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RESEARCH SUBMISSIONS

Headache as a COVID-19 onset symptom and post-COVID-19 symptom in hospitalized COVID-19 survivors infected with the Wuhan, Alpha, or Delta SARS-CoV-2 variants

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Abstract

Objective: This study looked at differences in the presence of headache as an onset symptom of coronavirus disease 2019 (COVID-19) and as a post-COVID-19 symptom in individuals previously hospitalized owing to infection with the Wuhan, Alpha, or Delta variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Background: Headache can be present in up to 50% of individuals during the acute phase of SARS-CoV-2 infection and in 10% of subjects during the post-COVID-19 phase. There are no data on differences in the occurrence of headache in the acute- and post-COVID-19 phase according to the SARS-CoV-2 variants.

Methods: A cross-sectional cohort study was conducted. Unvaccinated subjects previously hospitalized for COVID-19 caused by the Wuhan (n = 201), Alpha (n = 211), or Delta (n = 202) SARS-CoV-2 variants were scheduled for a telephone interview 6 months after hospital discharge. Hospitalization data were collected from hospital medical records.

Results: The presence of headache as a COVID-19 onset symptom at hospitalization was higher in subjects with the Delta variant (66/202, 32.7%) than in those infected with the Wuhan (42/201, 20.9%; odds ratio [OR] 1.83, 95% confidence interval [CI] 1.17–2.88) or Alpha (25/211, 11.8%; OR 3.61, 95% CI, 2.16–6.01) variants. The prevalence of post-COVID-19 headache 6 months after hospital discharge was higher in individuals infected with the Delta variant (26/202, 12.9%) than in those infected with the Wuhan (11/201, 5.5%; OR 2.52, 95% CI 1.22–5.31) or Alpha (eight of 211, 3.8%; OR 3.74, 95% CI 1.65–8.49) variants. The presence of headache as a COVID-19 onset symptom was associated with post-COVID-19 headache in subjects infected with the Wuhan (OR 7.75, 95% CI 2.15–27.93) and Delta variants (OR 2.78, 95% CI 1.20–6.42) but not with the Alpha variant (OR 2.60, 95% CI 0.49–13.69).

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

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Conclusion: Headache was a common symptom in both the acute- and post-COVID-19 phase in subjects infected with the Wuhan, Alpha, and Delta variants but mostly in those infected with the Delta variant.

KEYWORDS
Alpha, coronavirus disease 2019 (COVID-19), Delta, headache, variants, Wuhan

INTRODUCTION

Headache is one of the symptoms that may be experienced at the acute phase of coronavirus disease 2019 (COVID-19),[1] and it may be also experienced as a post-COVID-19 symptom.[2] A meta-analysis investigating headache and COVID-19 reported a prevalence of 47.1% of headache as an onset symptom and 10% as a post-COVID-19 symptom during the first 6 months after the infection.[3] Interestingly, the presence of headache as an onset symptom is associated with a more benign course of the disease[4] but is also associated with a higher prevalence of post-COVID-19 headache.[5] Therefore, proper understanding of the association between headache and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection seems to be crucial.

After the historical SARS-CoV-2 variant discovered in Wuhan, several variants have been identified (i.e., Alpha, Beta, Gamma, Delta, Epsilon, Zeta, Eta, Theta, Lota, Kappa, Lambda, and Omicron). Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and recently Omicron (B.1.1.529/BA.1) have been considered as variants of concern.[6] To date, all studies investigating the association of headache and COVID-19 have included individuals infected with the Wuhan variant.[3] Consequently, there are no data to our knowledge on the differences in the occurrence of headache in the acute- and post-COVID-19 phase according to the SARS-CoV-2 variants causing the disease. The aim of this study was to analyze headache as a COVID-19 onset symptom and as a post-COVID-19 symptom in patients hospitalized with three different variants of concern: Wuhan, Alpha, and Delta. We hypothesized that no differences in the presence of headache as a COVID-19 onset symptom or as a post-COVID-19 symptom would be observed between individuals infected with the Wuhan, Alpha, or Delta variants of SARS-CoV-2.

METHODS

Participants

A cross-sectional cohort study was conducted. Individuals who were hospitalized owing to acute SARS-CoV-2 infection in an urban hospital during the first, third, and fifth waves of the COVID-19 epidemic in Madrid, Spain, were recruited. The diagnosis of SARS-CoV-2 infection was confirmed with real-time reverse transcription-polymerase chain reaction assay of nasopharyngeal and oral swab samples, as well as consistent clinical and radiologic findings at hospitalization. At the third and fifth waves, the Sanger method of sequencing the receptor-binding domain was used to assess the SARS-CoV-2 viral lineage to determine the variant in all real-time reverse transcription-polymerase chain reaction assay samples positive for COVID-19. All participants from the first wave (March–April 2020) presented with the Wuhan variant, as no other variant existed. To be included, patients from the third wave (February–March 2021) had a confirmed diagnosis of infection with the Alpha variant (B.1.1.7), whereas those from the fifth wave (July–August 2021) had to be diagnosed with the Delta variant (B.1.617.2). To rule out an influence of vaccination on post-COVID-19 symptoms, we included people who had not received any vaccine dose. Two reasons led to this decision: (i) evidence about the effects of vaccination on post-COVID-19 symptoms is conflicting, with data suggesting that vaccines only minimally reduce the risk of post-COVID-19, while other data show no effect at all;[7] and (ii) COVID-19 vaccines may cause headache as a potential side-effect.[8] The study was approved by the Local Ethics Committee of Hospital Universitario Infanta Leonor (HUIL/092–20). Subjects gave informed consent prior to inclusion. As this study used telephone interviews, consent was obtained verbally in accordance with Spanish Law 41/2022 (BOE of November 14) before collecting any data to be included.

Data collection

Clinical and hospitalization data including age, sex, height, weight, medical comorbidities, pre-existing migraine history, the presence and features of headache as a COVID-19 onset symptom at hospitalization, and days at hospital were collected from hospital medical records. Participants were scheduled for a structured telephone interview focused on headache by trained health researchers 6 months after hospitalization. Those with referred headache were asked to systematically describe its pain features, including location, quality, intensity, and possible accompanying symptoms. Participants were considered to have post-COVID-19 headache if they had headache at COVID-19 onset or days after hospitalization and the headache persisted at the time of assessment. Headache phenotype was classified according to the criteria of the *International Classification of Headache Disorders*, 3rd edition,[9,10] by two neurologists.

Statistical analysis

The present study was a planned secondary analysis of data collected from the same sample included in another paper[11] but contains completely new unpublished data.

No statistical power calculation was conducted prior to the study owing to the lack of previous similar studies. Accordingly, the sample size was based on available data. There were no missing data. The analysis was conducted with STATA 16.1. Data are presented as mean (standard deviation [SD]) or number of cases (percentage) as appropriate. The Kolmogorov–Smirnov test was used to verify that the continuous data followed a normal distribution. Continuous variables of subjects infected with the Wuhan, Alpha, and Delta variants were compared by one-way analysis of variance tests. Differences in categorical variables, including the prevalence of headache as a COVID-19 onset symptom and as a post-COVID-19 symptom, were analyzed with the chi-square test. Finally, adjusted odds ratios (ORs) with their confidence intervals (CIs) were calculated by using a multivariate analysis with all hospitalization data as covariables for determining the association between variables collected at hospital admission, particularly headache as a COVID-19 onset symptom and the presence of pre-existing migraine with post-COVID-19 headache. The level of significance was set at $p < 0.05$ with a two-tailed testing hypothesis.

RESULTS

Of the 750 patients recruited for this study during the three waves of the pandemic (250 in each wave), 614 were finally included: 201 infected with the Wuhan variant (mean [SD] age: 60.5 [10.5] years, 54.2% women), 211 with the Alpha variant (mean [SD] age: 70.0 [15.5] years, 51.1% women), and 202 with the Delta variant (mean [SD] age: 56.5 [21] years, 54.4% women). The reasons for exclusion were as follows: refusal to participate (25 patients), death (five), pregnancy (five), impossibility of contact after five attempts (20), one dose of vaccine (45), and double dose of vaccine (36).

Table 1 summarizes demographic, hospitalization, and headache data of patients infected with each of the three variants. Individuals infected with the Alpha variant were older than those with the Wuhan or Delta variants ($p < 0.001$). There was no significant differences in the presence of pre-existing history of migraine ($p = 0.941$) among patients infected with the Wuhan (5.5%), Alpha (6.2%), or Delta (5.4%) variants. The presence of headache as a COVID-19 onset symptom at hospital admission was higher in patients infected with the Delta variant (32.7%) as compared with those infected with the Wuhan (20.9%; OR 1.83, 95% CI 1.17–2.88; $p = 0.008$) or Alpha (11.8%; OR 3.61, 95% CI 2.16–6.01; $p < 0.001$) variants. Overall, headache as a COVID-19 onset symptom adopted features of tension-type-like headache.

Participants were assessed 6 months after hospital discharge (mean [SD]: Wuhan, 6.5 [1.0] months; Alpha, 6.0 [1.2] months; Delta, 6.3 [1.0] months). The prevalence of post-COVID-19 headache was higher in people infected with the Delta variant (12.9%) than in those infected with the Wuhan (5.5%; OR 2.52, 95% CI 1.22–5.31,

TABLE 1 Demographic, hospitalization, and headache data by severe acute respiratory syndrome coronavirus 2 variant

	Wuhan ($n = 201$)	Alpha ($n = 211$)	Delta ($n = 202$)	p
Age, years, mean (SD)[a]	60.5 (15.5)	70.0 (15.5)	56.5 (21.0)	<0.001
Sex, male/female, *n* (%)	92 (45.8)/109 (54.2)	103 (48.8)/108 (51.2)	92 (45.5)/110 (54.5)	0.878
Weight, kg, mean (SD)	75 (14)	75.5 (16.5)	77 (13.5)	0.576
Height, cm, mean (SD)	168 (14)	165 (12)	166 (10)	0.254
Medical comorbidities, *n* (%)				
Hypertension	63 (31.3)	83 (39.3)	72 (35.6)	0.396
Diabetes	25 (12.4)	21 (10)	28 (13.9)	0.501
Cardiovascular disease	32 (15.9)	43 (20.4)	27 (13.4)	0.208
Rheumatological disease	3 (1.5)	1 (0.5)	1 (0.5)	0.423
Asthma	11 (5.4)	11 (5.2)	19 (9.4)	0.186
COPD	12 (6.0)	14 (6.6)	12 (5.9)	0.949
Obesity[a]	8 (4)	19 (9)	53 (26.2)	<0.001
Hospital stay, days, mean (SD)[a]	14 (12.5)	19 (17)	11.5 (10.7)	<0.001
ICU admission				
Yes/no, *n* (%)	20 (10)/181 (90)	33 (15.6)/178 (84.4)	19 (9.4)/183 (90.6)	0.121
ICU stay, days, mean (SD)	13.5 (11)	14.3 (16)	10.5 (7)	0.684
Previous history of migraine, *n* (%)	11 (5.5)	13 (6.2)	11 (5.5)	0.941
Exacerbation of previous migraine after COVID-19, *n* (%)	6 (54.5)	7 (53.8)	7 (63.6)	0.721
Headache as onset COVID-19 symptom, *n* (%)[a]	42 (20.9)	25 (11.8)	66 (32.7)	0.001
Post-COVID-19 headache, *n* (%)[a]	11 (5.5)	8 (3.8)	26 (12.9)	0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ICU, intensive care unit; SD, standard deviation.
[a]Statistically significant differences.

$p = 0.012$) or Alpha (3.8%; OR 3.74, 95% CI 1.65–8.49; $p = 0.001$) variants. Post-COVID-19 headache adopted similar features to tension-type headache in 90% of the patients and to migraine in 10%, with no significant differences between the three groups.

The presence of headache as a COVID-19 onset symptom was associated with the development of post-COVID-19 headache in patients infected with the Wuhan (OR 7.75, 95% CI 2.15–27.93; $p = 0.002$) or Delta (OR 2.78, 95% CI 1.20–6.42; $p = 0.015$) variants but not in those infected with the Alpha (OR 2.60, 95% CI 0.49–13.69; $p = 0.257$) variant. Of the 42 patients in the Wuhan cohort who had headache at onset, eight (19%) persisted with post-COVID-19 headache. Of the 66 patients in the Delta cohort with headache at onset, 16 (24.2%) had post-COVID-19 headache. Finally, of the 25 patients in the Alpha cohort having headache at onset, three (12%) had post-COVID-19 headache.

No other significant association between any hospital admission variable, including the presence of pre-existing migraine (Wuhan: OR 1.80, 95% CI 0.21–15.48, $p = 0.592$; Alpha: OR, not applicable; Delta: OR 0.96, 95% CI 0.11–8.18, $p = 0.974$) and development of post-COVID-19 headache was observed.

DISCUSSION

To the best of the authors' knowledge, this is the first study to date investigating differences in headache as a COVID-19 onset symptom and as a post-COVID-19 symptom in previously hospitalized patients infected by different SARS-CoV-2 variants. We found that headache was more prevalent as a COVID-19 onset symptom and as a post-COVID-19 symptom in individuals infected with the Delta variant, followed by those infected with the Wuhan variant. Albeit some differences were identified in our study, the underlying mechanisms explaining the development of headache may be not associated with any specific SARS-CoV-2 variant. In fact, current literature supports that SARS-CoV-2 variants' differences include higher transmissibility, different responses to current vaccines, or the possibility of future re-infections,[6] but molecular and immune responses elicited by the SARS-CoV-2 virus seem to be similar for all the variants.

The development of headache in the acute- or post-COVID-19 phase could be related to a complex and multifactorial pathophysiology. Biological factors such as activation of trigeminal nerve pathways could play a relevant role.[12] Other potential factors could be the potential ability of SARS-CoV-2 virus to enter the central nervous system,[13] although this theory is currently questioned.[14] However, differences among the variants might also be related to psychosocial factors surrounding the COVID-19 outbreak at that moment. The first wave (Wuhan) was associated with higher levels of uncertainty, catastrophizing, and psychological distress.[15] Nevertheless, this would not explain the higher prevalence of headache with the Delta variant. We cannot determine the cause of the differences found in the occurrence of headache with the three SARS-CoV-2 variants, but they are indicative of the clinical heterogeneity of COVID-19 across successive waves.

An important finding was that the presence of headache as a COVID-19 onset symptom but not a history of migraine before the infection was associated with development of post-COVID-19 headache in patients infected with the Wuhan or Delta variants, in agreement with some studies.[5,16] Accordingly, monitoring headache at the acute phase of SARS-CoV-2 infection may alert clinicians of a systemic inflammatory response and potential development of post-COVID-19 headache. Interestingly, no difference in the clinical pattern of headache among the three SARS-CoV-2 variants was found, because it consistently took on features similar to migraine or tension-type headache, as previously described.[17]

We recognize the following limitations. First, the results can be only applicable to hospitalized COVID-19 survivors who usually present a more severe clinical picture of COVID-19 than non-hospitalized patients, are typically older, and have more comorbidities than the general population. The evolution of headache depending on the SARS-CoV-2 variant in non-hospitalized patients is still unknown. Second, we must recognize the bias involved in collecting acute-phase data from medical records retrospectively. As COVID-19-related headache has been gaining prominence in clinical practice, we cannot rule out that its presence has been more comprehensively reported in medical records over time. In addition, no data were collected on the medical treatment received during hospitalization, which could have conditioned the presence of headache or its recording. Third, we did not collect laboratory biomarkers or COVID-19 severity at hospital admission or follow-up, which could help to elucidate whether these parameters are risk factors for the occurrence of headache at COVID-19 onset or during the post-COVID-19 phase. Fourth, the cross-sectional design of the study did not allow us to accurately describe the evolution of post-COVID-19 headache, so it is difficult to exclusively attribute the presence of headache to SARS-CoV-2 virus 6 months after hospitalization. It is also not possible to outline the temporal pattern of the headache or to classify it as episodic or chronic. Further studies characterizing COVID-19 and post-COVID-19 headache and its specific management options are now needed. Finally, we were not able to collect data for Omicron (B.1.1.529/BA.1), the dominant variant at this moment.

CONCLUSION

This study found that headache is a relevant symptom to be considered in SARS-CoV-2 infection at the acute- and post-COVID-19 phase. The presence of headache as a COVID-19 onset symptom but not the presence of previous migraine, was associated with post-COVID-19 headache. Headache was more prevalent in individuals infected with the Delta or Wuhan variants. However, a variant-specific effect or an outbreak wave-specific phenomenon still needs to be elucidated. Headache should be carefully monitored from the beginning of SARS-CoV-2 infection.

AUTHOR CONTRIBUTIONS

Study concept and design: César Fernández-de-las-Peñas, Maria L. Cuadrado, Victor Gómez-Mayordomo, Juan Torres-Macho,

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CONFLICT OF INTERESTS

No conflict of interest is declared by any of the authors.

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