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RESEARCH SUBMISSION

Predictors of migraine interictal burden: The hidden role of subjective memory complaints

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Abstract

Background: The "interictal burden of migraine" (MIB) is a new concept that encompasses the overall impact of the disease between migraine episodes. However, the factors that contribute to this interictal burden are still unclear.

Objective: This study aimed to identify explanatory factors of interictal burden in patients with migraine.

Methods: This prospective cross-sectional observational including 200 patients with migraine (92% [$n=184$] female, with a mean [standard deviation] age of 44.8 [12] years, 53% [$n=106$] with chronic migraine) completed a clinical and questionnaire assessment targeting MIB, migraine impact, and depressive and cognitive complaints.

Results: More than three-fourths (76% [$n=152$]) of patients had moderate-to-severe interictal burden. Higher interictal burden (MIB Scale ≥2) was associated with higher headache frequency (eight vs. 14, $p=0.001$) and intensity (headache index score 17.0 vs. 30.0, $p=0.002$), higher headache impact (six-item Headache Impact Test score 59.2 vs. 63.9, $p=0.001$), and more subjective memory complaints (Subjective Memory Complaints Questionnaire [SMC] score 9.0 vs. 4.5, $p=0.001$), as well as anxiety (Hospital Anxiety and Depression Scale (HADS)-Anxiety score 5 vs. 10, $p<0.001$) and depression symptoms (HADS-Depression score 5 vs. 8, $p<0.001$). Once accounted for these potential explanatory variables, subjective memory complaints and impact of headache during ictal phase remained as individual determinants of the interictal burden, with SMC explaining 15% (odds ratio 1.15, 95% confidence interval 1.03–1.28; $p=0.010$) of the interictal burden.

Conclusion: This finding highlights the need to consider cognitive complaints as part of the construct of interictal burden of these patients to refine the focus of their management.

Plain Language Summary

The interictal burden of migraine is defined as the ways in which the disease affects patients between attacks, but we know very little about what factors influence this burden. This study found that 75% of patients experience moderate-to-severe interictal burden, and those who have frequent and severe headaches and feel anxious

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HIT-6, six-item Headache Impact Test; IQR, interquartile range; MIBS-4, four-item Migraine Interictal Burden Scale; SD, standard deviation; SMC, Subjective Memory Complaints Questionnaire.

or depressed appeared to have more interictal burden and subjective memory complaints. Memory complaints, in particular, which are often overlooked clinically, may contribute substantially to interictal burden.

KEYWORDS
cognition, interictal burden, migraine, subjective memory complaints

INTRODUCTION

Migraine has a substantial impact on a patient's life. While it was traditionally considered an episodic disorder marked by intermittent headache attacks separated by symptom-free periods, it has become apparent that patients can also experience chronic forms and/or exhibit non-headache symptoms outside the attacks.[1–3] These symptoms may occur in different combinations and include cognitive complaints, visual disturbances, sensitivity to light and odors, allodynia, motion sickness, vestibular disturbances, and cranial autonomic symptoms.[4–10] Some of these symptoms can have a significant impact on quality of life both during the peri-ictal phase (before or after the attack, known as pre- and post-ictal) or in between attacks (interictal phase). However, the transition between the interictal phase and the earlier and late phases of migraine attacks is still difficult to define with precision, namely because their duration is within a range that may change between attacks and possibly by the use of medications. Based on clinical, physiological, and imaging evidence, it has been proposed that the pre-ictal phase is considered up to 48 h before headache onset, and the post-ictal phase may extend up to 24 h after the end of the headache.[11] Importantly, some of these symptoms can have a significant impact on the quality of life both during and between migraine attacks. During the interictal phase, patients may also experience anxiety or worries regarding the timing of their next migraine attack and how it might interfere with their plans or daily activities.[12,13] Moreover, it has been recognized that migraine is associated with several comorbidities, particularly in patients with high frequency and chronic forms, that also contribute to disability.[12,14] The collective effects of such concerns and symptoms have been conceptualized as an "interictal burden of migraine", which refers to the overall impact of the disease between migraine episodes,[1] which has been possible to measure with a four-item questionnaire addressing work or school functioning, worry about planning social or leisure activities, impact on life when not having a headache and feeling helpless.[15] While there is a substantial amount of evidence concerning the impact of migraine attacks on work and career, family, and social and leisure activities, the interictal burden of migraine and its determinants remains poorly understood. Therefore, we hypothesized that headache severity, some migraine comorbidities (insomnia, depression, and anxiety), and cognitive complaints would explain a greater interictal burden in patients with migraine.

OBJECTIVES

This study aimed to identify the factors that explain the interictal burden in patients with migraine.

METHODS

Study design

This was a cross-sectional observational study involving adult patients with migraine who attended an Outpatient Headache Clinic of a University Hospital in Lisbon between January and July 2023. Ethical approval was obtained from the Local Ethics Committee, and all patients signed institutionally approved written informed consent.

Study population: selection and characteristics

Patients were recruited and invited to participate during their scheduled outpatient appointments following a consecutive sampling method. The diagnosis of migraine was made by the attending neurologist, according to International Classification of Headache Disorders third edition criteria.[16] Patients were included if they were aged >18 years, fulfilled criteria for episodic, high-frequency or chronic migraine with or without aura, were willing and able to cooperate in the study, and had no evidence of other brain disorders.

Patients aged >65 years, with concomitant diagnosis of other neurological, psychiatric disorders, cognitive impairment, substance use disorders, or uncontrolled medical conditions were excluded. Patients with >28 days of headache/month were also excluded, as there must be at least 3 consecutive days without pain as the target of the study was the interictal period.

Patients

Demographic and headache characteristics were collected during the visit and from medical records. This included age, sex, years of education, and age of onset of migraine. Attack frequency, duration, and intensity were extracted from headache diaries. Participants were provided with paper-pencil diaries and

instructed to report their headache episodes as they occurred throughout the day. A headache index was calculated (a composed metric that represents the sum of monthly headache days × intensity: 1 point for mild, 2 points for moderate, and 3 points for severe headache, ranging between 0 and 84). This measure allows weighting the number of headache days by their severity as someone experiencing infrequent but intense headaches or disabling headaches may have a higher index then someone with mild headaches.

Acute attack medication and number of days per month with acute medication intake, and current prophylactic medications, namely antiseizure medication (valproic acid and topiramate), were also collected.

Migraine comorbidities and burden assessment

Patients were asked to complete paper-based questionnaires aimed at directly assessing headache, its impact, and comorbidities. They completed the six-item Headache Impact Test (HIT-6),[17] a scale that measures the overall impact of headache on the ability to function on the job, at school, at home, and in social situations. Anxiety, depression, and insomnia were assessed using the Hospital Anxiety and Depression Scale (HADS)[18] and the Insomnia Severity Index,[19] respectively. Patients also fulfilled the Subjective Memory Complaints Questionnaire (SMC)[20,21] consisting of 10 items, with a total score ranging from 0 to 14, with values >3 representing significant memory complaints.

Interictal burden was assessed through the Portuguese version of the four-item Migraine Interictal Burden Scale (MIBS-4) (Malheiro et al. Portuguese Validation of MIBS-4, presented at Portuguese Neurological Society Conference 2023). Unlike the HIT-6, this one specifically refers to the period when the patient is not experiencing a headache and addresses four items: work or school functioning, worry about planning social or leisure activities, impacting life when not having a headache, and feeling helpless. Each item is rated from 0 to 3, with higher scores indicating a greater degree of burden. The total score, ranging from 0 to 12, corresponds to different levels of burden: a score of 0 corresponds to the absence of burden, while scores of 1 to 2 signify mild burden, 3–4 represent moderate burden, and scores ≥5 indicate severe burden. Based on their MIBS-4 score, patients were categorized into two groups: none-to-mild migraine interictal burden (MIBS-4 score <3) and moderate-to-severe migraine interictal burden (MIBS-4 score ≥3). This cut-off was considered relevant as it has been considered advisable to initiate preventive treatment for scores ≥3.[11]

STATISTICAL ANALYSIS

Data of continuous variables were tested for normality using the Kolmogorov–Smirnov test and variance homogeneity was evaluated with the Levene test. Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range [IQR]). Categorical variables were expressed as frequency and percentage (*n*; %).

The association between demographic, clinical, and the two categories of interictal burden was tested using the independent samples *t*-test or Mann–Whitney *U*-test, according to the normality distribution. The association between categorical variables was assessed using the chi-squared test or Fisher's exact test. The collinearity assessment between variables was performed using the variance inflation factor.

No statistical power calculation was conducted prior to the study. The sample size was based on our previous experience with this design.

Logistic regression analysis adjusting for confounding variables associated with migraine interictal burden was performed according to the new guidelines.[22] Given that all variables collected were selected based on theoretical considerations, as previously stated, variables with a $p < 0.10$ in univariate analysis were included. Summary receiver operating characteristics of that model was performed and the area under the curve for the summary receiver operating characteristics plot was calculated. A $p < 0.05$ was accepted as statistically significant. The hypothesis testing conducted in this study employed two-tailed testing. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 24.0 (IBM Corp. Armonk, NY, USA). This is the primary analysis of these data.

RESULTS

A total of 267 individuals were screened for eligibility, of which 233 patients were initially enrolled in the study. In all, 33 individuals were excluded from the analysis due to persistent daily headache (>28 days/month) precluding the evaluation of an interictal period or due to the presence of concomitant disorders. Therefore, 200 patients were included in the study. There were no missing data.

Among the participants, 184 (92%) were female and the mean (SD) age was 44.8 (12.0) years. Most of the participants (90.3% [*n* = 168]) had >9 years of education. Demographic and clinical characteristics of the study population are summarized in Table 1.

Patients reported a median (IQR) of 11 (6–24) headache days/month, with a median (IQR) headache index of 24 (12–45), and 53% (*n* = 105) had chronic migraine. Regarding the use of acute treatments, patients had a median (IQR) of 6 (4–12) days of acute medication/month. More than one-third (33.5% [*n* = 67]) of the patients met the criteria for medication-overuse headache.[16]

Table 2 presents the results of the HIT-6, Insomnia Severity Index, HADS, and SMC questionnaires. More than three-quarters (76% [*n* = 152]) of the patients had moderate-to-severe interictal burden (MIBS-4 score ≥3). The median (IQR) SMC score in our study cohort was 8 (4–12). In univariate analysis, several variables were associated with a moderate-to-severe interictal burden (Table 1). No

TABLE 1 Demographic and clinical characteristics, as well as assessment scales, within the study population and according to the four-item Migraine Interictal Burden Scale groups.

Characteristic	Total ($n=200$)	MIBS-4 score 0–2 ($n=48$)	MIBS-4 score ≥3 ($n=152$)	p
Age, years, mean (SD)	44.79 (12.04)	42.71 (13.4)	44.43 (11.5)	0.137
Age of migraine onset, years, mean (IQR)	15 (12–20)	15 (12–20)	16 (12–21)	0.466
Sex, female, *n* (%)	184 (92)	44 (91.7)	140 (92.1)	0.691
Education, >9 years, *n* (%)	168 (90.3)	40 (83.3)	128 (84.2)	0.709
Headache days/month, median (IQR)	11 (6–24)	8 (4–14.5)	14 (8–27)	**0.001**
Chronic migraine, *n* (%)	105 (53.0)	15 (31.3)	90 (59.2)	**0.001**
Headache index score, median (IQR)	24 (12–45)	17.0 (8.5–32.5)	30 (16–48)	**0.002**
Rescue medication, days, median (IQR)	6 (4–12)	6 (3–12)	8 (4–12)	0.201
Medication over-use headache, *n* (%)	67 (33.5)	13 (27.1)	54 (35.5)	0.181
Antiseizure medication (TPM or VPA), *n* (%)	106 (53)	21 (43.7)	85 (56)	0.089
HIT-6 score, mean (SD)	62.76 (6.43)	59.16 (7.38)	63.93 (5.64)	**0.001**
HADS-D score, median (IQR)	8 (5–10)	5 (4.0–8)	8 (5.5–11)	**<0.001**
HADS-D score >12, *n* (%)	20 (25)	2 (4.2)	48 (31.6)	**<0.001**
HADS-A score, median (IQR)	8 (5–12)	5 (4.0–8)	10 (6–12)	**<0.001**
HADS-A score >12, *n* (%)	68 (34)	7 (14.6)	61 (40.1)	**0.002**
ISI score, median (IQR)	11 (6–16)	11 (4–15.5)	13 (7–17)	0.116
SMC score, median (IQR)	8 (4–12)	4.5 (2.0–7)	9 (6–12)	**<0.001**
SMC score >3, *n* (%)	162 (81)	27 (56.3)	135 (88.8)	**<0.001**

Abbreviations: HADS, Healthcare Anxiety and Depression Scale; HADS-A, HADS subscore anxiety; HADS-D, HADS subscore depression; HIT-6, six-item Headache Impact Scale; IQR, interquartile range; ISI, Insomnia Severity Index; MIBS-4, four-item Migraine Interictal Burden Scale; SD, standard deviation; SMC, Subjective Memory Complaints Questionnaire; TPM, topiramate; VPA, valproic acid.

Bold values statistically significant at $p<0.05$.

TABLE 2 Multivariable logistic regression analysis of the four-item Migraine Interictal Burden Scale adjusted for confounders.

Variable	OR (95% CI)	p
Headache days/month (*n*)	1.00 (0.96–1.05)	0.937
HIT-6	1.07 (1.0–1.15)	**0.044**
SMC	1.15 (1.04–1.28)	**0.010**
HADS-A	1.09 (0.95–1.24)	0.206
HADS-D	0.93 (0.82–1.19)	0.992
Antiseizure medication (VPA or TPM)	0.65 (0.29–1.42)	0.282

Abbreviations: CI, confidence interval; HADS, Healthcare Anxiety and Depression Scale; HADS-A, HADS subscore anxiety; HADS-D, HADS subscore depression; HIT-6, six-item Headache Impact Scale; OR, odds ratio; SMC, Subjective Memory Complaints Questionnaire; TPM, topiramate; VPA, valproic acid.

Bold values statistically significant at $p<0.05$.

collinearity was observed between variables, particularly between the scales assessing headache impact HIT-6 and MIBS-4 (variance inflation factor 1.38).

Patients with a higher interictal burden had significantly higher impact of migraine during the ictal phase (HIT-6 score 63.9 vs. 59.2, $p=0.001$) and higher SMC scores (9.0 vs. 4.5, $p=0.001$) when compared to patients with a lower interictal burden. There were no differences between the two groups regarding the use of antiseizure medication in migraine prevention (56% vs. 43.7%, $p=0.089$).

A logistic regression analysis was performed, including the MIBS-4 score (<3 or ≥3) as the dependent variable, and migraine frequency, HIT-6, SMC, HADS-Anxiety subscore, and HADS-Depression subscore as independent variables. Cognitive complaints contributed to explaining 15% of the MIBS-4 score (odds ratio 1.15, 95% confidence interval 1.03–1.28; $p=0.010$) after adjustment for other variables associated with migraine interictal burden (Table 2). The model was well calibrated (Hosmer-Lemeshow chi-squared test, $p=0.62$), and the Nagelkerke R^2 was 0.26. This model had high discriminative power (area under the curve 0.78, 95% confidence interval 0.70–0.85; $p<0.001$).

DISCUSSION

This cross-sectional study evaluated factors that explain interictal burden in patients with migraine followed in a tertiary headache clinic. More than three-quarters of patients experienced moderate-to-severe interictal burden (MIBS-4 score ≥3), which is the line with prior research in the field.[3,23] This substantial level of interictal

burden remains consistent irrespective of factors such as the age of migraine onset, the presence of chronic migraine, insomnia, or medication-overuse headache.

An interesting observation that emerged from our study was the identification of variables associated with an increased interictal burden. These factors included not only headache metrics, headache frequency and intensity (headache index), the impact of headaches during the ictal phase (HIT-6), but also subjective memory complaints, as well as anxiety, depressive symptoms (HADS), and antiseizure medication as a preventive treatment. Remarkably, among these variables, only subjective memory complaints and the impact of headache during the ictal phase persisted as independent explanatory variables of interictal burden, after controlling for potential confounding factors.

The ictal impact of headache and its positive relation with interictal phase burden is not surprising and it is in line with previous studies in the field.[12] Patients with more frequent or severe and disabling attacks will more likely feel insecure about and anticipate future attacks. As previously mentioned, the MIBS-4 addresses work or school functioning, worry about planning social or leisure activities, impacting life, and feeling helpless when not having a headache.

Although cognitive aspects may be relevant in all items assessed by the MIBS-4, none of the scale items specifically addresses cognitive complaints. Moreover, depression and sleep disorders, which are frequent comorbidities of migraine can also interfere with cognition and are associated with cognitive complaints.[24,25]

People with migraine commonly report cognitive difficulties, particularly in chronic migraine, namely involving concentration, memory, and decision-making, that can extend beyond the headache phase, affecting the interictal period as well.[9,24–28] Vuralli et al.[29] uncovered in their review that standardized neuropsychological assessments reveal that migraine attacks are linked to diminished cognitive function compared to headache-free intervals. Beyond the attack, numerous clinic-based studies indicate poorer cognitive performance.[30] Conversely, most population-based studies suggest comparable cognitive performance during the interictal period.[29]

These complaints may arise from the underlying migraine pathophysiology, the adverse effects of medications, especially antiseizure medication, excessive use of rescue medication, or from the functional connectivity and structural changes associated with migraine.[31] Cognitive difficulties and impairment can be due to a cumulative effect of all those factors or may represent a vulnerable aspect of patients with migraine that augments the impact of the disease by interfering with their ability to overcome the daily challenges imposed by the disorder (requiring more attention, more complex decision making, for example). It is noteworthy to mention that despite the cognitive side-effects of the antiseizure medication, in this study, it did not seem to have a significant contribution to the interictal burden.

This study stands out for its novel approach to addressing a significant gap in our understanding of migraine. By focusing on the interictal phase and its determinants, our research sheds light on an area that has been understudied in the literature. This study is pioneering in using a measure of subjective memory complaints and incorporating it into an exploratory model of interictal burden. Given the high frequency of memory complaints in this population, especially in chronic migraine, these disturbances occurring across all phases of migraine should be evaluated as a contributing factor to the overall impact. The relationship found in this study may support the addition of a specific and targeted question regarding cognitive aspects when assessing interictal burden. A recent study showed that subjective perception of the ability to concentrate may improve with preventive treatment in chronic migraine and high-frequency episodic migraine.[32] Therefore, we propose that adopting a more comprehensive approach should become the standard of care to fully understand the best approach for a patient's overall health and well-being.

Moreover, this study highlights that quantifying the reduction in headache days or intensity may prove insufficient when assessing the real impact of migraine and perhaps the overall efficacy of the new treatments. The authors' perspective aligns with previous studies in the field,[14] and we also claim that there is a need for improved tools and increased awareness among healthcare providers regarding the oversight of interictal burden in current headache diaries. Moreover, rescue medications are often overlooked as they are frequently associated with ictal impact. Although we do not directly address acute medications, Lamp et al.[33] found that individuals who were "rarely" or "never" in control of their headaches (15.2% migraine) had significantly increased odds of interictal anxiety, avoidance, and other symptoms. Moreover, a recent meta-analysis[30] also showed that higher attack duration was associated with negative cognitive effects. This highlights the importance of not only focusing on the role of preventive treatments but also considering acute medication optimization.

One of the strengths of this study is its prospective nature, which involved the systematic collection of data on headache frequency and related metrics using headache diaries.

We acknowledge some limitations in this study. First, its design does not allow the establishment of cause–effect relationships or trends in variables over time. The study of causal relations is very useful to understand the importance of these complaints and to implement management plans to alleviate the burden. Additionally, there is a potential for selection bias, as the study may overrepresent patients with more severe disease burdens, potentially excluding those with milder migraine who attended the headache outpatient clinic less frequently. Moreover, the exclusion of patients with cognitive impairment and other psychiatric disorders could introduce bias, as these are common comorbidities in patients with migraine.

Further research is needed to explore the impact of new migraine treatment, calcitonin gene-related peptide monoclonal antibodies, and other therapies on subjective memory complaints and interictal burden, providing a more comprehensive understanding of how treatments can alleviate interictal burden.

CONCLUSION

Patients with migraine exhibit a substantial degree of interictal burden. In this study, the role of subjective cognitive complaints emerges, highlighting them as an independent explanatory factor of interictal burden.

AUTHOR CONTRIBUTIONS

Filipa Dourado Sotero: Conceptualization; formal analysis; investigation; methodology; writing – original draft. **João Nobre:** Data curation; formal analysis; writing – original draft. **Beatriz Nunes Vicente:** Formal analysis; investigation; writing – original draft; writing – review and editing. **Isabel Pavão Martins:** Conceptualization; methodology; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Filipa Dourado Sotero declares no conflicts of interest; **João Nobre** declares no conflicts of interest; **Beatriz Nunes Vicente** declares no conflicts of interest, and **Isabel Pavão Martins** declares no conflicts of interest.

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