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Impact of SARS-CoV-2 Infection and Vaccination on Migraine Symptoms during the COVID-19 Pandemic

Impacto da Infeção e Vacinação SARS-CoV-2 nos Sintomas de Enxaqueca durante a Pandemia COVID-19

Lénia Silva [1,*]; Adriana Lopes [2]; Ana Pontes [2]; Ana Gonçalves [2]; Arlinda Chiteculo [2]; Beatriz Soares [2]; Inês Teixeira [2]; Maria Gonçalves [2]; Maria Alves [2]; Maria Cardia [2]; Mariana Monteiro [2]; Raquel Eiras [2]; Sara Costa [2]; Inês Laranjinha [1]; Carlos Andrade [1]; Denis Gabriel [1]

1-Serviço de Neurologia / Centro Hospitalar Universitário de Santo António, Porto, Portugal
2-Instituto de Ciências Biomédicas Abel Salazar, Porto, Portugal

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***Autor Correspondente / Corresponding Author:**
Lénia Silva
Largo Prof Abel Salazar
4050-366 Porto, Portugal
leniasilva2@gmail.com

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Abstract

Introduction: Studies have shown the worsening of migraine associated with the COVID-19 infection and the pandemic more broadly. COVID-19 vaccination has also been associated with symptomatic headache, with high frequency among migraineurs. We aimed to assess the impact of COVID-19 diagnosis and vaccine administration on migraine, during the SARS-CoV-2 pandemic.

Methods: An online questionnaire was sent to migraine patients followed in a neurology outpatient clinic between March and November 2022. The survey inquired about migraine symptoms and treatment changes, as well as sleep changes, anxiety, and depressive symptoms during the pandemic, after a COVID-19 diagnosis and/or vaccination.

Results: Out of the 185 patients included, 108 (58.4%) reported a change in headache pattern (intensity, frequency, and/or pain quality) and 47% reported higher intensity and frequency. The pattern changes occurred before the COVID-19 diagnosis in 41%. Of all the participants with headache changes 72.2% needed to intensify medication (abortive or prophylaxis), regardless of infection status. High levels of insomnia, anxiety, and depressive symptoms were found among patients with worsening migraine, irrespective of COVID-19 diagnosis. After vaccination, 49 (27.1%) described a change in headache pattern, with a worsening pattern in 29 (16%). In half, this change occurred for up to 3 weeks.

Conclusion: Worsening of migraine was more likely associated with other factors related to the pandemic rather than COVID-19 diagnosis. COVID-19 vaccination might have acted as an additional but less relevant and temporary trigger for migraine worsening.

Resumo

Introdução: Os estudos têm demonstrado agravamento da enxaqueca associado à infeção COVID-19 e à pandemia mais especificamente. A vacinação contra a COVID-19 também tem sido associada a cefaleia sintomática, com elevada frequência nos doentes com enxaqueca.

Pretende-se verificar o impacto da COVID-19 na enxaqueca, durante a pandemia por SARS-CoV-2.

Métodos: Um questionário online foi enviado para doentes com enxaqueca seguidos na consulta externa de Neurologia, entre março e novembro de 2022. As questões incidiam sobre os sintomas da enxaqueca e alterações do tratamento, assim como alterações do sono, sintomas ansiosos e depressivos durante a pandemia, após o diagnóstico e/ou vacinação da COVID-19.

Resultados: Dos 185 doentes incluídos, 108 (58,4%) reportaram alteração no padrão da cefaleia (intensidade, frequência e/ou tipo de dor) e 47% reportaram aumento da intensidade e frequência. A alteração ocorreu antes do diagnóstico da COVID-19 em 41%. Do total de casos com alteração da cefaleia, 72,2% necessitaram de intensificar a medicação (abortiva ou profilática), independentemente se tiveram infeção. Verificaram-se elevados níveis de insónia e sintomas de ansiedade e depressão nos doentes que agravaram da enxaqueca, independentemente do diagnóstico de COVID-19. Após a vacinação, 49 (27,1%) descreveram uma alteração no padrão da cefaleia, com agravamento em 29 (16%). Em metade, esta alteração ocorreu nas primeiras 3 semanas após a vacinação.

Conclusão: O agravamento da enxaqueca esteve mais provavelmente associado a outros fatores relacionados com a pandemia do que ao diagnóstico de COVID-19. A vacinação pode ter tido um efeito adicional, mas foi um desencadeante menos relevante e temporário.

Introduction

Migraine is a chronic neurological disease characterized by recurrent headache episodes of moderate to severe intensity, pulsatile, usually unilateral, and interspersed with symptom-free periods. It is often accompanied by nausea and/or vomiting, as well as photophobia, phonophobia, and intolerance to smells and movement, symptoms that may precede the pain by hours or even days.[1] It is considered one of the most disabling chronic neurological diseases and migraine patients are particularly vulnerable to psychosocial stress and social isolation. Furthermore, 50%–60% of patients with migraine were found to be anxious and/or depressed, and around 40% complained of sleep disturbance.[2,3] They had significantly higher levels of stress than controls.[4] In a 90-day prospective daily-diary cohort study involving adults with episodic migraine, increased levels of stress were associated with a migraine episode the following day.[5] Also, perceived stress is associated with chronic migraine, depression, and anxiety.[6]

Several studies showed that the COVID-19 pandemic had a negative impact on patients with migraine.[5,7-9] More studies addressed changes in headache intensity or migraine episode duration (days) during the COVID-19 pandemic.[10,11] Conversely, other studies have shown improvement in migraine-related symptoms during the pandemic.[12,13] Owning an outdoor living space, maintaining a positive attitude throughout quarantine, and having a full-time job were all associated with an increased chance of migraine improvement.[14] Regarding COVID-19 diagnosis, several studies demonstrated that one-third of acute symptomatic headaches occurred in patients with a previous history of migraine.[13,15] Headache was a persistent symptom in 6% to 45% of patients.[16] Some patients did not fully recover after the acute phase of COVID-19 or reported a delayed headache onset, referred to as a post-COVID headache.[16,17] The latter includes a complex spectrum of presentations, including chronification of a previously existing migraine, late-onset newly persistent headache, or migraine-like headache without a prior history of such.

COVID-19 vaccination has also been associated with symptomatic headache, with a particularly higher frequency in patients with previous migraine.[11] However, the long-term evolution of migraine-related symptoms after vaccination is not yet known to date.

Of note, most papers that have studied the impact of the pandemic on migraine have excluded patients with COVID-19 diagnosis. Indeed, the question of whether the infection per se may contribute to a change in migraine features in the long term has not yet been fully addressed. Overall, despite an extensive report on the worsening of

migraine symptoms, the impact of COVID-19 diagnosis and vaccination in migraine patients has not been thoroughly assessed in previous studies, especially when considering the pandemic's impact separately.[7-9] Acknowledging the negative impact both at a personal level, but also at a social and professional level, we aim to assess the impact of the COVID-19 pandemic, SARS-CoV-2 infection, and COVID-19 vaccination in migraineurs.

Methods

Adult patients followed up in the neurology outpatient clinic of Centro Hospitalar Universitário de Santo António, in Northern Portugal, with a previous diagnosis of migraine were invited to participate in the study by phone (AL, AP, AG, AC, BS, IT, LS, MG, MA, MC, MM, RE, SC) between March and November 2022.

Migraine and the classification type (episodic and chronic migraine) were defined according to the International Headache Society diagnostic criteria.[1] An online questionnaire (supplemental material) was developed to collect the following information: (i) age, sex, and academic qualifications – elementary (4 years or less of education); secondary (5 to 12 years of education); superior (>12 years of education); (ii) change in headache pattern (on frequency, intensity, and pain quality) since the beginning of SARS-CoV-2 pandemic or COVID-19 diagnosis (confirmed by nucleic acid amplification test of nasal swab fluid sample); (iii) impact of vaccination on frequency, intensity and pain quality; (iv) impact of migraine on daily activities (MIDAS score) (18); (v) sleep pattern changes, diagnosis, and severity of chronic insomnia – based on the Portuguese version of the Pittsburgh Sleep Quality Index (19); (vi) symptoms of anxiety and depression – Portuguese version of the Hospital Anxiety and Depression Scale (20) – scores: normal (0-7); borderline abnormal (8-10); abnormal (11-21). Invitations were sent by email to patients who agreed to participate, to provide access to the online questionnaire.

Acute symptomatic headache was defined as a headache during the COVID-19 symptomatic phase with a maximum duration of 3 weeks. Persistent symptomatic headache was defined as acute symptomatic headache lasting more than 3 weeks but less than 3 months. Migraine symptoms were categorized as "worsened" if there was an increase in intensity or frequency, or both, "unchanged" if no change in headache pattern was noted, or "improved" if there was a reduction in intensity or frequency, or both, during the pandemic.

Preventive treatment history during the pandemic (2020-2022) was retrieved from the participant's medical records. Only drugs tried effectively were considered. Treatment trial was considered effective if undertaken for at least 8 weeks for oral drugs, at least 3 months for monthly injectable antibodies against *calcitonin gene-related peptide* (CGRP mAbs), and at least 6 months for quarterly CGRP mAbs.[21] Treatment with onabotulinumtoxinA was considered effective when improvement in monthly migraine attacks was above 30% after at least 2 cycles of treatment.[22] Oral drugs were also considered on effective minimal doses as follows: propranolol (40 mg daily); metoprolol (25 mg daily); topiramate (25 mg twice a day); sodium valproate (200 mg twice a day); amitriptyline (10 mg daily); venlafaxine (37.5 mg daily); candesartan (8 mg daily); flunarizine (5 mg daily)[23] and zonisamide (above 50 mg daily).[24] Regarding CGRP mAbs, the minimal effective doses considered were the following: erenumab (70 mg monthly); fremanezumab (225 mg monthly or 675 mg quarterly); galcanezumab (120 mg monthly).

Data confidentiality was ensured by pseudonymization, and all patients provided informed consent before accessing and filling out the online questionnaire. The study was approved by the local ethics committee [N/REF.ª 2022.056(045-DEFI/046-CE)].

Statistical Analysis

Demographic and clinical variables related to migraine pattern and treatment, as well as sleep pattern and mood symptoms during the pandemic were compared among patients according to COVID-19 diagnosis and COVID-19 vaccination status. The normality assumption of quantitative variables was assessed through visual methods (Q-Q plots) and normality tests (Kolmogorov-Smirnov test). Fisher exact test and Mann–Withney or Kruskall-Wallis tests were used to analyze the association between categorical and continuous variables, respectively. We reported nominal (categorical) variables as frequencies (percentages), and continuous variables as median and interquartile range (IQR). Statistical significance was set at $p<0.05$. STATA MP® version 14 was used for data analysis. Results are significant if a 2-sided p-value<0.05.

Results

Almost half of the invited subjects (n=388) agreed to take part in the study and filled out the questionnaire (185/48%). The flowchart depicting the study cohort is described in **Fig. 1**. Demographic and clinical characteristics of COVID-19 diagnosis are described in **Table 1**. The majority were diagnosed with episodic migraine (152/82.2%), followed by chronic migraine (33/17.8%). More than half (113/61%) were diagnosed with COVID-19, all with mild illness severity (no hospitalization required) and 9 (8%) with re-infection. The median time from COVID-19 diagnosis to survey was 4 (2-9) months.

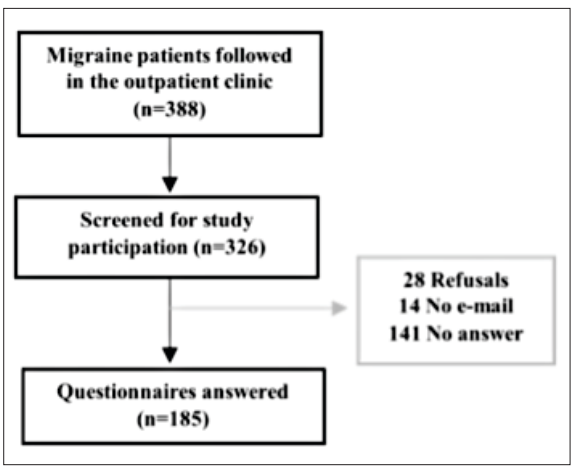

Figure 1. Flow-chart depicting the studied-cohort.

Migraine patients diagnosed with COVID-19 were younger (39 *vs* 45 years; $p=0.02$) and a high frequency of acute symptomatic headache was reported (90/79.7%). In fact, in 51 (56.7%) the headache presented migraine-like features, and more than a quarter (25/27.8%) had a persistent symptomatic headache.

Most of the respondents - 108 (58.4%) - reported a change in their headache pattern since the beginning of the pandemic, but no differences between groups (regardless of COVID-19 infection) were found ($p=0.36$). Headache pattern change was more frequently reported before COVID-19 diagnosis (28/41.2%), followed by up to 3 weeks after infection (21/30.9%). About a third (62/33.5%) reported a change in the pain quality (throbbing to pressing or vice-versa) during the pandemic, regardless of the timing, but higher in the COVID-19 group ($p=0.011$). Around half of the participants (87/47.0%) reported higher intensity and frequency of migraine, while 21 (11.4%) experienced an improvement in migraine symptoms during the pandemic. In this period, over a quarter of patients (31/28.7%) reported the need for acute treatment with intravenous agents and the majority (78/72.2%) intensified their preventive or abortive treatment. Of these, 52 (75.4%) were diagnosed with COVID-19 but no differences were found among groups ($p=0.38$). Additionally, no differences between patients were found regarding migraine-related quality of life (assessed by the MIDAS scale) in the three months prior to the date of survey completion.

COVID-19 diagnosis was significantly associated with sleep pattern change (70/62% *vs* 31/43.1%, $p=0.015$), with a trend toward a higher frequency of intermediate insomnia (44/62.9% *vs* 13/41.9%, $p=0.08$). Moreover, a non-significant higher rate of severe insomnia was reported (12.9% *vs* 6.5%, $p=0.33$). Sleep pattern change was also common among patients who reported change in headache pattern (68/67.3% *vs* 40/47.6%, $p=0.007$) during the pandemic, namely those reporting more intense and frequent headaches. Incidence of abnormal levels of anxiety (48.7%) and depression (33.5%) was high among respondents, with no significant differences among groups.

Patients who experienced acute symptomatic headache tended to report worsening symptoms (48/87.3% *vs* 42/72.4%, $p=0.09$) after COVID-19 (**Table 2**). **Table 3** shows the progression of migraine symptoms during the pandemic (worsened, no change, or improved). Despite a tendency towards a higher number of headache days per month in the previous 3 months before pandemic ($p=0.06$), no significant differences were found among groups concerning migraine severity (MIDAS score).

Patients who reported worsening migraine during the pandemic required significantly more intravenous rescue medication (93.6% *vs* 0% *vs* 6.5%, $p=0.03$) and preventive and/or abortive treatment intensification ($p<0.001$). Topiramate, venlafaxine, and amitriptyline were the most used oral preventive treatments, with no differences among groups. Under a third (48/26%) of participants did not take effective preventive treatment. Only 19% were treated with onabotulinumtoxinA and 4% with CGRP mAbs.

Altered sleep pattern (54/53.5% *vs* 33/32.7% *vs* 14/3.9%, $p=0.024$) and chronic insomnia (47/59.5% *vs* 25/31.7% *vs* 7/8.9%, $p=0.012$) were significantly more frequent in the group with worsening migraine during the pandemic. Prevalence of abnormal levels of anxiety (58.9% *vs* 35.6% *vs* 5.6%, $p=0.005$) and depression (58.1% *vs* 29% *vs* 12.9%, $p=0.002$) were also higher among these patients.

Table 1. Demographic and clinical characterization, total and by COVID-19 diagnosis, during the pandemic.

	Total (n=185)	COVID-19 (n=113/61%)	No COVID-19 (n=72/39%)	*p*-value
Age, median (IQR)	41 (32-49)	39 (29-48)	45 (35-53)	**0.02**
Female, n(%)	165 (89.2)	103 (91.2)	62 (86.1)	0.33
Education, n(%)				0.23
Elementary	25 (13.5)	12 (10.6)	13 (18.1)	
Secondary	62 (33.5)	42 (37.2)	20 (27.8)	
Superior	98 (53.0)	59 (52.2)	39 (54.2)	
Migraine, n(%)				0.72
Episodic	152 (82.2)	58 (51.3)	41 (56.9)	
Chronic	33 (17.8)	22 (19.5)	11 (15.3)	
The average number of days per month with headache in the last 3 months, median (IQR)	10 (6-19)	10 (6-15)	10 (6-25)	0.32
MIDAS score				0.94
I (0-5)	33 (18.1)	19 (17.1)	14 (19.7)	
II (6-10)	19 (10.4)	12 (10.8)	7 (9.9)	
III (11-20)	34 (18.7)	22 (19.8)	12 (16.9)	
IV (21+)	96 (52.8)	58 (52.3)	38 (53.5)	
Headache pattern change, n(%)	108 (58.4)	69 (61.1)	39 (54.2)	0.36
Headache quality change, n(%)				**0.011**
Throbbing to pressing	28 (25.9)	22 (78.6)	6 (21.4)	
Pressing to throbbing	34 (31.5)	25 (73.5)	9 (26.5)	
No change	46 (42.6)	22 (47.8)	24 (52.2)	
Treatment intensification for migraine, n(%)	78 (72.2)	52 (75.4)	26 (66.7)	0.38
Sleep pattern change, n(%)	101 (54.6)	70 (62)	31 (43.1)	**0.015**
Initial insomnia	64 (63.4)	42 (60)	28 (40)	0.37
Intermediate insomnia	57 (56.4)	44 (62.9)	13 (41.9)	0.08
Late insomnia	63 (62.4)	57 (81.4)	24 (77.4)	0.79
Sleep pattern change resolved, n(%)	19 (24.1)	13 (23.2)	6 (26.1)	0.78
Chronic insomnia, n(%)	79 (78.2)	56 (80)	32 (74.2)	0.60
Index of chronic insomnia severity, n(%)				0.33
Below insomnia threshold	53 (52.5)	38 (54.3)	15 (48.4)	
Clinically not relevant insomnia	9 (8.9)	4 (5.7)	5 (16.1)	
Moderate insomnia	28 (27.7)	19 (27.1)	9 (29.0)	
Severe insomnia	11 (10.9)	9 (12.9)	2 (6.5)	
HADS-A, n(%)				0.77
Normal	47 (25.4)	27 (23.9)	20 (27.8)	
Borderline	48 (26.0)	31 (27.4)	17 (23.6)	
Abnormal	90 (48.7)	55 (48.7)	35 (48.6)	
HADS-D, n(%)				0.87
Normal	78 (42.2)	48 (42.5)	30 (41.7)	
Borderline	45 (24.3)	26 (23.0)	19 (26.4)	
Abnormal	62 (33.5)	39 (34.5)	23 (31.9)	

IQR - interquartile range; MIDAS - Migraine Disability Assessment; HADS (Hospital Anxiety and Depression Scale) - anxiety (A) and depression (D).

Table 2. Acute symptomatic headache in patients diagnosed with COVID-19.

	Total (n=113)	<3 weeks	>3 weeks	*p*-value
Acute symptomatic headache, n(%)	113 (100%)	90 (79.7%)	65 (72%)	
Worsened migraine symptoms, n(%)	48 (87.3%)	29 (60.4)	19 (39.6)	0.009

Table 3. Migraine symptoms, associated disability and comorbidities and treatment, during the pandemic.

	Total (n=185)	Worsened (n=87/47%)	No change (n=77/41.6%)	Improved (n=21/11.4%)	*p*-value
Monthly migraine days in the last 3 months, median (IQR)	10 (6-19)	12 (7-25)	10 (6-16)	8 (5-10)	0.06
MIDAS score					0.22
I (0-5)	33 (18.1)	10 (30.3)	18 (54.6)	5 (15.2)	
II (6-10)	19 (10.4)	7 (36.8)	10 (52.6)	2 (10.5)	
III (11-20)	34 (18.7)	16 (47.1)	12 (35.3)	6 (17.7)	
IV (21+)	96 (52.8)	51 (53.1)	37 (38.5)	8 (8.3)	
Treatment intensification for migraine, n(%)	78 (72.2)	73 (93.6)	0 (0)	5 (6.4)	**<0.001**
IV rescue treatment for migraine, n(%)	31 (28.7)	29 (93.6)	0 (0)	2 (6.5)	**0.03**
Migraine preventive treatment, n(%)					
1st line					
Topiramate	69 (37.5)	35 (50.7)	27 (39.1)	7 (10.1)	0.73
Venlafaxine	38 (20.7)	21 (55.3)	14 (36.8)	3 (7.9)	0.50
Amitriptyline	38 (20.7)	20 (52.6)	13 (34.2)	5 (13.1)	0.56
Propranolol	29 (15.8)	15 (51.7)	11 (37.9)	3 (10.3)	0.92
Zonisamide	28 (15.2)	12 (42.9)	14 (50)	2 (7.1)	0.62
Sodium valproate	10 (5.4)	4 (40.0)	4 (40.0)	2 (20.0)	0.59
Candesartan	5 (2.7)	1 (20.0)	3 (60.0)	1 (20.0)	0.33
Metoprolol	3 (1.6)	1 (33.3)	0 (0)	2 (66.7)	0.04
Flunarizine	3 (1.6)	1 (33.3)	1 (33.3)	1 (33.3)	0.48
Nortriptyline	1 (0.5)	1 (100)	0 (0)	0 (0)	1
Total	0 (1-2)	1 (1-2)	1 (0-2)	1 (1-2)	0.46
2nd line					
OnabotulinumtoxinA	35 (19.0)	17 (48.5)	15 (42.9)	3 (8.6)	0.93
CGRP mAbs	8 (4.4)	2 (25.0)	5 (62.5)	1 (12.5)	0.38
Sleep pattern change, n(%)	101 (54.6)	54 (53.5)	33 (32.7)	14 (13.9)	**0.024**
Initial insomnia	64 (63.4)	38 (59.4)	20 (31.3)	6 (9.4)	0.14
Intermediate insomnia	57 (56.4)	34 (59.7)	16 (28.1)	7 (12.3)	0.38
Late insomnia	63 (62.4)	41 (65.1)	15 (23.8)	7 (11.1)	**0.009**
Chronic insomnia, n(%)	79 (78.2)	47 (59.5)	25 (31.7)	7 (8.9)	**0.012**
Index of chronic insomnia severity, n(%)					**0.004**
Below insomnia threshold	53 (52.5)	20 (37.7)	22 (41.5)	11 (20.8)	
Clinically not relevant insomnia	9 (8.9)	3 (33.3)	4 (44.4)	2 (22.2)	
Moderate insomnia	28 (27.7)	22 (78.6)	6 (21.4)	0 (0)	
Severe insomnia	11 (10.9)	8 (72.7)	2 (18.2)	1 (9.1)	
HADS-A, n(%)					**0.005**
Normal	47 (25.4)	14 (29.8)	26 (55.3)	7 (14.9)	
Borderline	48 (26.0)	20 (41.7)	19 (39.6)	9 (18.8)	
Abnormal	90 (48.7)	53 (58.9)	32 (35.6)	5 (5.6)	
HADS-D, n(%)					**0.002**
Normal	78 (42.2)	24 (30.8)	43 (55.1)	11 (14.1)	
Borderline	45 (24.3)	27 (60)	16 (35.6)	2 (4.4)	
Abnormal	62 (33.5)	36 (58.1)	18 (29.0)	8 (12.9)	

IQR - interquartile range; MIDAS - Migraine Disability Assessment; HADS (Hospital Anxiety and Depression Scale) - anxiety (A) and depression (D).

Most patients (171/92.4%) had received two or more doses of a COVID-19 vaccine at the date of the survey. Most (131/72.4%) received Comirnaty (Pfizer), followed by Spikevax (Moderna) (34/18.8%). Change in headache pattern after vaccination was reported by 49 (27.1%) respondents, with worsening headache pattern in 29 (16.0%)

and change in headache quality (throbbing to pressing or vice-versa) in 21 (11.6%). Almost half (12/48%) reported worsening up to 3 weeks after vaccine administration. Of these, 11 (41%) needed acute treatment with intravenous agents. Under a quarter (34/18.8%) eventually needed to intensify preventive and/or abortive treatment after COVID-19 vaccine administration.

Discussion

COVID-19 Infection and Related-Pandemic

Worsening migraine throughout the pandemic has been shown previously. Al-Hashel *et al* studied 1018 patients with migraine using an online survey and showed that more than half of them experienced an increase in migraine frequency and severity, in comparison to the pre-pandemic period.[25] However, many studies included a few patients diagnosed with COVID-19.[9] As a main finding of our study, almost half of the migraineurs reported worsening headache patterns during the COVID-19 pandemic, irrespectively of COVID-19 diagnosis, and treatment intensification was needed in most. The majority reported worsening before the COVID-19 diagnosis. This suggests that other important triggers other than SARS-CoV-2 might have had a significant role in migraine symptoms exacerbation during the pandemic period. In fact, we found that patients who reported worsening headache pattern had significantly higher levels of anxiety and depression, as well as higher frequency of sleep pattern change, especially with chronic insomnia.

In contrast, a fifth of our cohort reported a reduction in headache intensity or frequency. One might speculate that the reduction of work-related stress and/or healthier lifestyle routines adopted during the lockdown period may have contributed to this observation.[26] Other studies have described similar improvements in migraine severity. A previous study reported a similar reduction in headache days per month since the beginning of the pandemic (16%).[27] Verhagen *et al* reported a decrease in daily use of acute treatment and an improvement in well-being scores after the lockdown due to the COVID-19 outbreak despite an unchanged number of headache days per month.[10]

The rate of symptomatic headache was high among migraine patients, many with migraine-like features and persistent headache.[27,28] As in our study, a case-control study demonstrated an association between worsening of migraine-related pain after infection and incidence of acute symptomatic headache related to COVID-19 (58.6% *vs* 34.3%, $p<0.001$).[27] In our study, migraine patients with persistent symptomatic headache also tended to experience a worsening headache pattern. The fact that about half of our cohort had a disabling migraine (52.8% with baseline MIDAS score IV) may partly explain the high rate of persistent symptomatic rate we observed (27.8%).

In our study, a change in pain quality was noticeable in patients diagnosed with COVID-19. This finding is in line with those of Membrilla JA *et al* and Uygun O *et al*.[11,29] Although this change after the infection has been described, the pathophysiology is still unclear. It has been speculated that the pro-inflammatory state induced by the release of large amounts of pro-inflammatory cytokines during the SARS-CoV-2 infection might alter the perception of pain.[30,31]

Despite differences in migraine symptom severity, no differences were found regarding the average number of first-line preventive drugs tried and less than a quarter were given second-line preventive treatment. Moreover, around 1/4 of patients were not effectively taking any first-line preventive drug during the pandemic. However, this does not reflect well-controlled migraine symptoms. In fact, many patients had had to discontinue more than one oral drug due to adverse effects before the therapeutical trial was deemed effective. Others were transitioning to a second-line treatment at the time of the survey and conclusions regarding treatment effectiveness could not be ascertained. Additionally, in our center, it is not uncommon for several oral drugs to be tried before escalating to a second-line treatment.

Half of the participants in our cohort revealed symptoms of abnormally elevated levels of anxiety and a third reported depressive symptoms; of note, more than half of those reported a worsened headache pattern. While anxiety and depression might trigger more migraine attacks, more severe headaches might result in a higher incidence of mood disorders in migraineurs.[4] It has been previously shown that migraine patients are more likely to have experienced severe psychological distress during the COVID-19 outbreak compared to the general population.[25] Importantly, these symptoms were well-balanced among patients diagnosed with COVID-19 and those who remained COVID-free.

Sleep dysfunction is more common in migraine patients than controls, with insomnia being the main symptom.[32] The evidence in the last decades suggests that several areas in the brainstem and diencephalon (mostly

the ventrolateral periaqueductal gray matter and the posterior hypothalamus) are related to both headache and sleep pathways. Also, physiologic data showed the involvement of adenosine, melatonin, and orexin in both sets of disorders and dysregulation of either REM sleep or underlying arousal mechanisms in many headache disorders.[33] A high prevalence of sleep disorders was shown during COVID-19 quarantine and lockdown periods (possibly explained by fear of COVID-19, changes in sleep-wake habits, less light off-time, and delayed sleep onset time).[34] We showed a statistically significant higher frequency of chronic insomnia in patients with a worsened headache pattern. These patients also had a higher severity insomnia index during the pandemic. A significantly greater change in sleep pattern was identified in patients diagnosed with COVID-19, with a trend over a higher incidence of middle insomnia. We found no significant differences in insomnia severity between the groups (COVID-19 *vs* non-COVID-19). Hence, COVID-19-related sleep dysfunction might be part of the causal pathway of the worsening headache pattern in migraine patients after the acute symptomatic phase and even further in time, as sleep dysfunction was shown to be a long persistent symptom in COVID-19 patients.[34]

COVID-19 Vaccination

Despite not being yet listed in the International Classification of Headache Disorders, headache after vaccination was one of the most frequently reported adverse events after vaccination against SARS-CoV-2. Previously reported incidences among vaccine types and doses ranged from 1.4% after Moderna's vaccine administration to 52% after Pfizer's and 57% after AstraZeneca's, respectively.[35] Increased headache duration and pain intensity, as well as increased need to intensify preventive treatment after COVID-19 vaccine administration, has also been previously reported in patients with pre-existing primary headache disorders including migraine.[36-38] Silvestro M *et al* also showed that most patients perceived the headache attacks as "different" from those usually experienced, being characterized by higher pain intensity, longer duration, and reduced responsiveness to usually effective analgesic treatment.[39] In our study, headache pattern change (in intensity, frequency, or pain quality) was predominantly reported shortly after a vaccine administration, although with much lower frequency than acute symptomatic headache related to COVID-19 or during the pandemic overall. Moreover, this pattern change was transient (within the first 3 weeks) in almost half of the patients. The pathophysiological mechanisms of headaches attributed to vaccination against COVID-19 remain unclear. A previously proposed mechanism highlights the possibility that intracellular synthetization of the S glycoprotein of SARS-CoV-2 (by transcription of the gene supplied by the vaccine) might trigger an immune response resulting in migraine exacerbation.[40] Another explanation postulates that transient hyper-excitability of trigeminovascular neurons results in increased pain sensitivity even in patients without an underlying primary headache.[40] In patients with already sensitized trigeminovascular neurons, this trigger might result in pain with further increased duration and intensity.

Our study intended to address whether COVID-19 diagnosis and vaccine administration were significant triggers for migraine symptoms worsening during the pandemic. Major strengths of our study are the high number of included patients diagnosed with SARS-CoV-2-proven infection and the description of mood disorder symptoms and insomnia using validated self-reported scales. Furthermore, our study included patients from a well-characterized cohort of migraineurs according to diagnosis subtype and symptom severity.

This study has, however, several limitations. Firstly, patients recruited from the outpatient clinic are likely to have more severe migraine symptoms. This undermines the extrapolation of results to all migraine patients. One additional challenge is the wide temporal window of symptom fluctuations throughout the three years of the pandemic. Indeed, establishing a temporal relationship between changes in pain pattern and quality with changes in sleep pattern, anxiety, and depressive symptoms is difficult to ascertain. A high no-participation rate might have resulted in selection bias. Finally, negative information processing during the lockdown period might have negatively influenced self-perceived worsening.

Conclusion

Worsening migraine during the COVID-19 pandemic was more likely associated with other factors related to the pandemic rather than to the COVID-19 infection per se. Mood disorder symptoms and more severe chronic insomnia were contributing factors. COVID-19 vaccination might have acted as an additional transitory but less relevant trigger for symptomatic worsening among migraineurs. ■

Contributorship Statement / Declaração de Contribuição

LS: Data curation; Formal analysis; Investigation; Methodology; Software; Roles/Writing - original draft.

AL, AP, AG, AC, BS, IT, MG, MC, MM, RE, SC: Data curation.

IL, CA: Conceptualization; Validation; Writing - review & editing.

DG: Conceptualization; Methodology; Supervision; Validation; Writing - review & editing.

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Supplementary material 1

Caraterização do impacto da COVID-19 e respetiva vacinação na enxaqueca

Este estudo visa estudar o impacto da pandemia na enxaqueca, assim como da COVID-19 (se aplicável) e vacinação para a referida doença. Tendo sido diagnosticado(a) com enxaqueca e sendo seguido(a) no nosso Centro Hospitalar, convidamo-lo(a) a participar neste estudo respondendo a um breve questionário online.

Antes de aceder ao questionário necessitamos que nos autorize a utilizar as suas respostas, acedendo ao nosso consentimento informado:

Garantem que os dados obtidos nas respostas ao questionário serão analisados de forma anonimizada pelos elementos clínicos envolvidos no estudo. Também é garantido que todos os dados relativos à identificação dos participantes neste estudo são confidenciais e que será mantido o anonimato. Posso recusar-me a participar ou interromper a qualquer momento a participação no estudo, sem nenhum tipo de penalização por este facto. Compreendi a informação que me foi dada, tive oportunidade de fazer perguntas e as minhas dúvidas foram esclarecidas (enviar dúvidas como resposta ao *e-mail* que forneceu este *link*). Aceito participar de livre vontade no estudo acima mencionado.

Também autorizo a divulgação dos resultados obtidos no meio científico, desde que esteja garantido o anonimato.

Aceito participar neste estudo_____

Recuso participar neste estudo_____

Se selecionar a opção "Aceito participar neste estudo", segue-se o questionário:

N.º estudo (fornecido no *e-mail*)_____

1. Por favor indique a sua idade: ____

2. Por favor indique o seu sexo: Feminino____ Masculino ____

3. Por favor indique o seu grau de habilitações académicas: ensino básico ___ ensino secundário ___ ensino superior ___

4. Antes da pandemia, quantos dias (em média), costumava ter dores de cabeça? ____

5. Nos últimos 3 meses, quantos dias (em média), teve dores de cabeça? ____

6. Foi lhe diagnosticada COVID-19?

Sim _____
Não _____ (avançar para 12)

7. A infeção por COVID-19 foi confirmada após zaragatoa e análise num laboratório?

Sim _____
Não _____

8. Qual o mês e ano em que foi confirmado? ____/_____

9. Esteve internado devido à COVID-19?

Sim _____
Não _____

10. Em relação à fase em que esteve com COVID-19.

Supplementary material 2

10.1. Teve dor de cabeça?

Sim_____

Não_____ (avançar para 11)

10.2. Essa dor de cabeça foi semelhante à dor da sua enxaqueca?

Sim_____

Não_____

10.3. A dor de cabeça resolveu em quanto tempo?

Até 3 semanas_____

Mais de 3 semanas _____

11. Teve infeção por COVID-19 mais do que uma vez?

Sim _____

Não_____

12. Pense como evoluiu a sua dor de cabeça, desde o início da pandemia.

12.1. A dor de cabeça mudou de intensidade (mais ou menos forte) e/ou frequência (tem dores mais ou menos vezes) e/ou de qualidade (ex: "peso" ou "latejar")?

Sim____

Não____ (avançar para 13)

12.2. Qual foi a alteração?

Mais frequente____

Mais intensa____

Mais intensa e mais frequente_____

Menos frequente____

Menos intensa____

Menos intensa e menos frequente_____

12.3. A qualidade da dor passou de

"Pulsátil" (como se tivesse o coração dentro da cabeça) para "Pressão" (como se tivesse um capacete a apertar a cabeça) ____

"Pressão" (como se tivesse um capacete a apertar a cabeça) para "Pulsátil" (como se tivesse o coração dentro da cabeça) _____

Não alterou _____

2.4. Se teve infeção por COVID-19, em que altura a dor de cabeça alterou de padrão (intensidade, frequência ou qualidade da dor)?

Antes da infeção_____

Até 3 semanas depois _____

Entre 3 semanas e 3 meses depois _____

Supplementary material 3

Mais de 3 meses depois _____

12.5 Precisou, mais frequentemente ou de novo, de medicação administrada pela veia ou injetável para tratar as dores de cabeça?

Sim_____

Não_____

12.6 Foi necessário intensificar a medicação habitual (profilaxia e medicação abortiva) para controlar melhor a dor?

Sim_____

Não_____

13. Foi-lhe administrada vacina contra a COVID-19?

Sim_____ (1 dose ____ 2 doses ou mais ____)

Não_____ (avançar para 14)

13.1 Qual a vacina que lhe foi administrada?

Janssen (Johnson & Johnson) ___

Comirnaty (Pfizer) ___

Vaxzevria (Astrazeneca) ___

Spikevax (Moderna) ___

13.2. Desde que lhe foi administrada pelo menos uma dose, a dor de cabeça mudou de intensidade (mais ou menos forte) e/ou frequência (tem dores mais ou menos vezes) e/ou de qualidade (ex: "peso" ou "latejar")?

Sim____

Não____ (avançar para 14)

13.3. Qual foi a alteração?

Mais frequente____

Mais intensa____

Mais intensa e mais frequente_____

Menos frequente____

Menos intensa____

Menos intensa e menos frequente_____

13.4. O tipo de dor mudou?

Sim_____

Não____ (avançar para 13.7)

13.5. A qualidade da dor passou de

Supplementary material 4

"Pulsátil" (como se tivesse o coração dentro da cabeça) para "Pressão" (como se tivesse um capacete a apertar a cabeça) ____

"Pressão" (como se tivesse um capacete a apertar a cabeça) para "Pulsátil" (como se tivesse o coração dentro da cabeça) _____

Não alterou _____

13.6. Quanto tempo depois da vacina a dor de cabeça alterou de padrão?

Até 3 semanas _____

Entre 3 semanas e 3 meses _____

Mais de 3 meses _____

13.7 Desde que que foi administrada pelo menos uma dose precisou, de novo ou mais frequentemente, de medicação administrada pela veia ou injetável para tratar as dores de cabeça?

Sim_____

Não_____

13.8 Desde que lhe foi administrada a vacina, foi necessário intensificar a medicação habitual para controlar melhor a dor?

Sim_____

Não_____

14. Pense no impacto da dor de cabeça nas suas atividades.

14.1 Em quantos dias, nos últimos 3 meses, faltou à escola ou ao emprego devido às dores de cabeça?

_____

14.2 Quando ainda conseguiu ir à escola ou trabalhar, em quantos dias nos últimos 3 meses a sua produtividade esteve reduzida a metade ou mais, devido às dores de cabeça? (sem contar os dias considerados na pergunta anterior) _____

14.4 Em quantos dias, nos últimos 3 meses, teve de deixar de fazer os seus trabalhos domésticos por causa das dores de cabeça? ___

14.3 Quando ainda foi capaz de fazer os seus trabalhos domésticos, em quantos dias, nos últimos 3 meses, esteve a sua produtividade reduzida a metade ou mais devido à enxaqueca? (sem contar os dias considerados na pergunta anterior) ____

14.4 Em quantos dias, nos últimos 3 meses, teve de faltar a atividades com a sua família, atividades sociais ou de tempos livres por causa das dores de cabeça? ____

15. Pense na qualidade do seu sono, desde o início da pandemia.

15.1 Considera que a qualidade do seu sono alterou, relativamente ao período pré-pandemia?

Sim ____

Não ____ (avançar para 16)

15.2. Por favor, indique qual dos seguintes problemas teve:

15.2.1. Dificuldade em adormecer (demorar mais de 30 minutos)

Sim___ Não___

Supplementary material 5

15.2.2. Dificuldade em manter-se a dormir (despertares superiores a 30 minutos)

Sim___ Não___

15.2.3. Acordar demasiado cedo, antes da hora habitual (pelo menos 30 minutos)

Sim___ Não___

15.2.4. Dias com sonolência excessiva ou períodos de sono diurno

Sim___ Não___

15.2.5. Se respondeu afirmativamente a algum dos anteriores, o problema teve uma duração superior a 3 meses?

Sim_____ Não_____

15.2.6. Houve resolução do(s) seu(s) problema(s) de sono?

Sim_____ (avançar para 16) Não_____

15.2.7. Quanto tempo durou a alteração do padrão do sono?

Menos de 3 meses _____ Mais de 3 meses _____

16. As questões seguintes vão incidir sobre a sua perceção do impacto que a alteração do sono teve na sua vida.

16.1. Na sua perspetiva, quão graves são/foram os seguintes problemas para si? Classifique entre nenhuma, ligeira, moderada, grave ou muito grave.

16.1.1. Dificuldade em adormecer

Nenhuma_____ Ligeira_____ Moderada_____ Grave_____Muito grave _____

16.1.2. Dificuldade em manter-se a dormir

Nenhuma_____ Ligeira_____ Moderada_____ Grave_____Muito grave _____

16.1.3. Acordo demasiado cedo, antes da hora habitual

Nenhuma_____ Ligeira_____ Moderada_____ Grave_____Muito grave _____

16.2. Qual é/foi o grau de satisfação com o seu padrão de sono?

Muito satisfeito _____ Satisfeito _____ Neutro _____ Insatisfeito _____ Muito insatisfeito _____

16.3. Acha que o seu problema do sono interfere (ou interferiu) com o seu funcionamento diário? (ex: fadiga diurna, capacidade para trabalhar, concentração, memória, humor, etc.)

Não interfere nada _____ Pouco _____ Interfere moderadamente _____ Muito _____ Interfere muitíssimo _____

16.4. As outras pessoas notam (ou notaram) o impacto que o seu problema do sono tem na sua qualidade de vida?

Não notam nada _____ Pouco _____ Notam moderadamente _____ Muito _____ Notam muitíssimo_____

16.5. Está (ou esteve) preocupado com o seu padrão de sono?

Nada preocupado_____ Pouco _____ Moderadamente _____ Muito _____ Muitíssimo pouco_____

Supplementary material 6

17. Pense na forma como se sentiu desde o início da pandemia. A sua reação imediata a cada questão será provavelmente mais correta do que uma resposta muito ponderada.

17.1 Senti-me tenso(a) ou nervoso(a)

Quase sempre_____ Muitas vezes_____ Por vezes_____ Nunca_____

17.2 Na maioria dos dias, tive pouco interesse ou prazer nas coisas que costumava gostar

Quase sempre_____ Muitas vezes_____ Por vezes_____ Nunca_____

17.3. Tive uma sensação de medo, como se algo terrível estivesse para acontecer

Sim e muito forte____ Sim, mas não muito forte____ Um poco, mas não me aflige____

De modo algum___

17.4. Fui capaz de rir e ver o lado divertido das coisas

Tanto como antes___ Não tanto como antes___ Muito menos agora___ Nunca___

17.5 Tive a cabeça cheia de preocupações

A maior aprte do tempo___ Muitas vezes___ Por vezes___ Quase nunca___

17.6 Senti-me animado(a)

Nunca___ Poucas vezes___ De vez em quando___ Quase sempre___

17.7 Fui capaz de estar descontraidamente sentido/a e sentir-me relaxado(a)

Quase sempre___ Muitas vezes___ Por vezes___ Nunca___

17.8 Senti-me lento(a), como se fizesse as coisas mais devagar

Quase sempre___ Muitas vezes___ Por vezes___ Nunca___

17.9 Fiquei de tal forma apreensivo(a) (com medo), que até sinto um aperto no estômago

Nunca___ Por vezes___ Muitas vezes___ Quase sempre___

17.10 Perdi o interesse em cuidar do meu aspecto físico

Completamente___ Não dou a atenção que devia___ Talvez cuide menos interesse de sempre___ Tenho o mesmo interesse de sempre___

17.11 Senti-me de tal forma inquieto(a) que não consegia estar parado(a)

Muito___ Bastante___ Não muito___ Nada___

17.12 Pensei com prazer nas coisas que podem acontecer no futuro

Tanto como antes___ Não tanto como antes___ Bastante menos agora___ Quase nunca___

17.13 De repente, tive sensações de pânico

Muitas vezes___ Bastantes vezes___ Por vezes___ Nunca___

17.14 Fui capaz de apreciar um bom livro ou um programa de rádio ou televisão

Muitas vezes___ De vez em quando___ Poucas vezes___ Quase nunca___

Terminamos o questionário, muito obrigado pela sua participação.