exact test. Numerical variables were compared using the Mann-Whitney test.

Poisson's regression analysis was used to evaluate which of the variables were associated with the presence of CDH in patients who had had COVID-19. Variables

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that presented some association in univariate analysis (P value < 0.05) were initially included in the model through the stepwise backward method. Variables with P < 0.05 were kept in the model. Relative risk values were estimated. The Wald test was used to assess the acceptance of the model and the chi-square test was used to assess the goodness of fit. A confidence interval of 95% was defined and P values less than or equal to 5% were considered to rule out the null hypothesis.

RESULTS

Out of the 199 patients who reported having had headaches associated with COVID-19 infection in the first stage of the investigation, 123 (61.8%) were reinterviewed and included in the analysis. Patient losses had the following causes: not found even after three attempts (n = 62), refusal to participate (n = 9), and death (n = 1). Four patients were excluded because they were unable to recall the occurrence and characteristics of their COVID-19 headaches.

The median length of time between the acute phase of COVID-19 and the interview was 804 days (range: 739-892). The interviewees' median age was 50 years (41;58); 69/123 (56%) were female; and 95/123 (77%) had needed to be hospitalized during the acute phase of COVID-19.

1. Persistence of headache

The headache persisted beyond the acute phase of CO-VID-19 in 64 patients (52%). The median frequency of these patients' headaches over the first 90 days after the acute phase of COVID-19 was 32 days (10;68).

In 52/123 (42.3%), the headache persisted for more than 30 days; in 47/123 (38.2%) for more than 60 days; in 44/123 (35.8%) for more than 90 days; and in 42/123 (34.1%) for more than 120 days.

Thirty-seven patients (30.1%) reported that they were continuing to have headaches up to the time of the interview. Among these individuals, 23 reported that their headaches were improving, eight said that they were unchanged and six said that they were worsening.

2, CDH

Twenty-five out of the 123 patients (20.3%; 95% CI: 13.6–28.2) had CDH. Of these, 12/25 (48%) had daily headache over the first 90 days after the acute phase of COVID-19.

Eighteen patients (72%) reported that they were con-

tinuing to have CDH up to the time of the interview. Of these, ten reported that their headaches were improving, with regard to intensity (n = 7), frequency (n = 9) and duration (n = 3); five said that their headaches were unchanged; and three said that their headaches were worsening, with regard to intensity (n = 3), frequency (n = 2) and duration (n = 2). These patients reported that their headaches improved through use of pain medications (17/18; 94%) and neck stretching (1/18; 6%). The following were described as factors that worsened the headaches: noise (3/18; 17%), luminosity (2/18; 11%), emotional stress (2/18; 11%), physical activity (1/18; 6%), and menstruation (2/18; 11%).

Twenty-four patients (96%) reported that they had used headache medications during the last 30 days preceding the interview: ordinary analgesics (n = 24) or non-steroidal anti-inflammatory drugs (n = 1). Eleven patients (45%) were making excessive use of analgesics. The median frequency of use of headache medications was 12 days per month (3;30).

Seventeen patients reported that they had previously had headaches. However, 15/17 (88%) stated that the pattern of the CDH differed from that of their previous headaches.

Table 1 shows patient characteristics that were associated with the development of CDH. Individuals who had had primary headaches previously and those whose headaches were of greater intensity during the acute phase of COVID-19 presented significantly higher risk of developing CDH.

Comparison of patients with persistent post-COVID-19 headaches between those who fulfilled and those who did not fulfill the criteria for CDH

For most individuals with CDH, their headache had a severe intensity and a great impact on their lives. Their pain was bilateral and non-throbbing, worsened with physical exercise, and was associated with photophobia, phonophobia, and nausea.

Table 2 shows a comparison of the clinical characteristics of the patients with CDH with those of the other patients with persistent headache. Individuals with CDH were significantly more female; their headache had greater impact; they presented a higher percentage of headache persistence beyond the 120th day of COVID-19; and they presented a lower percentage of throbbing headache.

Table 1. Evaluation of patient characteristics that were associated with chronic daily headache (CDH)

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Characteristics		With CDH $(n = 25)$	Without CDH $(n = 98)$	RR (95% CI)	P value	Adjusted risk RR (95% CI)	P value
Sex	Female Male	20 (80) 5 (20)	49 (50) 49 (50)	1.28 (1.08–1.52)	0.007		
Age (yr)		51 (44;59.5)	50 (42;58)		0.868		
Needed to be hospitalized during acute phase of COVID-19	Yes	20 (80) 5 (20)	75 (77) 23 (23)	1.04 (0.85–1.27)	0.712		
Symptoms in the acute fase (first interview)							
Fever	Yes	18 (72) 7 (28)	83 (85) 15 (15)	0.83 (0.62–1.12)	0.139		
Cough	Yes	19 (76) 6 (24)	67 (68) 31 (32)	1.08 (0.90–1.29)	0.458		
Difficulty in breathing (dyspnoea)	Yes	21 (84) 4 (16)	77 (79) 21 (21)	1.07 (0.88–1.31)	0.547		
Drop in oxygen saturation	Yes	15 (60) 10 (40)	55 (56) 43 (44)	1.03 (0.86–1.23)	0.727		
Cyanosis	Yes	2 (8) 23 (92)	7 (7) 91 (93)	1.03 (0.72-1.47)	0.883		
Hyposmia/Anosmia	Yes	21 (84) 4 (16)	72 (73) 26 (27)	1.12 (0.94–1.34)	0.274		
Hypogeusia/Ageusia	Yes	21 (84) 4 (16)	78 (80) 20 (20)	1.06 (0.86–1.30)	0.620		
Myalgia	Yes No	17 (68) 8 (32)	51 (52) 47 (48)	1.14 (0.96-1.36)	0.152		
Headache intensity		8 (8.5;10)	7 (5;9.5)	1.3 (1.1-1.5)	0.007	1.3 (1.1-1.5)	0.005
Migraine-like headache (ID-Migraine)	Yes No	18 (72) 7 (28)	46 (47) 52 (53)	0.82 (0.68-0.98)	0.025		
Previous headache	Yes	18 (72) 7 (28)	45 (46) 53 (54)	1.24 (1.03–1.48)	0.020	2.3 (1.0–5.0)	0.045

Values are presented as number (%) or median (P_{25} ; P_{75}). RR: relative risk, CI: confidence interval, P_{25} : 25th percentile.



Table 2. Comparison of patients with persistent post-COVID-19 headaches between those who fulfilled and those who did not fulfill the criteria for chronic daily headache (CDH)

Characteristics	With CDH $(n = 25)$	Without CDH (n = 39)	P value
Age (yr)	51 (44;59.5)	48 (39;56.5)	0.413
Female	20/25 (80)	19/39 (49)	0.012
Previous headache	18/25 (72)	21/39 (54)	0.146
Needed to be hospitalized during acute phase of COVID-19	20/25 (80)	26/39 (66)	0.247
Headache characteristics			
Intensity	8 (8;9.5)	8 (5.5;10)	0.061
Bilateral	21/25 (84)	35/39 (90)	0.498
Pulsatile	11/24 (46)	28/39 (72)	0.039
Worsening through exercise	13/25 (52)	22/39 (56)	0.729
Phonophobia	21/25 (84)	25/39 (64)	0.084
Photophobia	19/25 (76)	24/39 (61)	0.229
Nausea	19/25 (76)	24/39 (61)	0.229
Vomiting	10/25 (40)	13/39 (33)	0.587
Headache Impact Test (HIT-6)	67 (55;70)	56 (48;65)	0.018
Headache duration			
> 120 days	21/25 (84)	21/39 (54)	0.013
> 360 days	18/25 (72)	19/39 (49)	0.066

Values are presented as number (%) or median (P₂₅;P₇₅).

P₂₅: 25th percentile, P₇₅: 75th percentile.

DISCUSSION

Headache persisted beyond the acute phase of COVID-19 in 64 of the patients. This corresponds to 52% of the patients who had headaches during the acute phase and who were reinterviewed. However, it should be noted that this proportion may be an overestimate, given that there was a loss rate of 38%. In the first interview, 79 patients reported that their headaches persisted for more than 14 days. The authors reinterviewed 81% of these patients. Thus, the loss rate was smaller among patients without persistent headache. If the losses are not taken into consideration, the incidence of persistent headache would be at least 64/288 (22%) of all the individuals who had COVID-19 and 64/199 (32%) among those who had headaches during the acute phase of the disease. These proportions are concordant with those of other studies [12,15,19,23].

In 35.8% of the patients, the headache persisted for more than 90 days. The International Classification of Headaches Disorders (ICHD3) provides two diagnostic possibilities for headaches that are triggered by systemic viral infections and that persist for more than 3 months after the acute phase of this infection: the chronic headache attributed to systemic viral infection and the new daily persistent headache (NDPH) [24]. All of these indi-

viduals fulfilled the criteria for chronic headache attributed to systemic viral infection [25]. They corresponded to 44/288 (15%) of all the patients who had COVID-19.

The prevalence of headache declined over the first two months after the start of the COVID-19 infection. After this period, the prevalence remained relatively stable. This behavior was also described in another cohort study [19]. Nonetheless, although the prevalence of headache remained stable, most of the patients who continued to have headaches reported that they were improving. This diminution of the severity of headaches over time constitutes important new clinical information with regard to persistent post-COVID headache, although this has already been described in relation to other secondary headaches [26–30].

Most of the patients with persistent headache presented headaches with characteristics similar to migraine. Other authors have reported the same finding [19,31], but not all [13]. Recently, in a case-control study in which magnetic resonance was used, alterations in the cerebral gray and white matter were found in patients with persistent post-COVID headache, similar to those found in migraine but with lower magnitude [32]. This, together with the data on the characteristics of persistent post-COVID headache, raises the possibility that this headache gives rise to physiopathological alterations similar to those of



migraine.

To the best of the authors' knowledge, this is the first study in which the objective was to analyze occurrences of CDH among patients who had COVID-19. It was found that the incidence of CDH was 20.3% among patients who had had headaches during the acute phase of the disease. If the losses are not taken into consideration, this incidence would be 25/199 (12.6%) among patients who presented headache during the acute phase of the disease and 25/288 (8.7%) among all the patients who had COVID-19. Even if this incidence is underestimated, it is still high. Most of the patients with CDH reported that this headache had a pattern that differed from the pattern of their previous headache, which thus emphasizes the causal relationship between their CDH and COVID-19. These patients with CDH had less chance of remaining headache-free, compared with the other patients whose headaches also persisted.

Systemic viral conditions have been reported to be one of the most frequent triggers for the development of NDPH [33,34]. Although there have been some reports of cases of NDPH after COVID-19 [23,35–38], little is known about its incidence among patients who had COVID-19.

The ICHD3 requires that for NDPH to be diagnosed, the pain should be continuous [25]. Although 12 of the patients experienced 90 days of pain over the three months after their COVID-19 infection started, the authors did not have any information about whether their pain was continuous. Nonetheless, NDPH is a concept that is still being developed [34]. The ICHD3 criteria are better than those of the previous classification, but perhaps do not take all patients into consideration. Cases of NDPH with daily headache but which are not continuous have been described [39–41]. Considering that these 12 patients presented with NDPH, the incidence of this headache among the patients who had COVID-19 would be at least 12/288 (4.2%).

CDH is at the most serious end of the spectrum of persistent post-COVID-19 headache. This is demonstrated not only by the higher frequency of headaches but also by their greater impact on patients' lives. However, in comparing the characteristics of CDH with those of other persistent headaches, it was noted that the only characteristic that differed was the greater frequency of a non-throbbing nature among the cases of CDH. In the authors' view, this raises the possibility that all of these persistent headaches have the same underlying physiopathological substrate.

The individuals with previous histories of headache and a higher intensity of headaches during the acute phase of COVID-19 were at higher risk of developing CDH after COVID-19. These findings have biological plausibility. However, previous migraine and need for hospitalization during the acute phase of COVID-19 were not risk factors.

The authors did not find any other studies in which the risk of CDH after COVID-19 was evaluated to make comparisons with the present study. In a *post hoc* analysis of Spanish studies, patients with lower-intensity headaches during the acute phase of COVID-19 presented lower chances for headaches to persist over a nine-month period after COVID-19. However, the risk of CDH was not assessed in that analysis [19]. There are divergent findings in the literature regarding the presence of previous headache as a risk factor for the persistence of headache in COVID-19 cases [2,19,23], and also regarding previous migraine [13,42,43]. The need for hospitalization during the acute phase of COVID-19 was also not a risk factor for the persistence of headache in other studies [12,16].

Excessive use of headache medications is known to be a factor associated with CDH [44]. In the present study, 96% of the patients with CDH reported that they had used headache medications during the preceding 30 days, and 45% of these individuals had made excessive use of analgesics. Given that these individuals' headaches were already occurring almost daily after the acute phase of COVID-19, there was probably not any causal association in this regard. Nonetheless, excessive use of medications may be a contributory factor with regard to perpetuation of CDH.

Our study has some limitations. No cerebral magnetic resonance or cerebrospinal fluid examinations were performed. Thus, the possibility that some of these patients may have had headaches that were secondary to complications of COVID-19 cannot be ruled out. No sample size calculation was performed. Thus, the authors cannot rule out the possibility that this study might not have had the power to detect small differences. This study was conducted in a single center, which may have limited its capacity for generalization. There was a loss rate of more than 30%, which may have interfered with the internal validity of the study. The authors only included patients who presented headaches during the acute phase of CO-VID-19. In this manner, they cannot rule out the possibility that patients who did not present headaches during the acute phase of the disease could have developed persistent headaches subsequently. Nonetheless, the results regarding the persistence of headaches are compatible with those found in other studies. No headache diaries were used, and the second interview was conducted



more than two years after the acute phase of the disease in most cases. Thus, it is possible that memory bias or imprecision regarding the temporal evolution of the patients' headaches may have occurred. Nonetheless, all the patients who had said that their headaches persisted beyond the acute phase of COVID-19 maintained their reports at the second interview.

Our study has some strong points. It was a prospective study, all the cases of COVID-19 were confirmed by means of RT-PCR, and both interviews were conducted by doctors or medical students who had received training to be able to assess neurological symptoms. In this manner, the authors hoped to diminish the chances of classification errors.

In conclusion, these patients who had COVID-19 had high incidence of persistent headache. Their headaches most often presented a pattern similar to migraine. The prevalence of headache diminished over the initial months, but then remained stable after this period. The incidence of CDH after COVID-19 was also high. CDH had a high impact on these patients' lives. Patients with higher intensity of headache during the acute phase of the disease and those with previous histories of headache were at higher risk of developing CDH.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

No funding to declare.

AUTHOR CONTRIBUTIONS

Larissa Clementino Leite Sá Carvalho: Acquisition and analysis of data, Drafting a significant portion of the manuscript or figures; Priscila Aparecida da Silva: Acquisition and analysis of data, Drafting a significant portion of the manuscript or figures; Pedro Augusto Sampaio Rocha-Filho: Conception and design of the study, Acquisition and analysis of data, Drafting a significant portion of the manuscript or figures.

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