Differences and similarities between COVID-19 related-headache and COVID-19 vaccine related-headache. A case-control study

Ana González-Celestino, Yésica González-Osorio, Cristina García-Iglesias, Ana Echavarría-Íñiguez, Álvaro Sierra-Mencía, Andrea Recio-García, Javier Trigo-López, Álvaro Planchuelo-Gómez, M. Luisa Hurtado, Leticia Sierra-Martínez, Marta Ruiz, María Rojas-Hernández, Carolina Pérez-Almendro, Marina Paniagua, Gabriela Núñez, Marta Mora, Carol Montilla, Cristina Martínez-Badillo, Ana G. Lozano, Ana Gil, Miguel Cubero, Ana Cornejo, Ismael Calcerrada, María Blanco, Ana Alberdi-Iglesias, César Fernández-de-las-Peñas, Ángel L. Guerrero-Peral, David García-Azorín

Introduction. Headache is a frequent symptom at the acute phase of coronavirus disease 2019 (COVID-19) and also one of the most frequent adverse effects following vaccination. In both cases, headache pathophysiology seems linked to the host immune response and could have similarities. We aimed to compare the clinical phenotype and the frequency and associated onset symptoms in patients with COVID-19 related-headache and COVID-19 vaccine related-headache.

Subjects and methods. A case-control study was conducted. Patients with confirmed COVID-19 infection and COVID-19-vaccine recipients who experienced new-onset headache were included. A standardised questionnaire was administered, including demographic variables, prior history of headaches, associated symptoms and headache-related variables. Both groups were matched for age, sex, and prior history of headache. A multivariate regression analysis was performed.

Results. A total of 238 patients fulfilled eligibility criteria (143 patients with COVID-19 related-headache and 95 subjects experiencing COVID-19 vaccine related-headache). Patients with COVID-19 related-headache exhibited a higher frequency of arthralgia, diarrhoea, dyspnoea, chest pain, expectoration, anosmia, myalgia, odynophagia, rhinorrhoea, cough, and dysgeusia. Further, patients with COVID-19 related-headache had a more prolonged daily duration of headache and described the headache as the worst headache ever experienced. Patients with COVID-19 vaccine-related headache, experienced more frequently pain in the parietal region, phonophobia, and worsening of the headache by head movements or eye movements.

Conclusion. Headache caused by SARS-CoV-2 infection and COVID-19 vaccination related-headache have more similarities than differences, supporting a shared pathophysiology, and the activation of the innate immune response. The main differences were related to associated symptoms.

Key words. COVID-19. Headache. Immunity. SARS-CoV-2. Vaccination. Virus diseases.

Valladolid Est Primary Care Basic Health Area (A. González-Celestino, C. García-Iglesias, M.L. Hurtado, L. Sierra-Martínez, **M. Ruiz,** M. Rojas-Hernández, C. Pérez-Almendro, M. Paniagua, G. Núñez, M. Mora, C. Montilla, C. Martínez-Badillo, A.G. Lozano, A. Gil, M. Cubero, A. Cornejo, I. Calcerrada, M. Blanco, A. Alberdi-Iglesias). Headache Unit. Department of Neurology. Hospital Clínico Universitario de Valladolid (Y. González-Osorio, A. Echavarría-Íñiguez, Á. Sierra-Mencía, A. Recio-García, J. Trigo-López, Á.L. Guerrero-Peral, D. García-Azorín). Department of Medicine. Faculty of Medicine. Universidad de Valladolid. Valladolid (D. García-Azorín). **Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine. Universidad Rey Juan Carlos. Alcorcón, Madrid, Spain** (C. Fernández-de-las-Peñas). **Brain Research Imaging Centre (CUBRIC). Cardiff University. Cardiff, United Kingdom** (Á. Planchuelo-Gómez).

Corresponding author:
Dr. Ángel L. Guerrero Peral.
Unidad de Cefaleas. Hospital Clínico Universitario de Valladolid.
Calle Rondilla Sta. Teresa, s/n.
E-47010 Valladolid.

E-mail:
gueneurol@gmail.com

ORCID:
0000-0001-7493-6002 (A.L.G.P.).

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Introduction

Headache is a common symptom that is experienced by 93-99% of people during their life [1]. Primary headache disorders, such as tension-type headache and migraine, are prevalent conditions [2]. Secondary headache disorders are highly prevalent, with infections and substances being some of the most frequent causes. In cases of systemic infections, patients may develop headache in 32-60% of the cases [3,4].

In 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) arose as an emergent pathogen, causing millions of cases and deaths. Headache is one of the most frequent symptoms experienced at the acute phase of the coronavirus disease 2019 (COVID-19), occurring in 20-70% of patients [5-7]. The most effective measure for pandemic control was the universal vaccination of the population. In 2021 several vaccines proved efficacy in the prevention of severe forms of COVID-19 [8-10]. Unfortunately, some adverse effects were also reported following vaccination to prevent COVID-19, being most of them infrequent [11]. Headache is also one of the most frequent symptoms reported after COVID-19 vaccines, described in 39-59% of patients in pivotal studies [8-10]. A recent systematic review of phase III vaccine randomized clinical

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trials not related to COVID-19 reported a median rate of headache of 15.6% –interquartile range (IQR): 9.6-37.6%–, a lower rate than the 39% (IQR: 28-50%) reported following COVID-19 related-vaccines [12]. In a study that evaluated 314,610 neurological adverse events reported to the United States Vaccine Adverse Events Reporting System, out of 306,907,697 COVID-19 vaccine doses administered, headache was the most frequently reported adverse effects [13].

To date, multiple studies have characterized the clinical phenotype of COVID-19 related- headache and COVID-19 vaccination related-headache, failing to identify any unique or highly specific feature. It has been hypothesized that both COVID-19 related-headache and headache post-immunization could be a manifestation of the immune response. In the present study, we aimed to compare the clinical phenotype and associated symptoms of COVID-19 related-headache and COVID-19 vaccination related-headache, to propose clinical clues that may help on its differentiation.

Subjects and methods

Study design

An observational analytic study with a case-control design was conducted. The study population were patients who experienced headache during the acute phase of COVID-19, and patients who experienced headache following COVID-19 related vaccination. The study was performed following the Strengthening in the Reporting in Observational Studies in Epidemiology (STROBE) initiative [14].

Study setting and study period

The study was conducted in the Headache Unit - an outpatient clinic of the Department of Neurology of Hospital Clínico Universitario de Valladolid, a third level, public, university hospital, with a reference area covering a 261,000 population. The study period was between March 8 and April 11, 2020, in the case of COVID-19 related-headache patients [5], and between December 12, 2021, and January 30, 2022, in the case of COVID-19 vaccine related-headache recipients. Data from COVID-19 patients were collected during May 2020. In both groups, the evaluation was done at least two weeks after the headache onset, to ensure that every possible associated symptom could be manifested.

Participants

Cases were patients with COVID-19 related-headache, and the comparative group included patients with COVID-19 vaccine related-headache. Both groups were matched regarding sex, age, and prior history of headache. The eligibility criteria were based on prior studies [5,15,16]. Cases were included if they had: a) new-onset headache, presented during the acute phase of COVID-19; b) confirmed SARS-CoV-2 infection by polymerase chain reaction assay and/or IgM anti SARS-CoV-2 antibodies; c) age of 18 years or older. Comparative group included subjects if they had: a) new-onset headache, present following COVID-19 vaccination; b) age of 18 years or older. Both cases and controls were excluded if: a) the headache was better accounted for by another International Classification of Headache Disorders criteria [17]; b) they had an unstable medical condition; c) had prior history of cognitive impairment; d) had speech or language disturbances; e) had been hospitalized; or, f) declined to participate.

Variables

A series of pre-specified variables were collected, based on prior studies [5,15,16]. Study variables included demographic data, prior history of headaches, associated symptoms and headache-related variables. Demographic variables included age at the moment of headache onset and sex. Variables related to prior history included prior history of headache, family history of headache, and presence of medical co-morbidities. Associated symptoms included arthralgia, asthenia, weakness, diarrhoea, dyspnoea, chest pain, expectoration, fever, anosmia, lightheadedness, myalgia, odynophagia, cutaneous rash, rhinorrhoea, cough, vomiting, syncope, and dysgeusia. Concerning headache phenotype, daily duration of headache, intensity of the headache in a 0-10 numerical rating scale (0: no pain, 10: worst possible pain), and the degree of disability caused by the headache (rated on a 0-100 scale, 0%: no disability, 100%: absolute disability). Regarding the topography of the headache, participants described whether the headache was holocranial or hemicranial. The presence of pain in the different regions was assessed. The presence of pressing and/or throbbing pain was evaluated. Patients reported the presence of photophobia, phonophobia, osmophobia, nausea, or vomiting. Worsening of the headache by physical activity, head movements and eye movements was evaluated. The presence of

headache-related red flags [16] was also systematically evaluated, including wake-up headache, progressive worsening of the headache, acute treatment resistance, worst headache ever experienced, sudden onset of the headache, confusion, altered level of consciousness and headache precipitation by cough.

Data sources

Data from cases were obtained from a prior study that included 351 COVID-headache patients [5]. Briefly, all consecutive patients with confirmed SARS-CoV-2 infection (n = 1,525) were screened for eligibility. Data were collected by a clinical interview conducted by a physician, who administered a predefined questionnaire. Due to the study design, interviewers were not blinded to the presence of headache. The comparative group was obtained from the students and personnel of the Faculty of Medicine of the Universidad de Valladolid via institutional email. The study questionnaire was adapted as a web-based survey, that included the same study variables [5,15,16] and was self-administered.

Bias management

Despite the same study questionnaire being used in both groups, data from COVID-19 vaccine related-headache was obtained from a web-based survey. To minimize detection bias, the studied population was composed by healthcare degrees students and professors. In both groups, the evaluation was done two weeks after the headache onset, to minimize recall bias. Both samples were selected in an outpatient setting, so the most severe population could not be represented in the study.

Study size

No formal sample size calculation was done. The number of cases was adapted to match them with comparative controls in terms of age, sex, and prior history of headache. Given the older age and higher frequency of prior headache history of patients with COVID-19 [5], the final proportion of matched COVID-19 vaccine recipients was 1.5:1 to ensure the comparability of the two groups.

Statistical analysis

Qualitative and ordinal variables are presented as frequencies and percentages. Quantitative variables are reported as mean and standard deviation or median and interquartile range, when the distribution was not normal. Normality of the variables was assessed with the Kolmogorov-Smirnov test. For hypothesis testing between quantitative variables, qualitative categorical variables, χ^2-test and Fisher's exact test were used. In the case of quantitative variables, Student t test or Mann-Whitney U test were used, according to the normality test. To evaluate the variables associated with COVID-19 related-headache, a logistic regression analysis was done. First, all variables were assessed in an univariable regression analysis, with COVID-19 related-headache as a dependent variable. All variables that had a p-value < 0.1 were included in a multivariate regression analysis. In all cases, p values were adjusted for multiple comparisons with the False Discovery Rate (FDR), according to the Benjamini-Hochberg procedure [18]. The statistical analysis was done by the Statistical Package for Social Sciences (IBM Corp. Released 2019. IBM SPSS Statistics for Mac, Version 26.0. Armonk, NY: IBM Corp).

Ethics

The study was approved by the Valladolid East Ethics Review Board (PI-GR-COVID-20-1881 and PI-21-2471).

Data availability

All data sheets are available for other researchers upon reasonable request to the corresponding author.

Results

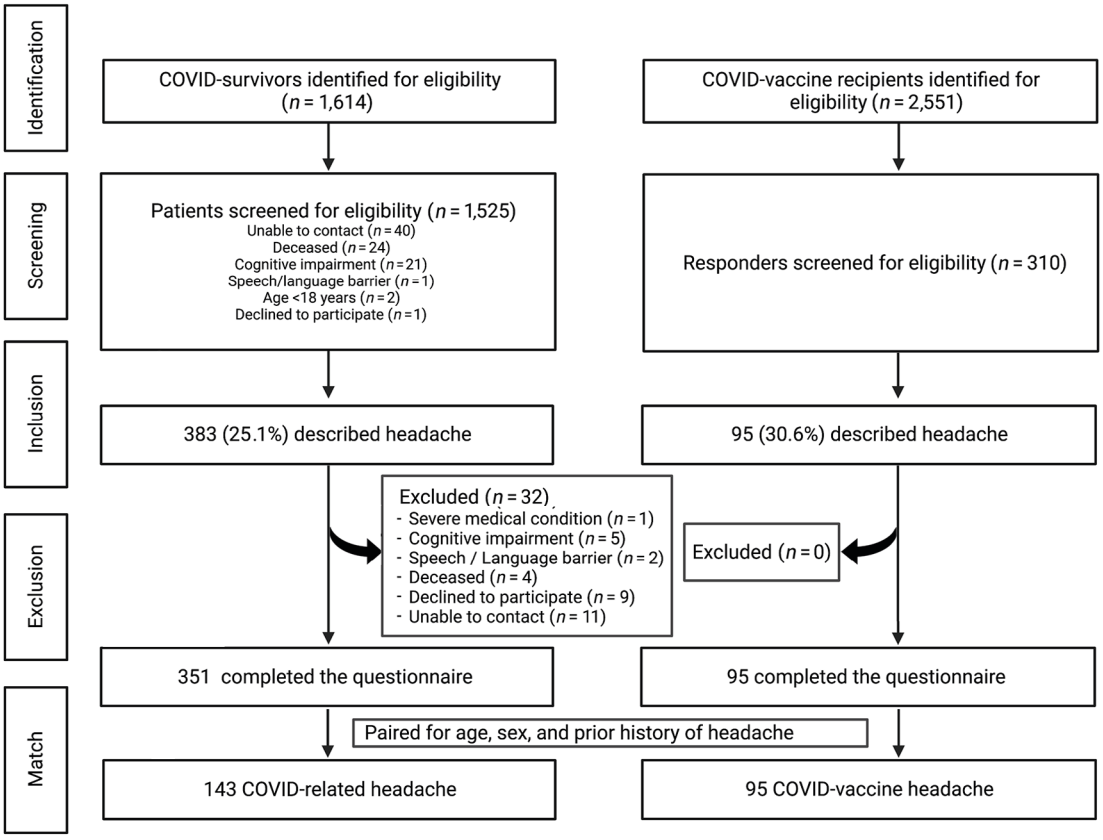
Participants

Figure 1 shows the flow diagram of the study. A total of 238 patients were enrolled, including 143 COVID-19 related-headache patients and 95 COVID-19 vaccine related-headache recipients. Vaccine related-headache occurred after the first dose in 57/95 (60%) cases, and after the second dose in 38/95 (40%) cases. The employed vaccine was Pfizer in 56/95 (58.9%), Moderna in 21 (22.1%), AstraZeneca in 15 (15.8%), and Janssen in three (3.2%).

Descriptive data

Table I summarizes the demographic characteristics and prior history. Patients with COVID-19 vac-

Figure 1. Flow diagram of screened, included, excluded and patient matching.



cine related-headache presented prior family history of headache more frequently than COVID-19 related-headache patients (47.4% vs. 23.1%; p < 0.001).

Associated symptoms

After adjusting for multiple comparisons, patients with COVID-19 related-headache had a higher frequency of arthralgia, diarrhoea, dyspnoea, chest pain, expectoration, anosmia, myalgia, odynophagia, rhinorrhoea, cough, and dysgeusia. Figure 2 compares the frequency of the associated symptoms where differences were statistically significant between both groups.

Headache phenotype

Variables related to the headache phenotype and its associated symptoms are listed in the table II, and headache-related red flags are presented in table III. After adjusting for multiple comparisons, patients with COVID-19 related-headache had a more prolonged daily duration of the headache and described the headache as the worst headache ever experienced more frequently. On the other hand, patients with COVID-19 vaccine-related headache, experienced more frequently pain in the parietal region (30.5% vs. 11.9%; p = 0.005); phonophobia (54.7% vs. 30.1%; p <0.001), worsening by head movements (60% vs. 31.5%; p < 0.001) and worsening by eye movements (41.1% vs. 16.8%; p < 0.001).

Variables associated with the presence of headache

In the univariate logistic regression analysis, the variables that were associated with the COVID-19 related-headache were arthralgia, diarrhoea, dyspnoea, chest pain, expectoration, anosmia, myalgia, odynophagia, rhinorrhoea, cough, dysgeusia, inten-

Table I. Variables related to demographic characteristics and prior history of patients.

	Entire study sample (*n* = 238)	COVID-19 related-headache (*n* = 143)	COVID-19 vaccine related-headache (*n* = 95)	FDR-corrected *p*-value
Median age, (SD)	35.5 (10.6)	36.2 (8.6)	30 (13)	0.438
Female sex, *n* (%)	180 (75.6%)	105 (73.4%)	75 (78.9%)	0.478
Prior history of headache, *n* (%)	32 (13.4%)	20 (14%)	12 (12.6%)	0.903
Family history of headache, *n* (%)	78 (32.8%)	33 (23.15)	45 (47.4%)	<0.001
Family history of migraine, *n* (%)	67 (28.2%)	33 (23.1%)	34 (35.8%)	0.214
Hypertension, *n* (%)	7 (2.9%)	2 (1.4%)	5 (5.3%)	0.387
Diabetes. *n* (%)	7 (2.9%)	2 (1.4%)	5 (5.3%)	0.309
Smoking, *n* (%)	27 (11.3%)	19 (11.3%)	8 (8.4%)	0.557
Cardiological disorders, *n* (%)	7 (2.9%)	4 (2.8%)	3 (3.2%)	0.999
Pulmonary disorders, *n* (%)	9 (3.8%)	7 (4.9%)	2 (2.1%)	0.525
Oncological disorders, *n* (%)	6 (2.5%)	3 (2.1%)	3 (3.2%)	0.89
Neurological disorders, *n* (%)	9 (3.8%)	5 (3.5%)	4 (4.2%)	0.999
Immunosuppression, *n* (%)	3 (1.3%)	0 (0%)	3 (3.2%)	0.287

FDR: false discovery rate; SD: standard deviation.

sity of the headache, worst headache ever, and precipitation by cough. The variables that were associated with COVID-19 vaccine related-headache were family history of headache, parietal localization of the pain, photophobia, phonophobia, and worsening of the headache by physical activity, head movements or eye movements (Table IV).

In the multivariate regression analysis, the variables that remained statistically significant were dyspnoea, rhinorrhoea, cough, periocular headache, phonophobia and worsening by eye movements (uncorrected $p < 0.05$). After adjusting for multiple comparisons, only cough (odds ratio: 21.316; 95% confidence interval: 4.298-105-725; $p = 0.0002$); and rhinorrhea (odds ratio: 15.433; 95% confidence interval: 3.104-76.721; $p = 0.012$) remained associated with COVID-19 related-headache.

Discussion

In the present study, patients with COVID-19 related-headache and patients with COVID-19 vaccine related-headache were compared. To ensure the comparability of both groups, a case-control design was selected, where cases were matched with controls based on patients' age, sex, and prior headache history. Both groups were similar regarding demographic variables and prior history of patients, except for family history of headache, that was 13% more frequent within patients with COVID-19 vaccine related-headache. As expected, associated symptoms were more frequently reported by patients with COVID-19 related-headache. Regarding the headache phenotype and symptoms associated, patients with COVID-19 vaccine related-headache experienced pain in the parietal region more often and suffered from phonophobia and worsening by head movements and eye movements more frequently. In contrast, patients with COVID-19 related-headache had a more prolonged headache and described the headache as the worst headache ever experienced in more cases.

There is no specific clinical phenotype of COVID-19 related-headache or COVID-19 vaccine relat-

Table II. Characteristics of the headache and headache-related symptoms.

	Entire study sample (*n* = 238)	COVID-19 related-headache (*n* = 143)	COVID-19 vaccine-related headache (*n* = 95)	FDR-corrected *p*-value
Duration of headache (hours), median [IQR]	7 [3-24]	12 [3-24]	6 [2-12]	0.007
Intensity of headache, median [IQR]	7 [6-8]	7 [6-8]	7 [5-7]	0.191
Disability of headache, median [IQR]	50% [20-70%]	50% [20-70%]	60% [20-70%]	0.446
Holocranial headache, *n* (%)	197 (82.8%)	117 (81.8%)	80 (84.2%)	0.902
Hemicranial headache, *n* (%)	53 (22.3%)	26 (18.2%)	27 (28.4%)	0.189
Frontal localization, *n* (%)	109 (45.8%)	66 (46.2%)	43 (45.3%)	0.999
Temporal localization, *n* (%)	79 (33.2%)	45 (31.5%)	34 (35.8%)	0.77
Parietal localization, *n* (%)	46 (19.3%)	17 (11.9%)	29 (30.5%)	0.005
Occipital localization, *n* (%)	33 (13.9%)	21 (14.7%)	12 (12.6%)	0.919
Periocular localization, *n* (%)	29 (12.2%)	22 (15.4%)	7 (7.4%)	0.194
Vertex localization, *n* (%)	15 (6.3%)	7 (4.9%)	8 (8.4%)	0.508
Cervical localization, *n* (%)	13 (5.5%)	8 (5.6%)	5 (5.3%)	0.999
Pressing quality, *n* (%)	181 (76.1%)	110 (76.9%)	71 (74.7%)	0.953
Throbbing quality, *n* (%)	33 (13.9%)	20 (14.0%)	13 (13.7%)	0.999
Photophobia, *n* (%)	78 (32.8%)	39 (27.3%)	39 (41.1%)	0.116
Phonophobia, *n* (%)	95 (39.9%)	43 (30.1%)	52 (54.7%)	<0.001
Osmophobia, *n* (%)	9 (3.8%)	6 (4.2%)	3 (3.2%)	0.999
Nausea, *n* (%)	30 (12.6%)	18 (12.6%)	12 (12.6%)	0.856
Vomiting, *n* (%)	11 (4.6%)	7 (4.9%)	4 (4.2%)	0.999
Worsening by physical activity, *n* (%)	172 (72.3%)	97 (67.8%)	75 (78.9%)	0.203
Worsening by head movement, *n* (%)	102 (42.9%)	45 (31.5%)	57 (60%)	<0.001
Worsening by eye movement, *n* (%)	63 (26.5%)	24 (16.8%)	39 (41.1%)	<0.001

FDR: false discovery rate; IQR: inter-quartile range.

ed-headache. In the first case, most patients report a bilateral headache, with frontotemporal location, moderate-to-severe intensity, pressing quality and accompanied by associated symptoms in approximately a third of patients [5,19]. In the case of COVID-19 vaccine related-headache, the clinical phenotype was also mostly a bilateral headache, of moderate-to-severe intensity, with predominantly frontal-temporal location, pressing quality, not frequently accompanied by associated symptoms, and aggravated by routine physical activity [20-22]. Differences between the two groups are not striking, and could be related to the studied population, including patients' age, sex, frequency of prior histo-

Table III. Headache-related red flags.

	Entire study sample (*n* = 238)	COVID-19 related-headache (*n* = 143)	COVID-19 vaccine-related headache (*n* = 95)	FDR-corrected *p*-value
Wake-up headache, *n* (%)	50 (21%)	35 (24.55)	15 (15.8%)	0.306
Progressive worsening, *n* (%)	24 (10.15)	10 (7%)	14 (14.7%)	0.192
Acute treatment resistance, *n* (%)	52 (21.8%)	20 (20.3%)	23 (24.2%)	0.787
Worst headache ever, *n* (%)	48 (20.2%)	39 (27.3%)	9 (9.5%)	0.006
Sudden onset, *n* (%)	14 (5.9%)	6 (4.2%)	8 (8.4%)	0.487
Confusion, *n* (%)	35 (14.7%)	20 (14%)	15 (15.8%)	0.89
Altered level of consciousness, *n* (%)	1 (0.4%)	1 (0.7%)	0 (0%)	0.999
Precipitated by cough, *n* (%)	42 (17.6%)	31 (21.7%)	11 (11.6%)	0.21

FDR: false discovery rate; IQR: inter-quartile range.

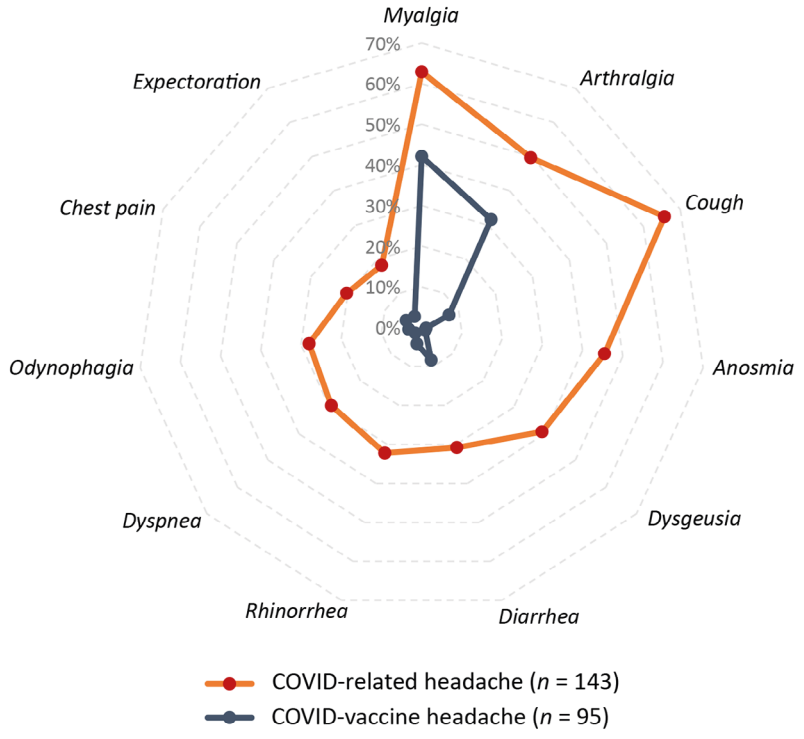
ry of headache [23], severity of COVID-19 [7], prior history of COVID-19 in the case of COVID-19 vaccine related headache recipients [22], and perhaps the type of COVID-19 vaccine that was administered [24,25].

Therefore, if the headache phenotype does not seem to be distinct, the differentiation between these headache disorders could be done based on the associated symptoms, as we observed in our study. COVID-19 is a systemic disease that causes multiple respiratory and systemic symptoms [19]. In the case of COVID-19 vaccine related-headache, the most frequently reported systemic symptoms were fatigue, fever or feverish sensation, arthralgia or dizziness [20-22]. In the COVID-19 vaccines randomized clinical trials, adverse events were reported by 27%-55% [8-10]. In another cross-sectional study that compared COVID-19 vaccine related-headache and COVID-19 related-headache in the same patients, patients with COVID-19 vaccine related-headache had hemicranial headache more frequently, and had less frequently associated symptoms, such as anosmia, ageusia, aggravation by physical activity, or nausea. Most differences were in the range of 10-20% between groups, except for anosmia and ageusia, which were 50% more frequent in the COVID-19 group [22]. Important to note, COVID-19 cases that were included in this study were infected during the first wave, with no prior infections or vaccination, so the frequency of associated symptoms could be higher than the expected in a properly vaccinated individual nowadays.

In March 2021, cases of thrombosis in uncommon locations, associated with severe thrombocytopenia were reported in individuals vaccinated with non-replicant adenovirus vector-based vaccines [26]. Vaccine-induced thrombosis with thrombocytopenia syndrome (TTS) is caused by the platelet activation and consumption, triggered by anti-platelet factor-4 antibodies [27]. Headache is the most frequent symptom of TTS, and may even precede thrombosis [28,29]. The most specific feature to differentiate between the conventional vaccine-induced headache and TTS-related headache is the delayed onset of the headache, needed to produce the responsible antibodies [30]. In addition, in TTS, patients exhibit thrombocytopenia and raised D-dimer levels, however, in case of atypical features or headache-related red flags, patients should be investigated, and a cerebral venous sinus thrombosis must be ruled out [30].

In the case of COVID-19 related-headache and COVID-19 vaccine related headache, the pathophysiology seems associated with the immune response. Patients with headache during the course of COVID-19 have a better prognosis [15,31], with higher levels of anti-inflammatory cytokines and lower-levels of pro-inflammatory cytokines that patients without headache [32], suggesting a more efficient immune response. In the case of COVID-19 vaccine related-headache, the immune response

Figure 2. Frecuency of associated symptoms.



triggered by the immunization causes the headache and the other systemic symptoms, while headache can be more frequent and prominent in patients with prior history of COVID-19 [22].

Our study has important limitations. First, the sample size is modest, and some statistical analyses were restrictive, which could imply false negative results. The participants were students and staff working at the university, so there might be confounding factors due to educational level and it might be easier for them to identify the phenotypic characteristics of their headache. The sample could not be representative of other ethnic backgrounds and severe patients, to guarantee the comparability of cases and controls, although patients hospitalized for COVID have been previously analyzed in other articles of the research group [7,15,16,32]. Also, COVID-19 patients were enrolled during the first wave of the pandemic, so most of them were infected by the Wuhan variant, prior to the vaccination campaigns. The instruments that were used differed, from a clinical interview to an online-based questionnaire, which could cause some degree of detection bias, despite the questionnaire was adapted and included the same variables.

Conclusion

In the present study, the clinical phenotypes of COVID-19 related-headache and COVID-19 vaccine related-headache were similar, being the presence of systemic symptoms the most specific difference between both groups. COVID-19 vaccine related-headache was affected the parietal region more frequently and worsened by head and eye movements in more cases. In contrast, COVID-19 related-headache lasted longer and was described as the worst headache ever experienced by more patients.

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Table IV. Logistic regression analysis – variables associated with COVID-19 related headache.

	Odds ratio	95% confidence interval lower bound	95% confidence interval upper bound	*p*-value
Sex	0.737	0.397	1.366	0.332
Age	1.016	0.991	1.042	0.202
Prior history of headache	1.125	0.522	2.424	0.764
Family history of headache	0.333	0.19	0.584	<0.001
Presence of arthralgia	2.137	1.242	3.677	0.006
Asthenia	1.074	0.558	2.066	0.831
Weakness	1.52	0.893	2.588	0.123
Diarrhea	4.833	2.158	10.827	<0.001
Dyspnea	19.337	4.553	82.123	<0.001
Chest pain	5.787	1.963	17.06	0.001
Expectoration	6.815	2	23.22	0.002
Fever	1.376	0.816	2.321	0.232
Anosmia	78.333	10.626	577.461	<0.001
Lightheadedness	1.302	0.721	2.352	0.382
Myalgia	2.335	1.374	3.967	0.002
Odynophagia	11.909	3.564	39.797	<0.001
Rash	3.875	0.839	17.892	0.083
Rhinorrhea	10.789	3.734	31.171	<0.001
Cough	24.117	10.374	56.066	<0.001
Vomiting	1.236	0.441	3.464	0.687
Syncope	0.327	0.029	3.663	0.365
Dysgeusia	60.506	8.199	446.53	<0.001
Intensity of the headache	1.208	1.041	1.401	0.013
Wake-up headache	1.728	0.884	3.379	0.11
Progressive worsening	0.435	0.185	1.025	0.057
Treatment resistance	0.796	0.428	1.483	0.473
Worst headache ever	3.583	1.644	7.81	0.001
Sudden onset	0.476	0.16	1.42	0.183
Confusion	0.867	0.419	1.793	0.701

	Odds ratio	95% confidence interval lower bound	95% confidence interval upper bound	*p*-value
Holocranial location	0.844	0.421	1.693	0.632
Hemicranial location	0.56	0.302	1.036	0.065
Frontal topography	1.037	0.616	1.745	0.893
Temporal topography	0.824	0.476	1.425	0.488
Parietal topography	0.307	0.157	0.599	0.001
Occipital topography	1.191	0.556	2.551	0.654
Periocular topography	2.286	0.935	5.587	0.07
Vertex topography	0.56	0.196	1.599	0.278
Cervical topography	1.067	0.338	3.365	0.912
Pressing quality	1.127	0.616	2.062	0.699
Throbbing quality	1.026	0.483	2.176	0.947
Photophobia	0.538	0.311	0.933	0.027
Phonophobia	0.356	0.207	0.61	<0.001
Osmophobia	1.343	0.328	5.506	0.682
Clinophilia	0.562	0.307	1.03	0.062
Precipitation by cough	2.114	1.005	4.447	0.049
Worsening by walking	0.507	0.274	0.94	0.031
Worsening by head movement	0.306	0.178	0.526	<0.001
Worsening by eye movement	0.29	0.159	0.527	<0.001
Nausea	0.996	0.456	2.176	0.992
Vomiting	1.171	0.333	4.115	0.806
Prior history of hypertension	0.255	0.048	1.344	0.107
Prior history of diabetes	0.255	0.048	1.344	0.107
Smoking	1.666	0.698	3.979	0.25
Prior history of cardiac disorders	0.882	0.193	4.035	0.872
Prior history of pulmonary disorders	2.393	0.486	11.777	0.283
Prior history of oncological disorders	0.657	0.13	3.327	0.612
Prior history of neurological disorders	0.824	0.216	3.152	0.778

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Diferencias y similitudes entre la cefalea relacionada con la COVID-19 y la cefalea relacionada con la vacuna de la COVID-19. Un estudio de casos y controles

Introducción. La cefalea es un síntoma frecuente en la fase aguda de la enfermedad por coronavirus 2019 (COVID-19) y también uno de los efectos adversos más comunes tras la vacunación. En ambos casos, la fisiopatología de la cefalea parece estar relacionada con la respuesta inmunitaria del huésped y podría presentar similitudes. Nuestro objetivo fue comparar el fenotipo clínico y la frecuencia de los síntomas asociados y los síntomas de inicio en pacientes con cefalea relacionada con la COVID-19 y cefalea relacionada con la vacuna de la COVID-19.

Sujetos y métodos. Se realizó un estudio de casos y controles. Se incluyó a pacientes con infección confirmada por COVID-19 y receptores de la vacuna de la COVID-19 que experimentaron un nuevo inicio de cefalea. Se administró un cuestionario estandarizado que incluyó variables demográficas, antecedentes previos de cefaleas, síntomas asociados y variables relacionadas con la cefalea. Ambos grupos se emparejaron por edad, sexo y antecedentes previos de cefaleas. Se realizó un análisis de regresión multivariante.

Resultados. Un total de 238 pacientes cumplieron con los criterios de elegibilidad (143 pacientes con cefalea relacionada con la COVID-19 y 95 sujetos con cefalea relacionada con la vacuna de la COVID-19). Los pacientes con cefalea relacionada con la COVID-19 presentaron una mayor frecuencia de artralgia, diarrea, disnea, dolor torácico, expectoración, anosmia, mialgia, odinofagia, rinorrea, tos y disgeusia. Además, los pacientes con cefalea relacionada con la COVID-19

experimentaron una duración diaria más prolongada de la cefalea y describieron la cefalea como la peor que habían experimentado. Los pacientes con cefalea relacionada con la vacuna de la COVID-19 experimentaron con más frecuencia dolor en la región parietal, fonofobia y empeoramiento de la cefalea por movimientos de la cabeza o de los ojos.

Conclusión. La cefalea causada por la infección por el SARS-CoV-2 y la cefalea relacionada con la vacunación de la COVID-19 presentan más similitudes que diferencias, lo que respalda una fisiopatología compartida y la activación de la respuesta inmunitaria innata. Las principales diferencias estuvieron relacionadas con los síntomas asociados.

Palabras clave. Cefalea. COVID-19. Enfermedades virales. Inmunidad. SARS-CoV-2. Vacunación.