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Research Submission

Spectrum of Headaches Associated With SARS-CoV-2 Infection: Study of Healthcare Professionals

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Background.—Series of patients with SARS-CoV-2 infection report headache in 6%-15% of cases, although some data suggest that the actual frequency is higher, and that headache is not associated with fever. No study published to date has analyzed the characteristics of headache in these patients.

Objective.—To analyze the characteristics of COVID-19 related headaches.

Methods.—We conducted a survey of Spaniard healthcare professionals who have been infected by SARS-CoV-2 and presented headache during the course of the disease. The survey addressed respondents' medical history and headache characteristics, and we analyzed the association between both.

Results.—We analyzed the responses of a sample of 112 healthcare professionals. History of migraine was reported by 20/112 (17.9%) of respondents, history of tension-type headache by 8/112 (7.1%), and history of cluster headache was reported by a single respondent; 82/112(73.2%) of respondents had no history of headache. Headache presented independently of fever, around the third day after symptom onset. The previous history of migraine was associated with a higher frequency of pulsating headache (20% in patients with previous migraine vs 4.3% in those with no history of migraine, $P = .013$).

Conclusion.—Headache is often holocranial, hemicranial, or occipital, pressing, and worsens with physical activity or head movements. Because the characteristics of the headache and the associated symptoms are heterogeneous in our survey, we suggest that several patterns with specific pathophysiological mechanisms may underlie the headache associated with COVID-19.

Key words: COVID-19, SARS-CoV-2, headache, migraine, neurological symptoms, healthcare professionals

Abbreviations: PCR polymerase chain reaction, PPE personal protective equipment

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INTRODUCTION

In December 2019, the World Health Organization reported cases of pneumonia associated with a new coronavirus, SARS-CoV-2, in Wuhan (Hubei province, China); the associated disease (COVID-19) quickly became a global pandemic. Numerous hospital case series and observational studies have described the clinical characteristics of patients in symptomatic phases; headache is recorded among these symptoms. Meta-analysis of these studies shows that headache is

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reported in 6%-15% of patients.[1-8] All these data are from studies conducted in China; however, preliminary data from our setting suggest that approximately 60% of patients with COVID-19 presented with headache.[8]

While headache is a frequent symptom of infection, it can present independently of fever in patients with SARS-CoV-2; most case series report no association between headache and fever. Despite this, no study assessing the presence of headache during the course of COVID-19 has analyzed the characteristics of the pain or the potential association with a personal history of headache. The accurate description of headache characteristics associated with COVID-19 might be relevant in terms of the diagnosis, as headache may be the presenting symptom.[9-11] In addition, considering that headache is present in patients with COVID-19, the differential diagnosis with other types of headaches (including primary headaches and headaches associated with personal protective equipment, PPE) is important in the current pandemic situation. We hypothesized that headache associated with COVID-19 infections may have some particular clinical characteristics, which may be different in those patients with a previous history of migraine.

A key characteristic of this pandemic has been the exposure of healthcare professionals, as well as frequent situations of anxiety, which may promote the appearance of headache in the absence of infection.[12] Headache is reported more frequently among healthcare professionals with SARS-CoV-2 infection (53%-57%) than in the case studies cited above, probably because healthcare professionals are better able to recognize symptoms.[13,14] For these reasons, healthcare professionals with COVID-19 may constitute an appropriate source for identifying the characteristics of headache during the clinical phase of the disease. In this study, we aimed to analyze the characteristics of headaches associated with COVID-19.

METHODS

Study Design.—We performed a descriptive, cross-sectional, observational study of the clinical characteristics of headache in healthcare professionals with clinically diagnosed and/or serologically confirmed SARS-CoV-2 infection, not requiring hospital admission, who presented headache. Clinical diagnosis included suggestive symptoms (fever, cough, shortness of breath, chills, muscle pain, sore throat, and new loss of taste or smell) and the clinical diagnosis by the Department of Workplace Health in each centre, which motivated the quarantine of the healthcare worker. Laboratory diagnosis included RT-PCR or serological tests. Laboratory testing was not performed in all cases because the availability of tests at the onset of the pandemic was low, and cases requiring hospital admission or with unclear diagnosis were prioritized. Participants were recruited amongst healthcare professionals included in an electronic information group about COVID-19. The survey was open to other professionals that acknowledge the study through word of mouth. Data were gathered using an anonymous, self-administered online questionnaire. The questionnaire was accessible through Google Docs and sent to healthcare professionals by text message. The survey was voluntary, and participants did not receive any incentive. A total of 957 healthcare professionals with COVID-19 were invited, although the survey was restricted to those with headache. Healthcare professionals with clinical diagnosis of SARS-CoV-2 infection, positive test findings for the virus, or under quarantine pending testing due to symptoms compatible with infection were asked to complete the questionnaire. The questionnaire was available between 16 and 18 April 2020 and responses were stored in a database. The questionnaire was completely anonymous. The study included healthcare professionals from the Region of Madrid. According to official sources, there were 194,416 cases of SARS-CoV-2 infection in Spain on that day.[15]

The questionnaire comprised 9 sections: (1) Demographic data, including age, sex, medical history, and risk factors. (2) Profession (physician, nurse, nursing assistant, other). (3) Use of personal protective equipment (which may be associated with headache). (4) Headache characteristics (quality, location, accompanying symptoms, trigger factors). (5) Temporal pattern of onset of headache (concurrently with other symptoms of infection; after the onset of viral infection symptoms; predominant, with few other

Conflict of Interest: None

symptoms; and others [not classifiable]). (6) Treatment received for the infection. (7) Treatment received for headache. (8) Temporal pattern of the resolution of headache. (9) Prior diagnosis of primary headache, based on the diagnosis conducted by a primary physician or a neurologist, with the recommendation of use of the International Classification of Headache Disorders.[16]

The Ethics Committee from the Hospital Clinico San Carlos (Madrid, Spain) approved the research protocol (code 20/318-E). All participants gave written informed consent. The study was reported according to the CHERRIES checklist.[17]

Statistical Analysis.—Statistical analysis was conducted using SPSS Statistics 20. Descriptive data are shown as number (percentage) or mean ± standard deviation. Kolmogorov-Smirnov test was used to check the normal distribution of quantitative variables. Data were analyzed for the total group and for subgroups of individuals with positive test results for SARS-CoV-2 and those diagnosed clinically. Chi-squared test was used to evaluate the association between categorical variables. A P value <.05 was considered statistically significant. A P value between .05 and .10 was considered a trend toward significance. Primary analyzes were about the characteristics of headache. Secondary analyzes investigated the potential influence of the previous history of migraine in the headache characteristics during COVID-19 infection. No statistical power calculation was conducted prior to the study, and the sample size was based on the available data.

RESULTS

We received 112 responses to the questionnaire; 78/112 respondents (69.6%) were physicians, 11/112 (9.8%) were nurses, 8/112 (7.1%) were nursing assistants, and 15/112 (13.4%) worked in other roles. The completion rate was 100%. The majority was diagnosed clinically; polymerase chain reaction (PCR) or serological confirmation was reported in 47.3% of cases. The ratio of women to men was 4.3:1; the mean age of the sample was 43.4 ± 11.4 years; 5/112 individuals (4.5%) presented arterial hypertension; 15/112 (13.4%) had dyslipidemia; and none had diabetes or had undergone any neurosurgical procedure.

Table 1.—Data From Our Sample of Survey Respondents on Demographic Variables, History of Headache, the Use of Personal Protective Equipment, and Serological Confirmation of SARS-CoV-2 Infection

N = 112	
Demographic variables	
Age, mean (SD)	43.4 (11.4)
Sex (females) N(%)	91 (81.3%)
History of arterial hypertension	5 (4.5%)
History of diabetes mellitus	0
History of dyslipidemia	15 (13.4%)
History of neurosurgical procedures	0
Profession	
Physician	78 (69.6%)
Nurse	11 (9.8%)
Nursing assistant	8 (7.1%)
Other	15 (13.4%)
History of headache	29 (25.9%)
Migraine	20 (17.9%)
Tension-type headache	8 (7.1%)
Cluster headache	1 (0.9%)
Trigeminal neuralgia	0
Other primary headaches	0
PPE use	83 (74.1%)
Occasional	23 (20.5%)
Over 50% of the time	27 (24.1%)
All the time	33 (29.5%)
Diagnosis	
Clinical	71.43 (80%)
PCR/serology	28.57 (20%)

Data are expressed as numbers and percentages of patients, unless otherwise indicated.

Eighty-three respondents (74.1%) had used PPE, with 60/112 (53.6%) using it throughout or for more than half of their shift. Sixteen individuals (14%) had been treated for COVID-19. Regarding personal history of headache, 20/112 (17.9%) reported migraine, 8/112 (7.1%) reported tension-type headache, and 1 reported cluster headache. No cases of trigeminal neuralgia or other primary headaches were reported. The remaining 83 respondents did not report history of headache (Table 1).

Regarding the presentation and characteristics of headache, the meantime from onset of viral infection symptoms to the onset of headache was 3.9 ± 6.0 days; temperature was below 37.5ºC at the time of headache onset in 99/112 cases (88.4%). Headache was hemicranial in 52/112 cases (46.0%), holocranial in 48/112 (42.5%), and occipital in 20/112 (17.7%). Pain was

described as pressing in 90/112 cases (80.4%), stabbing in 12/112 (10.7), and pulsating in 8/112 (7.4%); 2 (1.8%) individuals described electric-shock-like pain. Twenty-five respondents presented some autonomic symptoms over the course of the headache (rhinorrhea, tearing, or palpebral ptosis). Pain was exacerbated by physical activity in 57/112 cases (50.9%), by head movements in 52/112 (46.4%), and by both in 67/112 (60%). Phonophobia and photophobia were reported by 46/112 and 32/112 individuals (41.0% and 28.6%, respectively), and 11/112 respondents (9.8%) reported osmophobia. Nausea was recorded in 21 cases (18.7%) and vomiting in 4/112 (3.6%). No respondent reported trigger points, but 5/112 (4.4%) reported allodynia. Aura was not reported in any case. Forty-four respondents (39.3%) attributed headache to PPE use; 25% of this group had a history of migraine (Table 2).

Table 3 compares the clinical characteristics of headache in individuals with and without a history of migraine. Respondents with history of migraine more frequently reported exacerbation with activity, nausea, and vomiting; none of these differences were statistically significant. Osmophobia and phonophobia were more frequent in the group with a history of migraine ($P = .091$ and $P = .058$, respectively); patients with a history of migraine did show a higher frequency of pulsating pain (20% in patients with previous migraine vs 4.3% in those with no history of migraine, $P = .013$). Sixty participants (53%) used PPE for at least half of their shift; 44/60 of them (73%) attributed headache to PPE use, of whom 11/44 (25%) had a history of migraine.

Table 2.—Headache Characteristics (Duration, Location, Quality, and Association With the Use of Personal Protective Equipment) in Our Sample

N = 112	
Duration	
>4 hours	28 (24.8%)
4-12 hours	16 (14.2%)
12-24 hours	6 (5.3%)
24-72 hours	22 (19.5%)
72 hours-7 days	12 (10.6%)
>7 days	12 (10.6%)
Headache has not resolved	16 (15.0%)
Time (days) between the onset of viral infection symptoms and onset of headache, mean (SD)	3.95 (6.04)
Location	
Holocranial	48 (42.5%)
Hemicranial	14 (12.4%)
Both eyes	38 (33.6%)
Occipital	20 (17.7%)
Frontal, unilateral	27 (23.9%)
Periorbital, unilateral	8 (7.1%)
Facial, unilateral	2 (1.8%)
Cheek, unilateral	1 (0.9%)
Quality	
Pulsating	8 (7.1%)
Pressing	90 (80.4%)
Stabbing	12 (10.7%)
Electric-shock-like, continuous	1 (0.9%)
Electric-shock-like, brief	1 (0.9%)
Characteristics	
Exacerbated with activity	57 (50.9%)
Exacerbated with head movement	52 (46.4%)
Nausea	21 (18.7%)
Vomiting	4 (3.6%)
Phonophobia	46 (41.1%)
Photophobia	32 (28.6%)
Osmophobia	11 (9.8%)
Trigger points	0
Causes wakening	31 (27.7%)
Autonomic symptoms	22 (19.6%)
Allodynia	5 (4.5%)
Pulsating	8 (7.1%)
Pressing	90 (80.4%)
Stabbing	12 (10.7%)
Headache attributed to PPE use	44 (39.3%)

Data are expressed as the numbers and percentages of patients, unless indicated otherwise.

DISCUSSION

We consider healthcare professionals to be an appropriate population for analyzing clinical descriptions of headache in this context, which would be less straightforward in other patient populations. The low rate of PCR and serology testing is explained by government recommendations that testing should not be performed in patients with symptoms indicative of infection. Our main conclusion is that the infection can trigger headache in patients without a history of frequent headache: 74.1% of our sample had no history of primary headache. Headache may be explained by several factors, including psychological factors or by the action of the virus itself. Headache was not associated with high fever, as is observed for other infectious processes: temperature was below 37ºC in 88.4% of cases. Pain onset typically occurred over 3 days after the onset of viral symptoms (ie, fever, cough, muscle pain, etc.); this may suggest that headache was mediated by

Table 3.—Characteristics of Headache Associated With COVID-19 in Respondents With and Without a History of Migraine

N = 112	Migraine (N = 20)	No Migraine (N = 92)	χ^2	*P* value
Male/female (% of females)	1/19 (95%)	20/72 (78.3%)	3.81	.115
Exacerbated with activity	12 (60%)	45 (48.9%)	0.80	.369
Exacerbated with head movement	10 (50%)	42 (45.7%)	0.12	.724
Nausea	6 (30%)	15 (16.3%)	2.02	.155
Vomiting	2 (10%)	2 (2.2%)	2.23	.146
Phonophobia	12 (60%)	34 (37.0%)	3.60	.058
Photophobia	8 (40%)	24 (26.1%)	1.55	.212
Osmophobia	4 (20%)	4 (4.3%)	2.84	.091
Trigger points	0	0	—	—
Causes wakening	7 (35%)	24 (26.1%)	0.65	.420
Autonomic symptoms	2 (10%)	20 (21.5%)	1.43	.231
Allodynia	2 (10%)	3 (3.2%)	1.74	.185
Pulsating	4 (20%)	4 (4.3%)	6.06	.013*
Pressing	14 (70%)	76 (81.7%)	1.65	.198
Stabbing	2 (10%)	10 (10.7%)	0.01	.909

*Statistically significant at *P* value <.05.

the virus itself. The choice of healthcare professionals has several advantages for the aims of this study. First, the incidence of COVID-19 in healthcare workers has been high. Second, we used a questionnaire that was filled by the participant. Thus, better knowledge about symptoms is probably more necessary than when a questionnaire is administered by trained personnel. And third, participants were very motivated to participate in the study, which favored the participation and the full completion rate of the questionnaire by all cases.

Our study found a noticeable heterogeneity of associate symptoms in headache during COVID-19. However, most common characteristics were the holocranial, hemicranial, or occipital location, pressing, and the worsening with head movements or physical activity. The comparison of headache characteristics between individuals with and without a history of migraine is of particular interest, and suggests that some characteristics may be modulated by the previous history of migraine. The percentage of individuals reporting a history of migraine is consistent with published epidemiological data for Spain.[18,19]

Although our study is not designed to discriminate between subtypes of headache, several main causes of headache could be distinguished from a pathophysiological perspective:

1. In a first group, PPE use may play a role: This type of headache has previously been described,[20] and is included in the International Classification of Headache Disorders as "probable external-compression headache" (4.6.3.1). Pain is typically pressing, with variable location, and presents in half of individuals who use PPE. In this regard, in our study, individuals without a history of migraine more frequently attributed headaches to PPE use.[20]
2. A second group may present with a less specific, pressing headache without accompanying symptoms.
3. A third group may include those individuals with history of migraine (or other primary headaches) who presented headache compatible with their medical history; if migraine, this group more frequently presented exacerbation with physical activity, nausea, vomiting, phonophobia, osmophobia, and photophobia. Pulsatile pain presented a significant association with history of migraine ($P = .013$). This is consistent with a recent study about headaches associated with PPE, in which worsening of pre-existing headaches was observed with the use of PPE.[20]
4. Finally, the fourth group accounts for those individuals who we consider may present with headache secondary to SARS-CoV-2 infection. In this group, pain may be exacerbated with activity and head movement; may be holocranial or hemicranial; and

may be accompanied by phonophobia and less frequently by photophobia, nausea, or vomiting.

This latter type of headache is of particular interest because exacerbation with effort/head movements and the presence of photo-/phonophobia are highly suggestive of meningeal inflammation.[21] Although evidence is still limited, this observation is relevant as it may show the potential spread of the virus to the central nervous system,[22-24] which has been demonstrated in CSF in encephalitis and in brain tissue in postmortem pathological examination.[25-27] Cases have also been reported of patients presenting SARS-CoV-2 RNA in the cerebrospinal fluid and magnetic resonance imaging findings of meningeal contrast uptake.[28] The virus may reach the cerebrospinal fluid through the hematogenous route; however, given the prevalence of olfactory and gustatory alterations in patients with COVID-19, it has also been suggested that it may be transported through the olfactory system,[29] as olfactory endothelial cells express the ACE2 receptor.[30] The virus may also reach the central nervous system by crossing the cribriform plate.[31] Another hypothesis is that the virus may also enter the central nervous system through the trigeminovascular system; this is consistent with the fact that 22% of respondents in our sample reported autonomic symptoms. Coronaviruses are neurotropic and are able to access and remain in the central nervous system,[32] spreading through trans-synaptic and axonal transport.[33]

Finally, headache characteristics may be associated with inflammatory mechanisms. SARS-CoV-2 acts on both the innate and the adaptive immune responses,[34] and can cause the so-called cytokine storm, characterized by the release of chemokines and such cytokines as IL-6,[35,36] which are also associated with pain.[37] Because cytokine storm presents during the clinical course of the infection, this may suggest that the pattern of headache could change during the disease.

Further studies specifically designed to evaluate the number of latent groups of individuals according to the pattern of symptoms and the characteristics of headache are necessary. In this regard, larger sample sizes, more comprehensive questionnaires, and multivariate statistical analysis or clustering algorithms would be required.

An interesting point is the high percentage of females in our study. On the one hand, in our setting the percentage of females amongst healthcare professionals is high. On the other hand, sex matters in COVID-19, in which males are more prone to present severe pulmonary disorders, while headache or anosmia may be more frequent in females.[38]

Our study does present some limitations. The low mean age of our respondents is mainly due to the fact that we sampled a population of actively employed professionals, who contracted the virus through direct contact with patients, leading to mild-to-moderate symptoms. Pre-existing headache was defined according to the medical diagnosis with the recommendation of the use of ICHD-3 criteria, but headache diagnosis was not confirmed as a part of the research protocol. However, because participants are healthcare professionals with easier access to specialized care, the percentage of misdiagnosis of type of headache is probably low than in other populations. We cannot specify the response rate of our survey, because the survey was focused only on professionals that presented headache, but the invitation was general for healthcare professionals with COVID-19. Since we invited a total of 957 subjects and considering the frequency of headache reported in the case series of patients with COVID-19,[8] the response rate would be high, but we cannot reliably estimate it. In addition, the questionnaire has not been previously validated against a clinical diagnosis based on standardized criteria. However, the questionnaire was developed by consensus by a multidisciplinary team of neurologists and ophthalmologists, with experience in the development of questionnaires for epidemiology in migraine.[18] Few respondents had undergone PCR or serology testing because of a Government decision at the onset of the pandemic; however, headache has been reported at similar frequencies among patients who have and have not undergone these tests.[39] In any case, the analysis of other patient groups may confirm the association of these types of headache with COVID-19. Furthermore, prospective studies are required to confirm our findings.

In conclusion, our study analyzed the characteristics of headache in the context of SARS-CoV-2 infection. Headache is often holocranial, hemicranial, or occipital, pressing, and worsens with physical activity or head movements. Because the characteristics of the headache and the associated symptoms are

heterogeneous in our survey, we suggest the possibility that several patterns with specific pathophysiological mechanisms may underlie the headache associated with COVID-19.

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