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Evaluation of the Impact of the COVID-19 Lockdown in the Clinical Course of Migraine

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Abstract

Objective. Previous studies have demonstrated that emotional stress, changes in lifestyle habits and infections can worsen the clinical course of migraine. We hypothesize that changes in habits and medical care during coronavirus disease 2019 (COVID-19) lockdown might have worsened the clinical course of migraine. **Design.** Retrospective survey study collecting online responses from migraine patients followed-up by neurologists at three tertiary hospitals between June and July 2020. **Methods.** We used a web-based survey that included demographic data, clinical variables related with any headache (frequency) and migraine (subjective worsening, frequency, and intensity), lockdown, and symptoms of post-traumatic stress. **Results.** The response rate of the survey was 239/324 (73.8%). The final analysis included 222 subjects. Among them, 201/222 (90.5%) were women, aged 42.5 ± 12.0 (mean±SD). Subjective improvement of migraine during lockdown was reported in 31/222 participants (14.0%), while worsening in 105/222 (47.3%) and was associated with changes in migraine triggers such as stress related to going outdoors and intake of specific foods or drinks. Intensity of attacks increased in 67/222 patients (30.2%), and it was associated with the subjective worsening, female sex, recent insomnia, and use of acute medication during a headache. An increase in monthly days with any headache was observed in 105/222 patients (47.3%) and was related to symptoms of post-traumatic stress, older age and living with five or more people. **Conclusions.** Approximately half the migraine patients reported worsening of their usual pain during the lockdown. Worse clinical course in migraine patients was related to changes in triggers and the emotional impact of the lockdown.

Key Words: Headache; COVID-19; SARS-CoV-2; Migraine; Lockdown

Introduction

Migraine is a highly prevalent disease with rates of up to 21.7% for women [1] that frequently affects the working population [2]. A global burden of migraine study has published that the global migraine prevalence is 14.4% (18.9% for women and 9.8% for men) [3]. This prevalence is in line with recent data from the United States, with a prevalence rate of 15.0% (20.3% for women and 9.5% for men) [4], and this rate has been reported to be similar in China for the total population (14.3%, a different percentage compared to that reported in the global burden study) but lower in Japan (6.0%) [5]. There are triggers [6] and aggravating [7] factors for migraine attacks, including emotional stress [8] and changes in lifestyle such as sleep disturbances [9], food consumption, and physical exercise [10]. Furthermore, the prevalence of psychiatric comorbidity in migraine patients is frequent [11, 12], with anxiety [13] and depression [14] prevalence being higher in these patients than in the general population. It must be noted that these commented triggers have also been reported in tension-type headache [15], and higher prevalence of anxiety and depression has also been identified in these patients [16].

Recent studies have shown that the novel coronavirus disease 2019 (COVID-19) lockdown has caused a psychological impact on the general population in which higher levels of stress, anxiety and symptoms of post-traumatic stress have been observed [17]. In this context and for the rest of the text, lockdown is referred to as confinement in which people are required to stay in their homes with restricted activities outside home involving public contact. In this sense, the clinical course of migraine can worsen after situations of intense stress [18]. The pandemic and the consequent situation of lockdown have also caused changes in the lifestyle habits [19, 20] of the patients with migraine that could have impacted their migraine.

In addition, access to healthcare has been modified during the COVID-19 pandemic [21]. In-person consultations in headache units have been reduced, hindering access to treatments [22]. Telemedicine, mainly conducted through telephone consultations, was implemented in order to reduce the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission between healthcare providers and patients [23], leaving the number of face-to-face consultations in the minimum necessary, like treatments that require in-person intervention [24]. Telemedicine has led to increased access for healthcare in patients with migraine, as it has been reported before the COVID-19 pandemic, with higher convenience and shorter visit times compared to in-person visits, with no negative impact on headache days or migraine severity [25]. Telemedicine has also been reported to be noninferior and as safe and efficient as in-person consultations in nonacute headaches and medication overuse headache [26, 27].

To our knowledge, there are two previous studies reflecting the impact of the COVID-19 disease pandemic on migraine in Italian [28] and Kuwaiti populations [29]. Our hypothesis was that the rigorous lockdown of eight weeks and its consequences, related to changes in lifestyle habits and access to treatments and in-person consultations, may have worsened the health of the patients with migraine. In relation to in-person consultations, we also evaluated the possible effect of telemedicine (telephonic or email contact). In Spain, the rigorous lockdown implied that no activities outside home were allowed with some exceptions such as going to the hospital, doing the shopping (only indispensable products) or going to work, which was also restricted during some days. The objective of this work is to evaluate the possible influence of these changes related to the COVID-19 pandemic, including its psychological impact, on the clinical course of the patients with migraine.

Methods

The study was approved by the Ethics Review Board of Valladolid East health area (PI 20–1832), based in the Hospital Clínico Universitario de Valladolid (Valladolid, Spain). The study settings were the reference headache units of three academic hospitals sited in Madrid, Valladolid, and Zaragoza, Spain. We performed a retrospective study with a single data collection (one set of responses per person in a unique period of time) in patients with migraine following the STROBE guidelines for observational studies [30]. The data collection method was a web-based survey composed of 108 questions. The survey was launched on June 2nd and remained open until July 22nd, 2020. In Spain, the state of alarm and the consequent lockdown in the whole country began on March 14th, and finished on June 21st, with some relaxation measures from mid-May in some specific regions. Data about the situation before and during lockdown were gathered, considering that in Spain the most restrictive lockdown measures ceased to be applied when the survey was launched, and no lockdown measures remained when the survey was closed. Additional details of the survey and data collection are provided at the end of this subsection and the "Survey instrument" subsection. Variables related to migraine and any headache, lockdown, and symptoms of post-traumatic stress were collected. An evaluation of the "change in the state of the migraine" was carried out, for which the situation, measured by maximum intensity of migraine episodes and monthly headache (any headache, including migraine) and migraine days, before and after the pandemic was compared in each subject, as well as its relationship with the other variables.

The combined variable "migraine status" during lockdown was obtained based on the overall self-reported feeling of each patient. Number of headache and

migraine days per month and/or maximum intensity of the migraine attacks before the lockdown (median of the previous three months) and during the last month of lockdown were gathered from the headache diary.

Participants

All consecutive patients with a migraine diagnosis made by a headache specialist, that were being followed-up in three reference headache units were invited to participate in the study. Patients were asked to define the frequency of any headache and migraine and maximum intensity of migraine attacks according to their headache diary as the local standard of care, using numerical values. The survey was distributed through email after telephonic contact or in-person appointment in a Headache Unit to patients who had been seen by a neurologist specialized in headache prior to lockdown. It is worth noting that the patients from the in-person appointments were cited before the beginning of the lockdown, and there were no visits planned because of the need for immediate care during the confinement. Inclusion criteria were patients with a diagnosis of migraine according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) [31], voluntary participation in the survey, and suffering from migraine at least for one year. Exclusion criteria were serious neurological or systemic disease that could hinder understanding or communication, age under 18 years, positive diagnosis of COVID-19 via polymerase chain reaction (PCR) or suspected by a primary care physician, and presence of headache disorders different to migraine, except infrequent tension-type headache and medication overuse headache. Verbal informed consent to participate in the study was obtained from all participants, with an additional confirmation through the survey platform.

Survey Instrument

The web-based survey questions were related to demographic and clinical data, migraine treatment and triggers, specific migraine and headache characteristics, and post-traumatic stress. The survey followed the guidelines from the Checklist for Reporting Results of Internet E-survey [32]. The unique criterion not met from the checklist was that there was no "rather not to say" option in the mandatory questions. In contrast, the participants had the option to leave the survey at any moment before the final submission. In that case, no answer from the subject was stored. The link to the survey was provided via email.

Concerning the response variables of this study, the survey included questions about the self-perceived subjective worsening of migraine during lockdown (better, similar, or worse than before the lockdown). This variable was used to summarize the diverse aspects related to the migraine experience. The other response variables gathered from the survey were the maximum intensity of migraine attacks, and the frequency of headache and migraine, all of them obtained according to the headache diary fulfilled by the patients. More details about these variables are detailed in the following paragraphs of this section and in the statistical analysis subsection. The remaining variables extracted from the survey were employed as covariates and are commented in the following paragraphs of this subsection, together with the previous response variables.

The first group of questions was referred to demographic data, age of migraine onset, need of neurological evaluation related to migraine during the lockdown, everyday situations before and during the lockdown, insomnia and diagnosed anxiety and depression before and during the lockdown (including need of specific treatment for those), and current perceived stress related to going outdoors. The assessed variables can be found in the Supplementary Data.

In the second group of questions, the patients were asked to clarify diverse aspects related to their symptomatic and preventive treatment, previous presence of migraine triggers and possible changes in them during the lockdown, and self-perceived overall change in the migraine status (subjective worsening). These variables are detailed in the Supplementary Data.

The third group included questions about the maximum intensity of migraine episodes and monthly frequency of headache and migraine before the lockdown (three months) and during the last lockdown month, and a comparison of migraine symptoms during the lockdown with respect to the baseline. The variables of this group are thoroughly described in the Supplementary Data.

Finally, the participants were asked about clinical symptoms related to COVID-19 and symptoms of post-traumatic stress at the moment that the survey was answered. The psychological impact of the lockdown was assessed using the impact of event scale (IES) [33]. We employed the IES to analyze the psychological response specifically related to the COVID-19 lockdown, as it has been performed with previous epidemics, such as the quarantine associated with the severe acute respiratory syndrome epidemic in Canada in 2003 [34].

The IES is composed of 15 items, and each of them follows a four-option Likert type scale (0 = not at all, 1 = rarely, 3 = sometimes, 5 = often). This tool was conceived to evaluate subjective distress because of a traumatic life event. The primary cluster includes items from the clinically derived intrusion subset with seven items, while the second cluster was composed of eight items of clinically derived avoidance items. The intrusion subscale is related to intrusive thoughts and feelings or imagery, nightmares, and dissociative-like re-experiencing. The avoidance subscale is associated with impaired response capacity, and evasion of feelings, situations, and ideas. In this study, we employed the Spanish validated version of IES [35], which has shown good psychometric properties.

The symptoms of post-traumatic stress were assessed to evaluate the specific response of the patients to the restrictive COVID-19 lockdown, which may be different compared to symptoms of a more general stress.

Statistical Analysis

For the nominal and ordinal variables, group proportions were obtained, while for the interval and ratio variables, mean, standard deviation, median, and interquartile range were calculated. Ordinal variables were treated like the nominal variables, considering the negative value (absence) as the reference category for the analysis, or the quantitative version was directly used when possible. In the case of the interval and ratio variables related to intensity of migraine attacks and frequency of headache and migraine, the subtraction of the value during and before the lockdown was used for the analysis and described using the same values as the interval and ratio variables. Cronbach's alpha was used to evaluate the reliability of the IES subscales, obtaining the 95% confidence interval (95% CI) with 1,000 bootstrap samples. A threshold alpha value of 0.8 (or greater) was considered as a very good level of reliability, while a value of 0.7 was an acceptable level of reliability.

To evaluate whether the worsening and improvement of migraine during the lockdown were different to that expected by chance, we performed a binomial test ($P = 1/3$ as null hypothesis, according to worsening, similar situation, and improvement). The subjective worsening and improvement were obtained from the direct answer from the participants (more details in the Supplementary Data). The worsening and improvement of the frequency of headache and migraine, and intensity of attacks, were obtained according to the difference of the numerical values reported by the patients according to their headache diary.

Our first outcome was the self-reported status of migraine during the lockdown. We compared a reported worsening of the migraine against an improved or similar situation during the lockdown. A logistic regression model was employed for the assessment of this outcome. The same analysis was repeated for the secondary outcomes, which were each of the characteristic migraine symptoms.

For the analysis of the other outcomes, that is, intensity of migraine attacks, and the frequency of headache and migraine, generalized linear models (GLM) with a Gaussian distribution were used to assess their association with the independent variables described at the Survey instrument subsection. The response variable in each of the three cases was the difference between the value during the last month of lockdown, and the median value of the 3 months before the lockdown. For the three variables, a paired sample *t*-test was carried out to determine whether the lockdown has modified the intensity and headache and migraine frequency. As secondary analysis, the assessment of the univariate models for each primary outcome was performed.

The final multiple GLM was built in two steps. In the first step, we obtained an initial estimation of the final model following an automatic stepwise strategy, with forward and backward steps, in combination with the Akaike's information criterion (AIC) [36]. The second step followed a backwards strategy from the model of the first step, and those variables with uncorrected *P* values $> .05$ were removed one by one, starting with the variable with the highest *P* values, until the AIC value was 1% higher than the value of the model from the first step, or the contribution of the diverse statistically significant variables (uncorrected *P* values) was considerably altered. The objective of the second step was on the one hand to reduce the number of variables to avoid overfitting, considering the high number of assessed variables, and on the other hand to focus on the individual effect of the analyzed variables rather than to obtain a better prediction model.

To assess multicollinearity, the variance inflation factor was employed, and a value of 10 was used as a threshold to consider an important effect of multicollinearity. In case of collinearity, the affected variables were revised and one of the variables was removed. The model selection with the remaining variables and the multicollinearity analysis were repeated until no variance inflation factor value over 10 was found.

Another secondary analysis was performed. To measure the association between the subjective worsening of the migraine and the intensity of migraine, and frequency of headache and migraine (difference between during and before the lockdown), the point biserial correlation coefficients were obtained. Furthermore, to assess the reliability between the frequency and intensity measures between the two time points, during and before the lockdown, we calculated the Pearson's *r* correlation value.

A *P* values of .05 (two-tailed testing) was set as the threshold for statistical significance. Multiple comparisons were corrected by a false discovery rate (FDR) procedure with the Benjamini-Hochberg method [37], including the set of *P* values from the pertinent GLM in the correction. R statistical software, version 3.5.2, was used for the analysis. No previous sample size estimation was carried out. The survey was closed when there were either no answers or barely new answers during three consecutive days (excluding weekends). The survey was prepared in a way that all single- or multiple-choice questions were mandatorily answered, so there were no missing data in the corresponding variables. In other questions where the respondents should write the answer (e.g., feedback questions and indicate the personal preventive treatment), except those related to age and duration of migraine (mandatory answer), the answer was considered as "no" or "absence"; for example, use of topiramate was considered only if the patients wrote this option clearly.

Results

The survey was answered by 239 patients with migraine. The response rate was 239/324 (73.8%). Seventeen patients presented positive diagnosis of COVID-19 (via RT-PCR or suspected by a primary care physician) and were discarded from the analysis to avoid any possible bias caused by the infection, that is, a possible headache associated with COVID-19 different to migraine. The most important characteristics of the patients who presented a positive diagnosis of COVID-19 are described at the end of the Results section, with no statistical tests due to the low sample size. Among the remaining 222 patients, 201 were women (90.5%), aged 42.5 ± 12.0, with duration of migraine 23.5 ± 13.4 years. The migraine symptom with the highest percentage of worsening during the lockdown was increased allodynia (37/222; 16.7%), and the symptom with the lowest percentage was osmophobia (10/222; 4.5%).

More than half of the sample (125/222; 56.3%) presented moderate or severe post-traumatic stress scores according to IES, with similar scores for intrusion (13.8 ± 9.1, α = 0.87 [0.84, 0.90]) and avoidance (15.0 ± 9.2, α = 0.83 [0.79, 0.85]) items. The alpha value over 0.8 shows a very good level of reliability for the intrusion subscale, and in the case of the avoidance subscale, taking into account the limits of the confidence interval, the reliability would be acceptable.

The main demographic and clinical characteristics, including the description of post-traumatic symptoms, are shown in Table 1. The complete descriptive analysis can be seen in the Supplementary Data.

Migraine Status during the Lockdown

A total of 105/222 (47.3%) patients reported subjective worsening of migraine during the lockdown, while in 31/222 patients (14.0%) subjective improvement was described. Both proportions of subjective worsening (P values < .001) and improvement ($P < .001$) were significantly (statistically) different from the proportion expected by chance. Among the 105 patients with worsened status, 38/105 of them (36.2%) reported a severe subjective worsening of the migraine. Migraine change during the lockdown can be seen in Figure 1.

Regarding the primary analysis, in the model with several predictors, after multiple comparisons correction, subjective migraine change during the lockdown was significantly associated with changes in any migraine trigger, feeling a lot of stress related to going outdoors, and intake of specific food or drink as a migraine trigger. The model values were odds ratio (OR) = 5.5 (corrected $P < .001$) for changes in triggers, OR = 10.8 (corrected $P = .043$) for stress related to going outdoors, and OR = 2.72 (corrected $P = .043$) for intake of food variables. The complete results from the logistic regression model are shown in Table 2. Regarding a secondary analysis of the data, we asked the patients to report the reason for the change in their subjective worsening of migraine during the lockdown. According to the patients' answers, changes related to migraine worsening were altered employment status, including remote working and high work pressure, higher levels of stress, anxiety and worries, insomnia, wearing a face mask at work and being confined. Moreover, 47/222 (21.2%) patients also reported problems to acquire their medication, or that the beginning of a new treatment was delayed, although only some of these patients reported this issue as a serious problem during the lockdown (the answer to the associated question was optional).

The secondary analysis with the univariate models with statistically significant results and with the variables included in the model is shown in the Supplementary Data.

With respect to the secondary analysis of the association between the subjective worsening and the numerical main variables from the headache diary, we obtained a point biserial correlation value of $r_{pb} = 0.51$ with intensity of attacks, $r_{pb} = 0.33$ with frequency of headache, $r_{pb} = 0.37$ with frequency of migraine.

Intensity of Migraine Attacks

Mean intensity of migraine attacks increased during the lockdown in 67/222 (30.2%) patients, while in almost a quarter (54/222; 24.3%) it decreased. Proportion of decrease was significantly (statistically) different from that expected by chance ($P = .004$), with no significant difference in the case of increase ($P = .355$). There was no statistically significant difference between the intensity of attacks during (7.4 ± 2.5) and before (7.5 ± 1.9) the lockdown ($t = -0.56$, $P = .575$). In Figure 2A, the changes in intensity are depicted. The correlation between the intensity values from the two time points, during and before the lockdown, was $r = 0.49$ ($P < .001$), showing a moderate relationship.

After FDR correction, the primary analysis showed that higher intensity of migraine attacks during the lockdown was positively associated with female sex, need of neurological evaluation related to migraine during the lockdown, insomnia during the lockdown, specific food and/or drinks as migraine triggers, feeling a lot of stress related to going, and need of analgesics as symptomatic treatment. The model coefficients were β = 1.33 (corrected $P = .017$) for female sex, β = 0.81 (corrected $P = .017$) for need of neurological evaluation, β = 0.93 (corrected $P = .021$) for insomnia during lockdown, β = 0.88 (corrected $P = .017$) for specific food/drinks, β = 1.79 (corrected $P = .017$) for stress related to going outdoors, and β = 0.86 (corrected $P = .017$) for analgesics as symptomatic treatment variables. Lower intensity of migraine attacks was associated with the current use of onabotulinumtoxin-A as preventive treatment (β = −0.70, corrected $P = .045$) and changes in sleep as

Table 1. Main characteristics of the patients with migraine

Characteristics (N = 222)	Number (%)	Mean ± SD	Median [IQR]
Age	N/A	42.5 ± 12.0	43.5 [19.0]
Sex		N/A	N/A
Male	21 (9.5)		
Female	201 (90.5)		
Duration of migraine (years)		23.5 ± 13.4	22.0 [22.5]
Difference between during and before the lockdown			
Subjective worsening of migraine	105 (47.3) ***	N/A	N/A
Subjective improvement of migraine	31 (14.0) ***	N/A	N/A
Intensity of migraine attacks (1–10)		−0.1 ± 2.3	0.0 [1.0]
Worsening	67 (30.2) ˙		
Improvement	54 (24.3) **		
Frequency of headache (days/month)		1.6 ± 7.6	0.0 [6.0]
Worsening	105 (47.3) ***		
Improvement	59 (26.6) *		
Frequency of migraine (days/month)		0.6 ± 6.8	0.0 [5.0]
Worsening	84 (37.8) ˙		
Improvement	78 (35.1) ˙		
IES (symptoms of post-traumatic stress)		28.7 ± 16.7	29.5 [27.0]
Subclinical (IES < 9)	31 (14.0)		
Mild (9 ≤ IES ≤ 25)	66 (29.7)		
Moderate (26 ≤ IES ≤ 43)	81 (36.5)		
Severe (IES > 43)	44 (19.8)		
IES-avoidance		15.0 ± 9.2	16.0 [14.0]
IES-intrusion		13.8 ± 9.1	12.0 [15.0]

N/A= not applicable; IQR = interquartile range; SD = standard deviation.
Results for the binomial test ($P = 1/3$): *** $P < .001$, ** $P < .01$, * $P < .05$, ˙ $P \geq .05$ (all P values were two-sided).

migraine trigger (β = −1.02, corrected $P = .045$). The complete results are depicted in Table 3.

In the model shown in Table 3, it is worth noting that previous insomnia and insomnia during the lockdown followed opposite trends, that is, there was an apparent reduction of intensity of migraine attacks during lockdown in patients with previous insomnia (β = −0.53), but an increase in the case of insomnia during lockdown (β = 0.93). Frequency of insomnia has increased during the lockdown period in our sample (from 108/222, 48.1%, to 156/222, 70.3%), and most of the patients with previous insomnia suffered from insomnia during the lockdown (100/108, 92.6%). Migraine attack intensity increased almost one point (0.93; maximum intensity = 10) in people with new onset of insomnia (no previous insomnia and present insomnia developed during the lockdown) adjusting by the effect of the other covariates. However, this increase of the intensity was lower in those patients with insomnia before and during the lockdown (0.93–0.53 = increase of 0.40 points compared to patients with no insomnia).

The secondary analysis with the univariate models with statistically significant results and with the variables included in the model is shown in the Supplementary Data.

Frequency of Headache

In 105/222 (47.3%) patients, the headache frequency increased during the lockdown, while it was reduced in approximately a quarter (59/222; 26.6%). Both proportions of increase (P values < .001) and decrease ($P = .033$) were significantly (statistically) different from the proportion expected by chance. A statistically significant increase in the number of monthly days with headache was observed ($t = 3.21$, $P = .002$) during the lockdown (14.7 ± 8.8) in comparison with the period before the lockdown (13.1 ± 8.5). In Figure 2B, the changes in frequency of headache are depicted. The correlation between the headache frequency values from the two time points, during and before the lockdown, was $r = 0.61$ ($P < .001$), showing a moderate relationship.

After FDR correction, statistically significant associations between higher frequency of headache, and the IES score, living with five or more people in the same home, age, and use of topiramate as preventive treatment were found. The model coefficients were β = 0.10 (corrected $P = 0.010$) for IES, β = 9.40 (corrected $P = 0.037$) for living with five or more people, β = 0.11 (corrected $P = 0.037$) for age, and β = 3.79 (corrected $P = 0.037$) for use of topiramate as preventive treatment variables. Lower frequency of headache was associated with previous insomnia (β = −2.40, corrected $P = .041$) and weather changes as migraine trigger (β = −2.96, corrected $P = .043$). The complete results can be found in Table 4.

The secondary analysis with the univariate models with statistically significant results and with the variables included in the model is shown in the Supplementary Data.

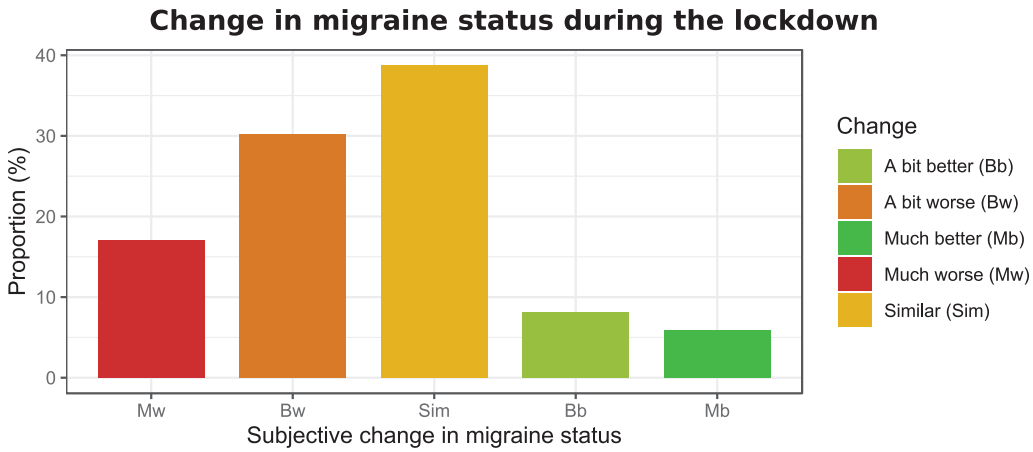

Figure 1. Self-reported subjective change of migraine status.

Table 2. Multiple logistic regression model for overall change in migraine

	Odds Ratio and 95% CI	Unadjusted *P*-Value	Adjusted *P*-Value (FDR)
Independent term	.45 [.14, 1.35]	.161	.187
Living with a baby	.210 [.040, .855]	.041	.107
Previous diagnosis of anxiety	1.90 [0.88, 4.16]	.104	.167
Medication for anxiety (dose)			
No changes vs none	.234 [.068, .717]	.014	.072
Higher vs none	.367 [.104, 1.246]	.111	.167
Diagnosis of depression during confinement	3.47 [.67, 19.35]	.141	.185
Previous insomnia	.48 [.22, 1.01]	.058	.121
Insomnia during confinement	1.85 [.80, 4.37]	.155	.188
Physical activity after confinement			
Lower vs no	.347 [.142, .817]	.017	.072
Equal vs no	.58 [.25, 1.32]	.198	.219
Higher vs no	.301 [.103, .828]	.023	.080
Stress related to going outdoors			
Some vs no	1.09 [.54, 2.18]	.803	.843
A lot vs no	10.8 [2.2, 70.4]	.006	**.043**
Changes in sleep as migraine trigger	2.32 [1.00, 5.56]	.053	.121
Food/drink as migraine trigger	2.72 [1.39, 5.48]	.004	**.043**
Weather changes as migraine trigger	.52 [.22, 1.19]	.123	.172
Familiar pressure as migraine trigger	.55 [.27, 1.10]	.094	.165
Change in any migraine trigger	5.5 [2.7, 12.2]	<.001	**<.001**
Use of analgesics	2.05 [1.07, 4.00]	.031	.094
Use of opiates	4.1 [0.9, 23.3]	.083	.158

Lower dose of medication for anxiety was removed from the table due to very low sample size (one subject) which produced illogical values. The sample size was N = 222. CI = confidence interval; FDR = false discovery rate.

Frequency of Migraine

In approximately a third of the patients (84/222; 37.8%) the migraine frequency increased, while it was reduced in a lower proportion of patients (78/222; 35.1%). There was no statistically significant difference for the increase ($P = .155$) or the decrease ($P = .570$) compared to the proportion expected by chance. No statistically significant change in the number of monthly days with migraine was appreciated ($t = 1.23$, $P = .220$) during the lockdown (10.6 ± 8.5) with respect to the previous period (10.0 ± 8.0). In Figure 2C, the changes in frequency of migraine are depicted. The correlation between the migraine frequency values from the two time points, during and before the lockdown, was $r = 0.66$ ($P < .001$), showing a moderate relationship.

After FDR correction, no statistically significant results were obtained in the primary analysis. The complete results can be found in Table 5.

The secondary analysis with the univariate models with statistically significant results and with the variables included in the multiple GLM is shown in Supplementary Data.

Figure 3 includes a summary of the main factors associated with the subjective worsening of migraine during the COVID-19 lockdown.

Patients with a Positive Diagnosis of COVID-19

Regarding the COVID-19 severity, 16/17 (94.1%) patients could stay at home with no severe complications associated with COVID-19, while the other patient was

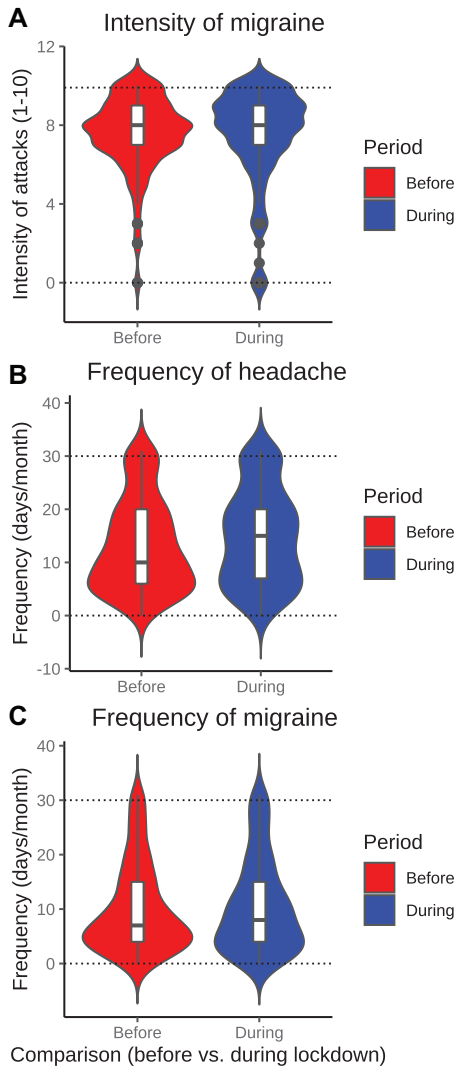

Figure 2. Comparison of the intensity of migraine attacks, and frequency of headache and migraine before and during the COVID-19 lockdown. Minimum intensity reported value was 0 (no attacks in the specified period), and maximum value was 10. Minimum frequency of headache and migraine reported value was 0 (no attacks in the specified period), and maximum value was 31.

admitted to an Intensive Care Unit because of COVID-19. Thirteen patients were women (76.5%), aged 44.1 ± 8.6, with duration of migraine 25.4 ± 11.3 years.

Compared to the 3 months prior to the COVID-19 infection, during the month with the infection, 9/17 (52.9%) patients reported subjective worsening of migraine during the lockdown, a similar percentage with respect to the patients with no diagnosis (47.3%), while in 4/17 patients (23.5%) subjective improvement was described. Mean intensity of migraine attacks increased during the month with the infection in 9/17 (52.9%) patients, a higher percentage with respect to the patients with no diagnosis (30.2%), while in 5/17 patients (29.4%) it decreased. In 10/17 (58.8%) patients, the headache frequency increased during the lockdown, a higher percentage with respect to the patients with no diagnosis (47.3%), while it was reduced in 4/17 patients (23.5%). In 9/17 patients (52.9%) the migraine frequency increased, a higher percentage with respect to the patients with no diagnosis (37.8%), while it was reduced in 5/17 patients (29.4%).

Discussion

The objective of the study was the evaluation of the effect of the COVID-19 lockdown on the clinical course of migraine. To that end, we assessed the subjective worsening of migraine and the difference between intensity of migraine attacks and monthly frequency of headache and migraine before and during the lockdown. We found out that in almost half of the patients the clinical course of migraine worsened according to their subjective impression, probably related with changes in their triggers. The most important triggers were either related to changes in their employment status and/or workload, or emotional alterations derived from lockdown. Regarding the effect of missed in-person consultations and the access to treatments, we found no statistically significant associations with the subjective worsening of migraine, migraine attack intensity or monthly days with headache and migraine. Moreover, with respect to telemedicine, we found no additional positive or particular negative effect related to telemedicine, i.e., telephonic or email contact with the neurologist. This last result may suggest that telemedicine has similar benefits compared to in-person consultations, especially in the patients who do not require specific care procedures (e.g., onabotulinumtoxin-A infiltration).

With respect to the data collected from the headache diaries, this article provides high quality and reliable data. It is worth pointing out that only patients who were being followed-up for at least one year at specialized Headache Units in Spain were recruited. These patients are well educated in migraine management and fulfill a monthly headache diary including days with migraine and any headache as well as days in need of medication intake. Moreover, in our Headache Units, following a headache diary is required for the use of certain treatments such as monoclonal antibodies or onabotulinumtoxin-A treatment. Thus, patients included in the study are optimal candidates and provide advantage for the reliability of the data obtained from the headache diary as compared with patients who are followed in the General Neurology outpatient service.

Self-Perceived Worsening of Migraine

First, our results showed that the proportion of the patients with self-perceived worsening of migraine was higher with respect to the proportion expected by chance. This result is in line with an increase in migraine severity reported in a study conducted in Kuwait [29], where the proportion of increased severity during COVID-19

Table 3. Generalized linear model for intensity of migraine attacks

	Coefficient and 95% CI	Unadjusted *P*-value	Adjusted *P*-value (FDR)
Independent term	−1.66 [−2.84, -.48]	.006	.017
Female sex	1.33 [.35, 2.30]	.009	**.017**
Contact with primary care physician	−.56 [−1.15, .02]	.061	.077
Need of neurological evaluation during confinement	.81 [0.22, 1.40]	.007	**.017**
Previous diagnosis of anxiety	−.52 [−1.17, .14]	.124	.134
Diagnosis of depression at the beginning of confinement	.94 [.00, 1.87]	.051	.071
Previous insomnia	−.53 [−1.18, .12]	.109	.127
Insomnia during confinement	.93 [.21, 1.65]	.012	**.021**
Stress related to going outdoors			
Some vs no	−.22 [−.84, .41]	.497	.497
A lot vs no	1.79 [.47, 3.12]	.009	**.017**
Changes in sleep as migraine trigger	−1.02 [−1.76, −.28]	.008	**.017**
Food/drink as migraine trigger	.88 [.30, 1.46]	.003	**.017**
Use of analgesics	.86 [.28, 1.43]	.004	**.017**
Use of Onabot A	−.70 [−1.32, −.08]	.029	**.045**

CI = confidence interval; FDR = false discovery rate; Onabot A = onabotulinumtoxin-A. The sample size was N = 222.

Table 4. Generalized linear model for headache frequency (days/month)

	Coefficient and 95% CI	Unadjusted *P*-value	Adjusted *P*-value (FDR)
Independent term	−4.61 [−10.07, .86]	.100	.120
IES score	.10 [.04, .16]	<.001	**.010**
Age	.11 [.03, .20]	.007	**.037**
Number of people in the same home			
1 vs alone	−.63 [−4.55, 3.30]	.755	.755
2–4 vs alone	1.30 [−2.47, 5.08]	.499	.545
5 or more vs alone	9.40 [2.10, 16.69]	.012	**.037**
Previous diagnosis of depression	−2.59 [−5.23, 0.06]	.057	.091
Depression at the beginning of confinement	3.17 [−.25, 6.59]	.070	.094
Previous insomnia	−2.40 [−4.35, −.45]	.017	**.041**
Food/drink as migraine trigger	1.92 [−.08, 3.91]	.061	.092
Weather changes as migraine trigger	−2.96 [−5.47, −.45]	.022	**.043**
Use of topiramate	3.79 [.93, 6.65]	.010	**.037**

The sample size was N = 222. CI = confidence interval; FDR = false discovery rate.

Table 5. Generalized linear model for migraine frequency (days/month)

	Coefficient and 95% CI	Unadjusted *P*-Value	Adjusted *P*-Value (FDR)
Independent term	−.61 [−4.93, 3.70]	.781	.781
IES score	.07 [.01, .12]	.018	.061
Female sex	3.09 [.10, 6.08]	.044	.061
Problems to acquire medication	2.01 [−.32, 4.34]	.092	.107
Changes in treatment application	−2.32 [−4.55, −.08]	.043	.061
Stress as migraine trigger	−4.00 [−7.38, −.62]	.021	.061
Use of topiramate	2.70 [.10, 5.31]	.043	.061

The sample size was N = 222. CI = confidence interval; FDR = false discovery rate.

lockdown was higher compared to our study (64.1% compared to 47.3%). These results reflect that the lockdown may be negatively related to the clinical course of migraine in a considerable proportion of patients because of possible changes in the routine.

According to our results, the self-perceived worsening was associated with changes during lockdown at least in one migraine trigger, patients with food or drinks as migraine trigger, and stress related to going outdoors. Among migraine triggers, it is known that stress is an important trigger for migraine [8], and COVID-19 lockdown has caused stressful situations in concordance with the patients' feedback and a previous study [38]. Therefore, a possible increase of stress related to the COVID-19 crisis seems to be linked to the clinical course of migraine during lockdown. Other events such as changes in the employment status or the lockdown itself may have also contributed to the self-perceived worsening. Regarding the worsening of migraine with possible relation to the diet, changes in eating habits have been reported during the pandemic [39], which would be in line with the commented results and might have altered

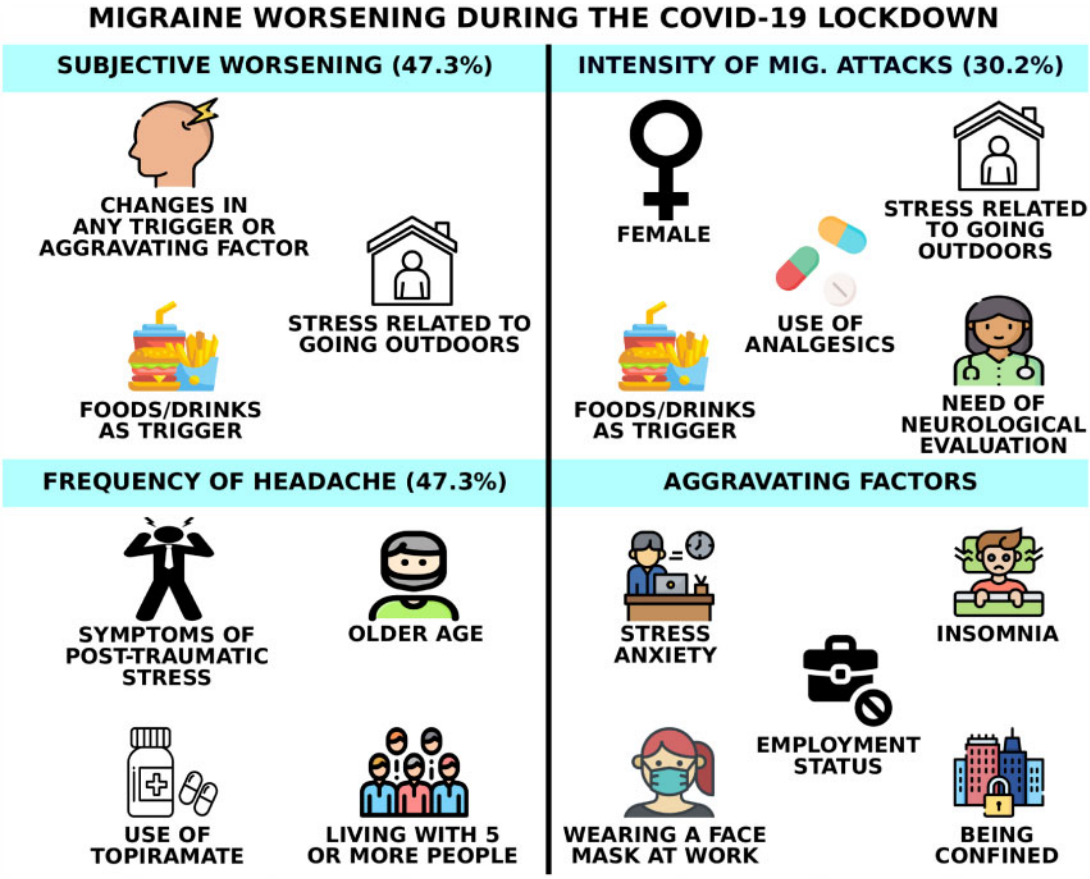

Figure 3. Factors associated with migraine worsening during the COVID-19 lockdown. Aggravating factors reported by the patients are also presented. MIG: migraine.

the clinical course of migraine. Moreover, the increased stress and changes in routines during the COVID-19 pandemic have been pointed out as important factors in the development of seizures in patients with epilepsy, an episodic neurological disorder influenced by similar triggers compared to those of migraine [40].

Intensity of Migraine Attacks

With respect to the overall clinical course of migraine, the factors which significantly (statistically) influenced the subjective worsening of migraine were also associated with the intensity. This result suggests that the intensity of migraine attacks was a key factor contributing to the subjective worsening, especially considering the correlation value of both variables ($\rho = 0.51$). The intensity of attacks would not be the unique factor related to the subjective worsening considering the difference between patients who reported self-perceived worsening (105/222; 47.3%) and those who reported higher intensity of attacks (67/222; 30.2%). Hence, important variations in migraine triggers may be related to higher intensity of attacks and, consequently, to worsening of the migraine course during the lockdown.

Concerning the change of the intensity of migraine attacks during the lockdown, there was no significant difference between the proportion of the increase of intensity in this sample and the proportion expected by chance. This result is partially expected considering that intensity of headache in migraine is moderate-to-severe, and a worsening implies an extreme pain produced by factors infrequently related to daily activity, except if there were important changes in the routine.

Some factors with significant results in the intensity model were changes during sleep, the use of onabotulinumtoxin-A as preventive treatment and the use of analgesics as symptomatic treatment. With respect to changes during sleep, positive effects were related to better sleep habits during lockdown, remarking the importance of good sleep quality in patients with migraine, as it has been suggested [41]. The postponement of onabotulinumtoxin-A injections [42] and lower intensity related to its use highlight the importance of the follow-up in treatments which require in-person applications. The association between use of analgesics and higher intensity of migraine attacks may be linked to a possible development of medication overuse during lockdown [43, 44] due to problems in the adjustment of the medication.

Headache and Migraine Frequency

Bearing in mind headache frequency, statistically significant increase of headache frequency was identified

compared to that expected by chance. Regarding the mean frequency of headache in our sample (Supplementary Data), this increase (1.6 attacks more per month) would possibly imply a change from high frequency episodic to chronic migraine in a part of the patients. A higher headache frequency during COVID-19 lockdown was also reported by Al-Hashel and Ismail (2.3 attacks more per month) [29]. Thus, the COVID-19 lockdown may be associated with clinically significant variations related to the clinical course of migraine.

Regarding the factors contributing to the headache and migraine frequency, we observed a statistically significant increase in headache frequency associated with the emotional impact of the COVID-19 lockdown, i.e., high IES scores ($\beta = 0.10$; an extra headache attack per month for each additional 10 IES points). Similar but lower increase was observed for migraine frequency ($\beta = 0.07$), but it was not statistically significant after the correction for multiple comparisons. More than half of the sample exhibited post-traumatic stress symptoms (125/222; 56.3%), similar to previously published scores in the general population [17]. In any case, the relationship between the emotional impact of a traumatic situation, possibly linked to anxiety and/or depression, and the migraine and headache (of any type) frequency should be assessed in future studies.

Alterations in daily activity related to migraine triggers have been suggested to increase migraine susceptibility [45]. Hence, our results suggest that the alteration of daily activity due to the COVID-19 lockdown may be negatively linked to the migraine situation in a considerable percentage of patients with migraine.

Additionally, we found statistically significant higher frequency of headache in patients with topiramate as preventive treatment, being used at adequate doses (100 mg/day in most patients) and combined with triptans in a similar proportion, compared to patients without topiramate use. Mood changes have been described with topiramate treatment, which could also influence migraine worsening [46, 47].

A confounding variable which was present in the headache frequency model was the diagnosis of depression. Following a similar situation to that described about insomnia and intensity of attacks, patients with recent diagnosis of depression and no previous history presented higher scores compared to those with previous history. The recent diagnosis of depression variables (at the beginning or during the lockdown) were also included in the models assessing overall subjective worsening and intensity of migraine attacks. This fact may reflect that patients with depression, which is more prevalent in migraine than in the general population [14], have been more affected than those with no depression during the lockdown.

Despite the lack of significant increase of intensity of migraine attacks and migraine frequency during lockdown, the patients have reported statistically significant self-perceived worsening of migraine according to our results. This result may be caused by the emotional processing of pain in patients with migraine during the lockdown. Regarding emotional processing, it has been suggested that psychiatric comorbidities decrease the quality of life in patients with migraine [48, 49], particularly in those with anxiety and depression [50]. Furthermore, it has also been proposed that, in patients with migraine and comorbid psychiatric problems, the lower quality of life may reflect a worse clinical course and/or altered perception of life circumstances [48]. Considering the possible high emotional impact of the COVID-19 crisis [51], the emotional processing of pain may play a key role in the self-reported worsening of migraine during lockdown, given the fact that no association with a quantitative or objective worsening score was obtained. The emotional processing of pain would be especially associated with symptoms of stress, anxiety, depression, which may have increased throughout the lockdown [17], and post-traumatic stress.

Limitations

There are some limitations worth mentioning in this study. First, the retrospective nature of this study prevented us from a detailed follow-up through the lockdown, with possible changes throughout the lockdown, especially at the first month with a remarkable initial impact and the consequent effects on the routine. Furthermore, the answers from the patients might have led to inaccuracies in few answers (e.g., inadequate description of treatment), but all answers where patients should write (not just select an option) were manually checked to correct this issue. Regarding the symptomatic treatment, the days with acute treatment were not asked and therefore we were unable to confirm a possible medication overuse. The nature of the study includes a recall bias that implies that patients remember their former state as better or worse than it actually was, and give different responses in pretest and thentest [52]. This recall bias may have influenced the values regarding the subjective impression of the migraine status. Another possible factor influencing reported self-perceived worsening could be the effects of the lockdown in highlighting facilitated memory processing for negative information [53]. It must be noted that this bias does not affect deeply the values of frequency of headache and migraine, and intensity of migraine attacks, as these values were directly extracted from the headache diary. Regarding the headache diary, we did not measure the adherence of the patients, which might have led to inaccuracies in some employed values (e.g., slight overestimation or underestimation of the frequency of migraine), although the patients from our sample were optimal for this study. With respect to some reported results related to the main variables of interest, we reported significant results related to some migraine triggers or lifestyle habits, such as specific food or drinks, or insomnia, but we did not measure in detail associated aspects, e.g., the diet or number of sleeping hours. This lack of details about lifestyle

habits and the nature of the study makes it difficult to establish clear causal relationships. Moreover, according to a recent study, only a few reported triggers (higher stress, menstruation and lower caffeine intake) are useful to establish a model to predict migraine attacks based on triggers [54], considering that the obtained model presented a prediction capability slightly higher than chance. This result indicates that there is a high variability of the individual trigger effects between patients with migraine, making particularly difficult to associate a specific trigger with migraine outcomes. We did not include more detailed variables evaluating lifestyle habits to avoid an excessively long survey. In relation to the previous limitation and the triggers, we evaluated only triggers associated with migraine, but not with other types of headache, which might have influenced the results, especially considering statistically significant increase of headache frequency, but not migraine frequency. The assessment including patients with other headache disorders should be carried out to clarify this point. Anyway, in our sample only patients with migraine were included, with the possible coexistence of infrequent tension-type headache and medication overuse headache, which limits the effects of other headache disorders.

Conclusions

As a whole, our study shows a negative influence of the lockdown in migraine in approximately half of the patients according to their subjective impression. The self-perceived worsening of migraine was associated with higher intensity of attacks and the emotional impact of the COVID-19 crisis, associated with higher levels of post-traumatic stress, anxiety, depression and stress. A weaker correlation was also found between subjective worsening and higher frequency of headache and migraine. Increased values of intensity and frequency during lockdown were related to new onset triggers such as changes in life habits or insomnia, and the emotional impact of the COVID-19 lockdown, reflected by the IES scores showing moderate-to-severe symptoms of post-traumatic-stress. Bearing this in mind, long term effects of the emotional impact of the COVID-19 crisis in patients with migraine should be evaluated in order to improve migraine management in the case of a new lockdown.

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Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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