Clinical Pain Research

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Disability, burden, and symptoms related to sensitization in migraine patients associate with headache frequency

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Abstract

Objectives: This observational study aimed to assess the difference in disability, burden, and sensitization between migraine patients with low-frequency headache attack (1–8 headache days/month), high-frequency headache attack (9–14 headache days/months), and patients with chronic migraine (>14 headache days/months).

Methods: Migraine patients with or without aura were divided into three groups according to headache frequency (low-frequency episodic migraine; high-frequency episodic migraine; chronic migraine). Questionnaires were used to assess the burden of headache, quality of life, phycological burden, and symptoms related to sensitization (estimated by the Central Sensitization Inventory). Differences among migraine groups were assessed using Chi-Quadro test, ANOVA, or Kruskal–Wallis as appropriate.

Results: 136 patients were included (68 low-frequency episodic migraine, 45 high-frequency episodic migraine, 23 chronic migraine). Patients with high frequency episodic migraine and chronic migraine differed from patients with low frequency episodic migraine showing a worse burden of headache (p=0.002; p=0.002), worse level of physical (p=0.001; p<0.001) and mental (p=0.002; p=0.001) quality of life, worse level of depression (p=0.008; p=0.003), and increase presence of symptoms related to sensitization (p<0.001; p=0.003). No differences were found in any variables between patients with high-frequency episodic migraine and patients with chronic migraine (p>0.05).

Conclusions: Patients with high-frequency episodic migraine and chronic migraine could be considered in the same segment of the migraine population, with similar degrees of disability and sensitization related symptoms.

Keywords: chronic migraine; depression; episodic migraine; headache classification; headache frequency; level of disability; sensitization.

Introduction

Headache has been considered one of the worldwide leading causes of disability in the last decades [1]. The International Classification of Headache Disorders (ICHD) distinguishes chronic migraine (CM) from episodic migraine (EM) [2], with CM showing a worse individual and social burden compared to EM [3–5]. Even if the subdivision of migraine in EM and CM allowed the development of specific treatments modalities used for the most disabled segments of the migraine population [6], the overall disability due to migraine has increased in recent years [7] and migraine is today considered the first cause of disability for people younger than 50 years old [8]. Therefore, more efforts should be directed towards better identifying patients who present the worse clinical manifestation. EM could be further divided into a high-frequency EM with 8–14 headache days in a month with migraine characteristics and low-frequency EM with less than 8 headache days in a month [9]. However, this recent subdivision of EM is not recognized by ICDH. If patients present with 13 headache attacks per month with migraine characteristics, they are classified into the same subgroup of

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patients with 5 headache attacks in a month and a different subgroup compared to a patient with 8 headache attacks with migraine characteristics and seven with tension-type headache characteristic in a month. Despite this, current evidence suggests that patients with high-frequency EM share more similar characteristics with CM than with low-frequency EM [10–12]. According to these data, some authors sustained that the current diagnostic criteria used for CM could underestimate the real extent of the most disabled segment of the migraine population and propose that patients with high-frequency EM should be included in the CM subgroup [10]. The differences in clinical variables between low-frequency EM, high-frequency EM, and CM patients need to be further investigated before asserting one assimilation between CM and high-frequency EM [13]. The aims of this study were (1) to assess if patients with low-frequency EM, high-frequency EM, and CM differ regarding the burden of headache, quality of life, phycological burden, and presence of symptoms related to sensitization and (2) to assess the real percentage of patients accounting for the most disabled segment of the migraine population.

Method

Design

This study was a multicenter, cross-sectional, observational study conducted in the Headache Center of Parma and Genova (Italy) between April 2019 and January 2020. It was approved by the Ligurian regional ethic committee (244/2018) and by the ethic committee of "Area Vasta Emilia Nord" (18305/2019). All patients signed an informed consent form.

Population

Consecutive patients on waiting lists to receive the first visit to the Headache Center in Genova or Parma were invited to participate in this study. If they accepted, they were recruited. Men and women aged between 18 and 65 with EM (with and without aura) or CM were included. Migraine has to be present for at least 3 months, with at least one migraine attack in a month. Patients were excluded if they had: (1) any other primary or secondary headache; (2) any other neurologic or psychiatric pathology (with a medical diagnosis); (3) any systemic pathology with medical diagnosis (i.e. lupus, rheumatoid arthritis, fibromyalgia). (4) have received manual therapy in the cervical spine in the last 6 months; (5) have received anesthetic cervical block or botulin injection in the last 6 months; (6) have changed the prophylactic treatment in the last 3 months; (7) were unable to speak and understand Italian.

Procedure

The first screening was made by a telephone interview where patients were excluded if (1) they presented any signs of red flags [14]; (2) they reported at least one exclusion criteria. After the recruitment, two therapists blinded to the patient's diagnosis, one for each recruitment center (S.D. and M.C.), gave to the patients 4 questionnaires regarding the burden of headache, the quality of life, the presence of symptoms related to sensitization, and the level of anxiety and depression. The therapists also explained how to fulfill a diary where they had to record headache characteristics for the following four weeks. After four weeks from the first evaluation, patients were visited by a neurologist who performed a diagnosis of headache according to the International Headache Classification Criteria [2]. Patients that did not meet the inclusion criteria for migraine diagnosis were excluded (Figure 1). Migraine patients (with or without aura) were included. Then, they were divided into three subgroups according to the frequency of the headache attacks recorded in the diary [10]:

- Low-frequency episodic migraine (LFEM): patients who fulfilled the diagnostic criteria for migraine with aura or migraine without aura for at least 3 months with less than 8 days with headache in a month.
- High-frequency episodic migraine (HFEM): patients who fulfilled the diagnostic criteria for migraine with aura or migraine without aura for at least 3 months with 8 or more days with headache in a month
- Chronic migraine (CM): patients who fulfilled the diagnostic criteria for migraine with aura or migraine without aura for at least 3 months with 15 or more days with headache in a month. At least 8 or more migraine days had to fulfill the criteria for migraine with aura or without aura (Figure 1).

Assessments

For each patient, the following variables were assessed: sex, age, body mass index (BMI), educational level (primary school, middle school, high school, university), and use of prophylactic drugs. To assess the characteristic of headache attacks, we used a daily updated diary where patients recorded the frequency of headache attack (days in four weeks), the intensity of the headache attacks on an 11-points numerical pain rate scale (NPRS; 0: no pain, 10: the maximum pain), the mean duration of headache attack (mean hours for attack), total use of symptomatic drugs (the total number of tablets consumed in four weeks were reported), total years lived with the headache. Moreover, the following four questionnaires were submitted to each patient:

- Headache disability index (HDI): HDI questionnaire was used to assess the burden of the headache. This questionnaire uses 25 items that investigate the perceived impact of headache on emotional functioning and daily life activities and provides a 0–100 total score, with a higher score indicating a high level of disability. Thirteen items assess the emotional burden (HDI-E, maximum score: 52), whereas the remaining 12 items assess the physical burden (HDI-P, maximum score: 48) [15]. This questionnaire has demonstrated reliability ad validity [16] and was already used to assess disability in patients with migraine [17, 18].
- Medical Outcomes Study Short Form 36 (SF-36): SF-36 questionnaire was used to assess health-related quality of life. This questionnaire includes the following 8 domains: physical functioning, physical role, role-emotional, vitality, mental health, social function, bodily pain (pain interference), and general health. The total score ranges from 0 (the lowest quality of life) to 100 (the highest quality of life) [19]. This questionnaire could be

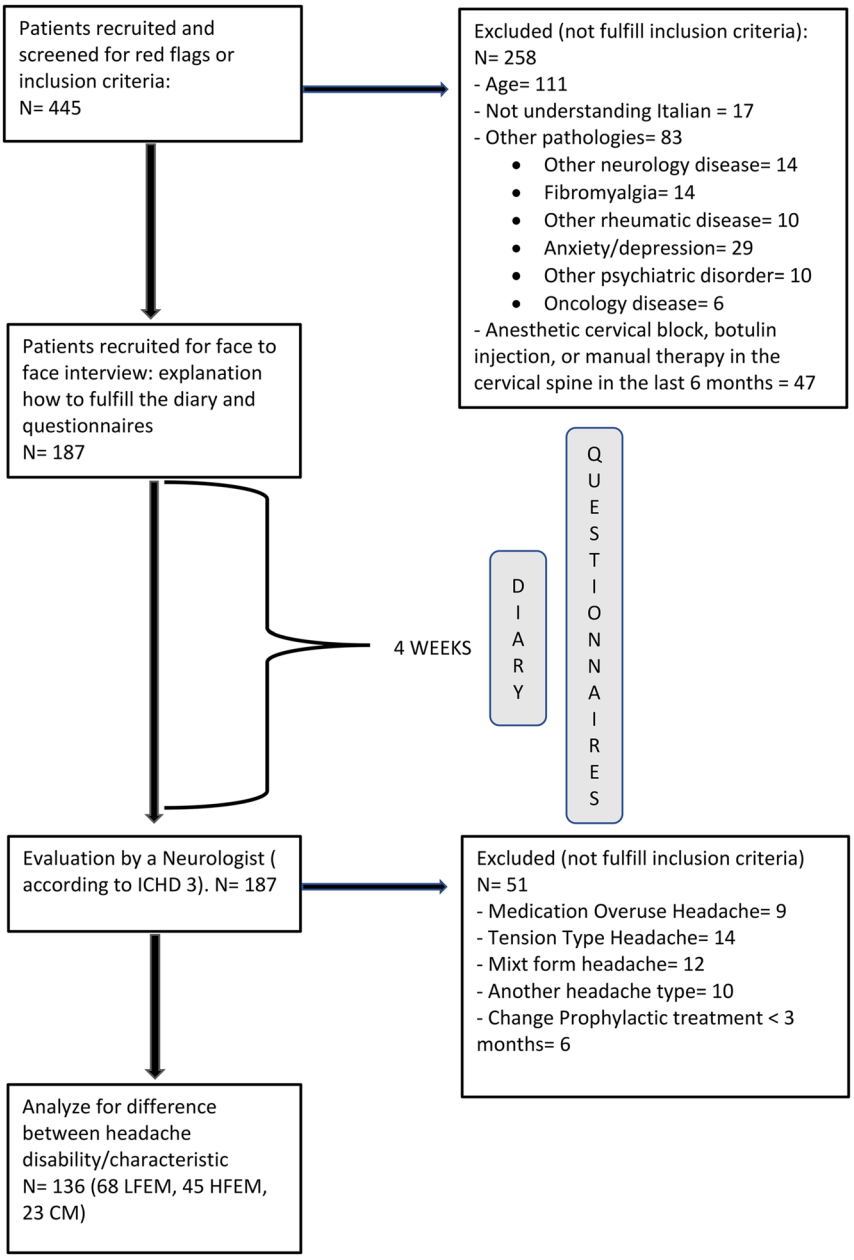

Figure 1: Flow chart.
CM, chronic migraine; HFEM, high frequency episodic migraine; ICDH, international classification headache disorders; LFEM, low frequency episodic migraine; N, number.

divided into two subscales: the physical health dimension (physical functioning, physical role, bodily pain, general health) and the mental health dimension (vitality, social functioning, role emotional, mental health) [20]. This questionnaire has demonstrated good reliability [21] and assessed health-related quality of life in patients with migraine [22].

– The hospital anxiety and depression scale (HADS): HADS is a 14-item self-report screening scale indicating the presence of anxiety and depressive symptom. It consists of seven items for evaluating anxiety (HADS-A) and seven for depression (HADS-D). Each item scores on a scale (0–3), giving a maximum score of 21 points for each subscale. A higher score indicates a higher level of anxiety and depressive symptoms [23]. This questionnaire is considered reliable and valid for assessing anxiety and depression [24] and was widely used in patients with migraine [25, 26].
– Central Sensitization Inventory (CSI): CSI is a patient-reported instrument designed to identify symptoms related to sensitization. It provides a 0–100 total score for 25 items on current health symptoms with five response options ranging from 'never' (0) to 'always' (4). The higher the score more symptoms related to central sensitization are present [27]. A cut-off score of 40 out of 100 was shown to have good sensitivity and specificity to identify a subgroup of patients with central sensitization syndrome [28]. The CSI results could also be used to divide patients into five categories with increasing severity: subclinical (0–29); mild (30–39); moderate (40–49); severe (50–59); and extreme (60–100) [29]. CSI could be considered a reliable, consistent, and valid questionnaire [30] and was already used to assess patient's symptoms related to sensitization in patients with migraine [31].

Statistical analysis

The sample size was calculated with G*Power 3.1 to achieve a medium/large effect size (f=0.35) in an analysis of variance between three groups (LFEM, HFEM, CM) with a power of 0.90 and an alpha level of 0.05 [32]. The required sample size was 108 participants. General characteristics, headache characteristics, and results from the questionnaires were presented as mean (standard deviation), median (interquartile range), or number (%) according to the type of the variable. Differences between LFEM, HFEM, and CM patients were investigated with the Chi-Quadro test, ANOVA, or Kruskal–Wallis test as appropriate, using the Kolmogorov-Smirnov test to verify normality. When between groups differences resulted statistically significant, we used Bonferroni-adjusted ANOVA or the Mann–Whitney test to run post-hoc analyses respectively for ANOVA and Kruskal–Wallis test. One score for HDI, two scores for SF-36 (Physical Health dimension and Mental health dimension), two scores for HADS (HADS-A and HADS-D), and one score for CSI were used for the preliminary analysis. Then, exploratory analyses were conducted to assess the different subscales of each questionnaire. Subsequently, if HFEM and CM subgroups showed comparable results in the headache characteristics and the questionnaires, they were included in one group as "the most disable segment of migraine population." Then, McNemar's test was used to assess if the percentage of patients considered as "the most disable segment of the migraine population" significantly increase if HFEM and CM instead of only CM patients were included in this subgroup. Patients that did not fulfill all the questionnaires were excluded from the analysis. The alpha level accepted for the significance of the results was $p<0.05$. Statistical analyses were performed using the SPSS software (version 24).

Results

A total of 439 patients were screened through a telephone interview. Of them, 252 were excluded for the presence of at least one exclusion criterion. The remaining 187 patients were recruited for the compilation of the diary/questionnaire and the neurological examination. After the neurological examination, 51 patients were excluded because they did not meet the inclusion criteria for migraine diagnosis. The remain 136 patients completed all questionnaires and were included for the final analysis (68 LFEM, 45 HFEM, 23 CM) (Figure 1). Out of the total sample, 82% of the patients (87% LFEM; 82% HFEM; 70% CM) had never visited the Headache Center before. The remaining 18% of the sample (13% LFEM; 18% HFEM; 30% CM) had already visited the Headache Center. There was no significant difference across groups regarding sex, age, BMI, educational level, and familiarity with headaches ($p>0.05$). The use of prophylactic drugs was higher in patients with CM compared to LFEM ($p=0.012$) and HFEM ($p=0.038$), with no differences between patients with LFEM and HFEM ($p=0.804$). In the LFEM group, there was a higher ($p=0.024$) number of patients with EM with aura (n=13) compared to HFEM (n=2) (Table 1).

There was no significant difference across groups regarding years of headache ($p=0.216$) or intensity of headache attacks ($p=0.130$). Patients with HFEM used a higher number of symptomatic drugs ($p<0.001$) compared to LFEM. Patients with CM had higher headache duration compared to LFEM ($p=0.003$) and HFEM ($p=0.032$) and used a higher number of symptomatic drugs ($p<0.001$) compared to LFEM. No other differences were found across groups in the characteristic of headache ($p>0.05$) (Table 2).

Questionnaires

Primary analyses indicated statistically significant differences across groups for the results of HDI, SF-36 Physical Health dimension, SF-36 Mental Health dimension, HADS-D, and CSI. No difference across groups was found for results in HADS-A (Table 3). Post-hoc analysis indicated significant differences between HFEM or CM patients and

Table 1: General characteristics.

	Group		
	LFEM (n=68)	**HFEM (n=45)**	**CM (n=23)**
N (%) females; N (%) male	54 (79%), 14 (21%)	39 (87%), 6 (13%)	19 (83%), 4 (17%)
Age (mean years ± SD)	36.37 ± 11.72	39.53 ± 13.12	38 ± 10.07
BMI (mean kg/m^2 ± SD)	22.74 ± 3.46	23.06 ± 3.09	24.07 ± 4.43
N (%) patients that had previously visited the headache center (never visited: previously visited)	59 (87%); 9 (13%)	37 (82%); 8 (18%)	16 (70%); 7 (30%)
N (%) patients for each education level (elementary, middle school, high school; university)	0 (0%); 7 (10%); 36 (53%); 25 (37%)	2 (4%); 7 (16%); 26 (58%); 10 (22%)	0 (0%); 4 (17%); 15 (65%); 4 (17%)
N (%) patients with episodic migraines with or without aura	13 (19%); 55 (81%)	2 (4%); 43 (96%) *	–
N (%) patients that use prophylactic drugs (no; yes stable>3 months)	60 (88%); 8 (12%)	39 (87%); 6 (13%)	15 (65%); 8 (34%) † *

BMI, body mass index; CM, chronic migraine; HFEM, high frequency episodic migraine; kg, kilogram; LFEM, low frequency episodic migraine; m^2, square meter; N, number; SD, standard deviation; *difference vs. LFEM $p<0.05$ †difference vs. HFEM $p<0.05$.

Table 2: Headache characteristics.

Test	LFEM (n=68)	HFEM (n=45)	CM (n=23)	Result from Kruskal–Wallis	Post-hoc test Mann–Whitney p-value		
	Median (IQR)	Median (IQR)	Median (IQR)	Between-group difference	LFEM vs. HFEM	LFEM vs. CM	HFEM vs. CM
Headache since, years	13(7–23)	15(7.5–34.5)	21(11–33)	p=0.216	p=0.195	p=0.115	p=0.835
Frequency, days/month	4(3–6)	11(9–12)	18(16–25)	**p<0.001**	**p<0.001**	**p<0.001**	**p<0.001**
Intensity (NPRS 0–10)	5.75(4.26–6.82)	6.4(4.74–7.20)	6(4.1–7)	p=0.130	p=0.043	p=0.844	p=0.254
Duration, hours/day	5.95(4–8.46)	6(3.27–9.75)	9.87(6.01–13.91)	**p=0.017**	p=0.913	**p=0.003**	**p=0.032**
Total use of drugs	3(2–5)	8(4–11)	8(5–17)	**p<0.001**	**p<0.001**	**p=0.000**	p=0.339

CM, chronic migraine; HFEM, high frequency episodic migraine; IQR, interquartile range; LFEM, low frequency episodic migraine; NPRS, numeric pain rating scale (0–10).

LFEM but not between HFEM and CM for all variables (Table 3). The number of patients with LFEM accounts for 50% of the total sample, while patients with HFEM and CM account for 33 and 17%, respectively. Combining patients with HFEM and CM in the same group, the percentage of patients accounting for the most disabled segment of the migraine population significantly increase from 17 to 50% (p<0.001).

The secondary analysis of HDI's subscale established a significant difference between groups regarding the HDI-P (p=0.002) and HDI-E (p<0.001) components. Post hoc analysis revealed a significant difference in HDI-P between LFEM and HFEM (p=0.035) and between LFEM and CM (p=0.006) with no significant difference between HFEM and CM (p=0.913). The same results were found in the HDI-E with a significant difference between LFEM and HFEM (p=0.003) and between LFEM and CM (p=0.001), but not between HFEM and CM (p=0.520) (Figure 2).

The secondary analysis of SF-36's subscales indicated a significant difference between groups regarding all subscales (p<0.05). The post-hoc analysis demonstrated a significant difference between HFEM or CM and LFEM for the following 4 domains: physical functioning, role emotional, social function, bodily pain (pain interference) (p<0.05). The difference in vitality and the physical role was established only between LFEM and CM (p<0.005), and the difference in mental health was established only

Table 3: Questionnaires.

Normal data	LFEM (n=68)	HFEM (n=45)	CM (n=23)	Result from ANOVA	Post-hoc test Bonferroni p-value		
Test	Mean (SD)	Mean (SD)	Mean (SD)	Between-group difference	LFEM vs. HFEM	LFEM vs. CM	HFEM vs. CM
HDI	38.77(18.03)	49.84(20.40)	54.52(17.44)	**p<0.001**	**p=0.008**	**p=0.002**	p=0.997
CSI	31.90 (12.11)	40.44(13.06)	40.43(11.99)	**p<0.001**	**p=0.001**	**p=0.015**	p=1.000
SF-36 physical health dimension	69.31(18.25)	59.25(18.12)	53.10(14.64)	**p<0.001**	**p=0.011**	**p=0.001**	p=0.529
HADS anxiety	6.51(3.61)	7.93(3.81)	7.57(4.27)	p=0.133	p=0.162	p=0.760	p=1.000
Non-normal data	**LFEM (n=68)**	**HFEM (n=45)**	**CM (n=23)**	**Result from Kruskal–Wallis**	**Post-hoc test Mann–Whitney p-value**		
Test	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Between-group difference**	**LFEM vs. HFEM**	**LFEM vs. CM**	**HFEM vs. CM**
SF-36 mental health dimension	69.56(58.71–80.22)	57.13(37.60–73.77)	60.33(37.42–69.67)	**p=0.001**	**p=0.003**	**p=0.001**	p=0.746
HADS depression	3(1–4)	5(2–8)	6(2–8)	**p=0.010**	**p=0.015**	**p=0.012**	p=0.789

CSI, central sensitization inventory; CM, chronic migraine; HADS, hospital anxiety and depression scale; HDI, headache disability inventory; HFEM, high frequency episodic migraine; IQR, interquartile range; LFEM, low frequency episodic migraine; n, number; SD, standard deviation; SF-36, study short form 36; vs.: versus.

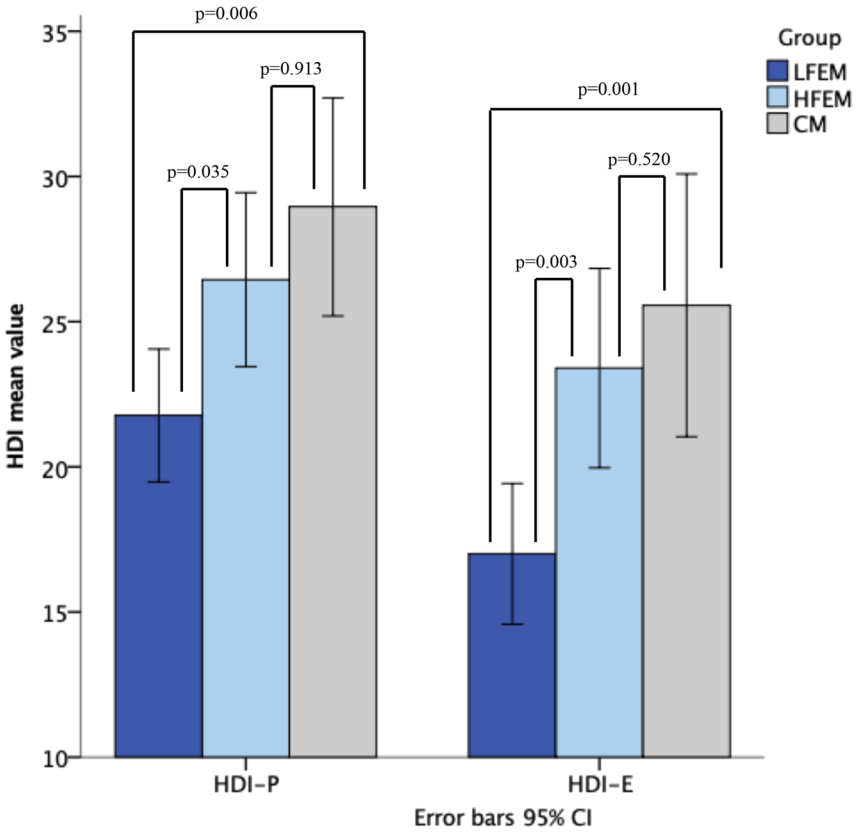

Figure 2: Headache disability inventory. CI, confidence interval; CM, chronic migraine; HDI, headache disability inventory; HDI-E, headache disability inventory emotional; HDI-P, headache disability inventory physical; HFEM, high frequency episodic migraine; ICDH, international classification headache disorders; LFEM, low frequency episodic migraine; p=p-value.

Table 4: Medical outcomes study short form 36.

Normal data	**LFEM (n=68)**	**HFEM (n=45)**	**CM (n=23)**	**Result from ANOVA**	**Post-hoc test Bonferroni p-value**		
Test	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Between-group difference**	**LFEM vs. HFEM**	**LFEM vs. CM**	**HFEM vs. CM**
SF-36 vitality	55.44(15.11)	50.44(15.37)	44.57(21.37)	**p=0.019**	p=0.345	**p=0.020**	p=0.492
SF-36 mental health	65.65(16.47)	56.89(19.33)	59.83(17.99)	**p=0.034**	**p=0.034**	p=0.526	p=1.000
SF-36 general health	63.67(18.07)	55.33(20.21)	53.48(20.19)	**p=0.025**	p=0.075	p=0.087	p=1.000
Non-normal data	**LFEM (n=68)**	**HFEM (n=45)**	**CM (n=23)**	**Result from Kruskal–Wallis**	**Post-hoc test Mann–Whitney p-value**		
Test	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Between-group difference**	**LFEM vs. HFEM**	**LFEM vs. CM**	**HFEM vs. CM**
SF-36 physical functioning	95(85–100)	90(80–95)	85(70–95)	**p=0.004**	**p=0.015**	**p=0.003**	p=0.271
SF-36 physical role	75(31.25–100)	50(12.5–100)	50(0–75)	**p=0.009**	p=0.061	**p=0.003**	p=0.200
SF-36 role emotional	100(66.67–100)	66.67(0–100)	66.67(0–100)	**p=0.010**	**p=0.016**	**p=0.009**	p=0.657
SF-36 social functioning	75(62.5–87.5)	50(43.75–75)	50(50–62.5)	**p<0.001**	**p=0.001**	**p=0.002**	p=0.931
SF-36 bodily pain	57.50(45–70)	45(33.75–55)	45(35–45)	**p=0.001**	**p=0.004**	**p<0.001**	p=0.563

CM, chronic migraine; HFEM, high frequency episodic migraine; IQR, interquartile range; LFEM, low frequency episodic migraine; n, number; SD, standard deviation; SF-36, study short form 36; vs.: versus.

between LFEM and HFEM (p=0.034). No difference was found in the post-hoc analysis for the General health demand (p>0.05). There was no difference in any subscale between HFEM and CM (p>0.05) (Table 4).

Discussion

In this study, many clinical variables were assessed across different migraine populations divided into three subgroups according to headache frequency. High-frequency episodic migraine (HFEM) and chronic migraine (CM) patients showed worse burden of headaches, quality of life, psychological burden, and higher number of symptoms related to sensitization than low-frequency episodic migraine (LFEM), and no differences were observed in these variables between HFEM and CM.

Disability

Our results suggest that patients with HFEM and CM have a worse level of headache-related and health-related disability compared to patients with LFEM, without differences between HFEM and CM.

Headache-related disability

The headache disability index (HDI) was used to assess the functional and emotional effects of headache on everyday life and the perceived disability [15]. In line with previous results, we found that patients with HFEM and CM had a higher level of headache-related disability than LFEM, with no differences between HFEM and CM [11, 12, 33]. These results may be explained by the fact that there is no linear correlation between headache-related disability and headache frequency in patients with migraine [34]. The level of disability gradually increases with the increase of headache frequency until a certain level of chronicity. Then, it remains similar even if the headache frequency further increases [35]. Two recent papers suggested that the headache day threshold to identify migraine patients with the most severe headache-related disability is 10 days in a month [12, 36], supporting the hypothesis that patients with HFEM and CM should both be considered as the most disabled migraine patients. However, other studies reported differences in headache-related disability between HFEM and CM patients [13, 37, 38]. Even if the magnitude of the differences in headache-related disability was higher between LFEM and HFEM than between HFEM and CM [37, 38], some authors argued that patients with HFEM should not be considered as disabled as CM patients [13]. Thus, future studies are needed to reach a consensus.

Health-related disability

While the HDI questionnaire was used to assess the effects of headache on everyday life (headache-related disability) [15], the SF-36 questionnaire was used to assess health-related quality of life without accounting for the cause of the perceived disability (health-related disability) [39]. Our results suggest that the overall quality of life was different between LFEM, HFEM, and CM patients. In particular, the physical health dimension and the emotional health dimension of the quality of life were similar between HFEM or CM patients who, in turn, showed worse results compared to LFEM patients. Similar to what was found for the headache-related disability, these results could be explained by the fact that health-related disability increases with increasing headache frequency leveling off at higher headache frequency [40]. Again, the headache day threshold to identify migraine patients with the most severe health-related disability is below 15 days in a month [40]. As our results are conflicting with a previous study [12, 13], more data is needed before concluding that there is a difference in the quality of life across LFEM, HFEM, and CM patients. However, this study provided a more precise understanding of the relationship between the frequency of headache attack and disability in patients with migraine as it excluded patients with most relevant comorbidities (see exclusion criteria in the population section), while previous studies did not exclude patients with other pathologies that could have enhanced the overall level of disability [12, 13, 37, 38].

Psychological burden

As was found by other authors, our results suggest that patients with HFEM and CM have a worse level of depression than patients with LFEM, whereas there are no differences among patients with HFEM and CM [10, 12, 37]. Migraine and depression seem to share overlapping genetic factors [41, 42] and are linked by a bidirectional relationship; patients with depression are more likely to have migraine, and those with migraine are more likely to have depression [43, 44]. Moreover, depression is one of the significant risk factors for migraine chronification [45, 46], and the severity of depression is positively correlated with the frequency of headache attacks [47]. Thus, these

two clinical conditions can not only be present together but could also affect each other. However, as was found for headache disability, the correlation between headache frequency and the level of depression is not linear [34]. The level of depression gradually increases with increased headache frequency until a turning point below 15 headache days in a month; then, it remains similar even if the headache frequency further increases [40]. The lack of a linear correlation between depression and headache frequency could explain the similarities observed in the level of depression between HFEM and CM and the higher level of depression found in these two subgroups compared to LFEM patients [10, 12, 37]. The close relationship we observed between headache frequency, disability, and depression suggested a correlation between the level of depression and disability [35]. Considering that a recent study showed that migraine patients with concomitant depression had a higher level of disability, independently of the frequency of headache [48], it is plausible that depression could have a role in mediating the perceived disability in patients with migraine. Thus, clinicians should early recognize migraine patients with concomitant depression and address this comorbidity.

Interestingly, unlike previous studies, we found no difference across migraine subgroups regarding anxiety levels [12, 37]. Two factors could explain these results. First, as for depression and disability, anxiety level increases with increasing headache frequency leveling off at higher headache frequency [40]. However, the headache day threshold to identify migraine patients with a higher level of anxiety was lower than depression and disability [40], with one study estimating this turning point to be three days in a month [36]. Thus, all subgroups of migraine patients included in our study showed the same level of anxiety. Secondly, in our study, we excluded patients with a medical diagnosis of any psychiatric pathology, including anxiety. For this reason, the impact of anxiety disorder in the migraine population could have been underestimated in our sample, particularly in patients with higher headache frequency [37].

Symptoms related to sensitization

How to assess signs and symptoms related to sensitization

"Central sensitization" is a term used to define "an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity" [49]. Even if no gold standard exists to assess sensitization, allodynia and hypersensitivity are considered signs of increased sensitization [49] and could be detected through psychophysical examination [50] or questionnaires [51]. On the other hand, the degree of symptomatology related to sensitization could be detected through the CSI questionnaire [52].

Signs and symptoms related to sensitization and migraine frequency

Our results suggested that patients with HFEM and CM showed a worse degree of symptomatology related to sensitization compared to LFEM patients with no differences between HFEM and CM. To the best of our knowledge, this is the first study that assesses the difference in the degree of symptomatology related to sensitization across LFEM, HFEM, and CM patients. However, the relationship between sensitization and migraine frequency has previously been studied, and it was proposed that an increase in sensitization mechanism could have a crucial role in migraine chronification [46, 53]. The migraine cycle is characterized by a cyclic increase in trigeminal and widespread sensitization that reaches its peak in the ictal phase restoring to baseline level afterwards [54, 55]. Increasing migraine frequency shortens the interictal period. Then, the threshold does not restore to baseline level, leading to increased interictal trigeminal and widespread sensitization in those migraine patients with higher migraine frequency than those with lower headache frequency [56, 57]. The increase in sensitization mechanism could increase susceptibility to a headache attack, leading to a vicious circle where the increase in migraine frequency becomes a risk factor for migraine chronification [45]. Our results, together with another study where signs of increased sensitization were enhanced in HFEM and CM patients compared to LFEM without differences between HFEM and CM [37], suggested that the turning point which identifies migraine patients with higher signs and symptoms related to sensitization is somewhere below the threshold of 15 days in a month. The similarity in sensitization level found between HFEM and CM patients could partially explain why some authors did not find a significant difference in signs of sensitization between EM and CM patients [26, 58, 59]. However, these results have to be carefully interpreted for two main reasons. First, the CSI questionnaire could only be considered a tool to assess sensitization symptomatology, which is different than clinical examination for signs of sensitization [60]. Its correlation with psychophysical tests has been inconsistent, varying among different studies according to the psychophysical test used and the population. CSI showed weak or fair correlation with local and widespread hypersensitivity, temporal summation, and no or weak correlation with conditioned pain modulation in

patients with shoulder pain, temporomandibular disorders, spinal pain, knee osteoarthritis [60–64]. On the other hand, even if a positive correlation was found between CSI and brain GABA level in migraine patients, a biomarker of migraine [31, 65], no study ever assessed the correlation between CSI and signs of sensitization in the migraine population. Thus, the CSI questionnaire could not be considered a direct proxy for sensitization in migraine patients. Secondly, even if one study found signs of enhancing ictal trigeminal sensitization in HFEM and CM compared to LFEM without differences between HFEM and CM [37], there is still no evidence of differences in interictal trigeminal or widespread sensitization across LFEM, HFEM, and CM subgroups. Moreover, different studies using psychophysical pain measures did not find a significant correlation between headache frequency and signs of sensitization [25, 66, 67]. Therefore, a better assessment of the difference in manifestations of sensitization between HFEM and CM with different quantitative sensory test modalities is necessary before drawing firm conclusions.

The most disabled segment of the migraine population

The present study supported that patients with HFEM could be considered similar to CM patients regarding disability and clinical characteristics. Therefore, these two subgroups of patients, who accounted for half of the total sample included, are the most disabled segment of the migraine population. Consequently, the current classification of headache underestimates the realistic percentage of patients with worse clinical manifestations of migraine. Due to minimal evidence available in support of this suggestion and the conflicting results, more data are needed to suggest changing the current definition of CM as already suggested by other authors [10, 13]. Considering that different authors used different numbers of monthly headache days as a cut-off value to define the difference between LFEM and HFEM [10–13], a general agreement about this cut-off value should be reached among researchers so that future studies in this field can be comparable. In the future, a Delphi study could be used to define a generally accepted definition of LFEM, HFEM.

Limitations

This study had several limitations. First, the population included, as only patients seeking medical help in a Headache Center were recruited in this study. Hence these are the most severely affected patients explaining why the total number of CM included in this study exceeded the overall prevalence of CM patients in the migraine population [68]. Secondly, given that slightly less than half of the patients initially recruited were excluded for age, concomitant pathologies, and concomitant diagnosis of medication overuse headache, the external validity of these results should be interpreted with caution without generalizing them to the entire migraine population. Thirdly, the sample size was small compared to most surveys assessing clinical and general characteristics in the headache population [10–12]. Another limitation of this study was the questionnaires used. Although the most recommended questionnaires to assess disability in the migraine population are Migraine Disability Assessment Scale (MIDAS) and HIT-6, Headache impact test (HIT-6) [69], the HDI questionnaire was used. The reason for selecting the HDI questionnaire was that the results are part of a larger cohort study that aims to assess differences in clinical variables among patients with primary headaches. HDI is more appropriate to assess disability when different types of headaches are included [70, 71]. However, the inclusion of another questionnaire to assess disability should have been considered to avoid this limitation. In order to assess the symptomatology of sensitization, the central sensitization inventory (CSI) questionnaire was used. Nevertheless, due to its weak correlation with signs of sensitization [60–62], this questionnaire cannot be considered a direct proxy for sensitization in migraine patients, and future studies should consider using psychophysical pain measures to assess differences in sensitization between LFEM, HFEM, and CM. Finally, a confounder that could have accounted for a reduction in the disability of the CM patients was the higher percentage of patients already in treatment with prophylactic therapy in this subgroup. Even if the inclusion procedure used in this study was designed to recruit patients at their first visit to the Headache Center, one-third of CM were already in treatment in the Headache Center. Since CM could be considered as a progression of EM over time [46], it is difficult to recruit patients with CM naïve to any prophylactic treatment and control for this limitation.

Conclusion

This study showed that patients with high-frequency episodic migraine and chronic migraine have a worse disability due to headache, worse health-related quality of life, an increasing number of symptoms related to sensitization, and a high level of depression compared to

patients with low-frequency episodic migraine. No differences regarding any of these variables were found between chronic migraine and high-frequency episodic migraine, suggesting that patients in these two subgroups were particularly impacted by their disease and could be included in the same segment of migraine patients.

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Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and has been approved by the Ligurian regional ethic committee (244/2018) and by the ethic committee of "Area Vasta Emilia Nord" (18305/2019).

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