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Allodynia in migraine patients with fibromyalgia comorbidity: focus on small fiber pathology

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ABSTRACT

Background: Cutaneous allodynia is a clinical marker of central sensitization in migraine and is associated with greater migraine severity and poorer outcomes. Fibromyalgia (FM) is a frequent comorbidity of migraine that may further enhance central sensitization, whereas small fibre pathology (SFP) has been identified in a substantial proportion of FM patients. Whether FM comorbidity and peripheral small-fibre abnormalities contribute to cutaneous allodynia in patients with migraine remains unclear. We investigated cutaneous allodynia and migraine characteristics in patients with migraine with and without FM and, within the FM cohort, according to skin biopsy findings.

Methods: In this retrospective cross-sectional study, 212 patients with migraine were included: 106 patients with FM who had undergone skin biopsy (65 with pathological and 41 with normal biopsy findings) and 106 patients without FM with the same sex distribution and comparable age. FM and migraine were diagnosed according to current clinical criteria. Cutaneous allodynia was assessed using a standardized clinical checklist. Skin biopsy was performed at the proximal thigh and distal leg, and SFP was defined by reduced intraepidermal nerve fibre density (IENFD). The comparison between patients with and without FM was the primary analysis; comparisons according to skin biopsy findings and correlations with IENFD were secondary analyses. Migraine characteristics, allodynia, and migraine-related disability were compared across groups.

Results: The proportion of chronic migraine (CM) was similar in patients with and without FM (19.8% *vs.* 21.7%; p=0.866). Cutaneous allodynia was more frequent in patients with FM than in those without FM (82.1% *vs.* 64.2%; p=0.005), and moderate-to-severe allodynia affected 50.9% *vs.* 16.0% of patients, respectively (p<0.001). Median allodynia scores were 6 (interquartile range [IQR] 4-8) in patients with FM and pathological biopsy findings, 6 (3-7) in those with normal biopsy findings, and 3 (2-5) in patients without FM (p<0.001; ε^2=0.133), with no difference between the two FM subgroups; allodynia scores were not associated with proximal or distal IENFD. Greater allodynia was associated with greater migraine-related disability among participants with available Migraine Disability Assessment (MIDAS) data, including after adjustment for age, headache frequency, and FM status (partial ρ=0.267, p=0.002).

Conclusions: FM comorbidity identifies patients with migraine with a greater burden of cutaneous allodynia, independently of migraine chronification. This sensory hypersensitivity was not clearly related to the presence or extent of structural small-fibre loss, supporting a predominant contribution of central sensitization. Structural and functional assessments of small fibres, including trigeminal territories, may further clarify the contribution of peripheral abnormalities to migraine-related allodynia in FM.

Key words: migraine; fibromyalgia; cutaneous allodynia; small fibre pathology; intraepidermal nerve fibre density.

Introduction

Cutaneous allodynia in migraine refers to pain elicited by normally non-painful thermal or mechanical stimuli applied to the skin or scalp. It typically develops during migraine attacks, initially involving cephalic regions and potentially spreading to extracephalic areas, and is considered a clinical manifestation of central sensitization along the trigeminovascular-thalamic pathway. (1) Approximately 60% of individuals with migraine included in the American Migraine Prevalence and Prevention study reported some degree of cutaneous allodynia, with severe allodynia occurring in approximately 20%. (2,3) Greater migraine severity is associated with a higher burden of allodynia in large population-based cohorts, (4) and the presence of allodynia has been associated with poorer migraine outcomes. (5)

Among the comorbid conditions that may contribute to the expression of central sensitization in migraine, fibromyalgia (FM) is of particular relevance. FM is a complex disorder characterized by widespread pain, fatigue, sleep disturbances, and cognitive symptoms ("brain fog"). (6) Headache is one of the main associated symptoms, together with bowel discomfort and depression. (6) Tension-type headaches and migraines are the most common headache disorders reported in FM cohorts. (7-10)

Migraine is one of the most frequent neurological comorbidities of FM, with a prevalence approaching 50-60%, whereas chronic migraine (CM) has been reported in approximately 10% of patients. (10-13) Conversely, patients with migraine and comorbid FM tend to have a higher risk of migraine chronification, greater disability, and poorer response to preventive treatments. (12,14-16) Because CM is characterized by persistent central sensitization and enhanced pain facilitation, (17) its coexistence with FM may identify patients with a greater burden of altered central pain processing.

Another important source of heterogeneity in FM is small fibre pathology (SFP). Reduced intraepidermal nerve fibre density (IENFD) has been reported in approximately half of patients with FM, suggesting that peripheral nociceptive abnormalities may contribute to pain generation in a substantial subgroup. (18-25) Rather than representing a classical peripheral neuropathy, SFP in FM may provide abnormal afferent input capable of maintaining or amplifying central sensitization. (20,21) Likewise, although migraine has traditionally been regarded predominantly as a disorder of altered central pain processing, activation of the trigeminovascular system and calcitonin gene-related peptide-mediated mechanisms highlight the interplay between peripheral and central mechanisms in migraine pathophysiology. (26,27)

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In a recent study by our group, (28) migraine comorbidity was associated with a greater burden of FM symptoms, whereas SFP identified by skin biopsy did not show a relevant association with FM clinical severity. However, patients with CM exhibited a more severe FM profile when peripheral small-fibre denervation was also present. This association may identify a subgroup characterized by greater functional impairment and symptom burden, potentially reflecting the interaction between persistent central sensitization and ongoing peripheral nociceptive input.

Comorbid FM is associated with a higher likelihood and greater severity of allodynic symptoms in patients with migraine. (29) Allodynia is also a common positive sensory sign in small-fibre neuropathy (SFN); however, its presence does not necessarily indicate greater structural small-fibre loss on skin biopsy, as pain and allodynia may result from nociceptor hyperexcitability and/or central sensitization in addition to structural denervation. (30) Accordingly, the relationship between SFP and the severity of allodynia remains debated in FM cohorts. (22,31) The coexistence of SFP and migraine may therefore contribute to the presence and severity of allodynia and to a more severe migraine phenotype, potentially providing a pathophysiological explanation for the more severe clinical profile that we recently observed in patients with FM, CM, and SFP. (28)

In the present study, we aimed to examine cutaneous allodynia and migraine attack characteristics in a cohort of patients with migraine and comorbid FM who underwent skin biopsy, and to investigate their relationship with the presence of SFP.

Results

Study population. The final sample included 212 participants, *i.e.*, 106 migraine patients with FM and 106 without FM. The two groups had the same sex distribution (98 women and 8 men in each group) and were comparable for age. The proportion of CM was comparable (19.8% *vs.* 21.7%; Fisher's exact p=0.866). Concerning the main migraine characteristics, bilateral pain was more frequent in patients with FM (72.6% *vs.* 40.6%; p<0.001). Photophobia (90.6% *vs.* 81.1%; p=0.075) and migraine with aura (5.7% *vs.* 14.2%; p=0.064) did not differ significantly between the two groups.

Allodynia (score ≥3) was present in 87 of 106 patients with FM (82.1%) and in 68 of 106 patients without FM (64.2%) (Fisher's exact p=0.005; odds ratio 2.56). The distribution of allodynia severity also differed between the two groups (χ^2=30.16, df=3, p<0.001; Cramér's V=0.377), with moderate-to-severe allodynia in 54 of 106 patients with FM (50.9%) compared with 17 of 106 patients without FM (16.0%) (Fisher's exact p<0.001). Total allodynia score was also higher in the combined FM group (median 6, interquartile range [IQR] 3.25-8) than in patients without FM (median 3, IQR 2-5), with both FM subgroups showing significantly higher scores than patients without FM (Holm-adjusted p<0.001 for both comparisons).

Secondary analyses across the three groups. Of the final sample, 106 patients had migraine without FM, 65 patients had migraine and FM with pathological skin biopsy findings, and 41 patients had migraine and FM with normal skin biopsy findings (**Table 1**). Women represented 92.5%, 93.8%, and 90.2% of the three groups, respectively (χ^2=0.47, p=0.792).

Median age was 48 years (IQR 43-53) in patients without FM, 50 years (44-55) in patients with FM and pathological biopsy findings, and 45 years (39-50) in those with normal biopsy findings. Age differed significantly across groups (Kruskal-Wallis H=8.25, p=0.016; ε^2=0.030), although the overall effect size was small. Patients with pathological biopsy findings were older than those with normal biopsy findings (Holm-adjusted p=0.016), whereas the difference between the pathological-biopsy and non-FM groups was not significant (Holm-adjusted p=0.375). The non-FM group was also slightly older than the normal-biopsy group (Holm-adjusted p=0.043).

Migraine characteristics. Age at headache onset and monthly migraine frequency did not differ significantly across groups. Median monthly migraine frequency was 6 attacks (IQR 3-10.8) in patients without FM, 7 (4-15) in patients with FM and pathological biopsy findings, and 6 (4-10) in those with normal biopsy findings (H=1.84, p=0.398).

CM was present in 23 of 106 patients without FM (21.7%), 13 of 65 patients with FM and pathological biopsy findings (20.0%), and 8 of 41 patients with FM and normal biopsy findings (19.5%), with no evidence of a difference across groups (χ^2=0.12, p=0.943; Cramér's V=0.024).

Bilateral pain was substantially more frequent in the FM groups than in patients without FM, occurring in 78.5% of patients with pathological biopsy findings, 63.4% of those with normal biopsy findings, and 40.6% of patients without FM (χ^2=24.52, p<0.001; Cramér's V=0.340; false discovery rate [FDR]-adjusted q<0.001). Pairwise differences were significant for the pathological-biopsy *vs.* non-FM groups (Holm-adjusted p<0.001) and the normal-biopsy *vs.* non-FM groups (Holm-adjusted p=0.033), but not between the two FM groups (Holm-adjusted p=0.118).

Photophobia was reported by 81.1% of patients without FM, 84.6% of patients with pathological biopsy findings, and 100% of those with normal biopsy findings (χ^2=8.78, p=0.012; FDR-adjusted q=0.050). Photophobia was more frequent in the normal-biopsy group than in both the non-FM group (Holm-adjusted p=0.003) and the pathological-biopsy group (Holm-adjusted p=0.013).

Table 1. Demographic and migraine characteristics across the three study groups.

Variable	Migraine without FM (n=106)	FM + pathological biopsy (n=65)	FM + normal biopsy (n=41)	Overall test
Women, n (%)	98 (92.5)	61 (93.8)	37 (90.2)	χ^2=0.47; p=0.792
Age, years, median (IQR)	48 (43-53)	50 (44-55)	45 (39-50)	H=8.25; p=0.016; ε^2=0.030
Monthly attacks, median (IQR)	6 (3-10.8)	7 (4-15)	6 (4-10)	H=1.84; p=0.398
Chronic migraine, n (%)	23 (21.7)	13 (20.0)	8 (19.5)	χ^2=0.12; p=0.943; Cramér's V=0.024
Bilateral pain, n (%)	43 (40.6)	51 (78.5)	26 (63.4)	χ^2=24.52; p<0.001; Cramér's V=0.340
Photophobia, n (%)	86 (81.1)	55 (84.6)	41 (100)	χ^2=8.78; p=0.012
Migraine with aura, n (%)	15 (14.2)	3 (4.6)	3 (7.3)	χ^2=4.49; p=0.106

FM, fibromyalgia; χ^2, chi-square test; IQR, interquartile range; H, Kruskal-Wallis statistic; ε^2, epsilon squared. Bilateral pain remained significant after false discovery rate correction (q<0.001), whereas photophobia reached the significance threshold (q=0.050).

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Pain quality, phonophobia, osmophobia, nausea, and vomiting did not differ significantly across groups after correction for multiple comparisons. Migraine with aura was present in 14.2% of patients without FM, 4.6% of patients with pathological biopsy findings, and 7.3% of those with normal biopsy findings, without a significant group difference (χ^2=4.49, p=0.106) (**Table 1**).

Migraine-related disability. Migraine Disability Assessment (MIDAS) scores were available for all 106 patients without FM but for only 27 of the 106 patients with FM. Among participants with available data, median MIDAS score was 24.5 (8.0-49.8) in patients without FM, 32.5 (22.3-55.0) in patients with FM and pathological biopsy findings, and 56.0 (24.0-75.0) in those with normal biopsy findings (**Table 2**). The overall three-group difference was not significant (H=3.96, p=0.138). Neither the pathological-biopsy group (Mann-Whitney U=1005.0, Holm-adjusted p=0.234) nor the normal-biopsy group (U=765.0, Holm-adjusted p=0.179) differed significantly from the non-FM group. When the two FM subgroups were combined, MIDAS scores were slightly higher than in the non-FM group, although the difference did not reach statistical significance (median 38.0, IQR 23.5-58.5; U=1771.0, p=0.057).

Cutaneous allodynia. Total allodynia score differed significantly across groups (H=29.84, p<0.001; ε^2=0.133). Median scores were 3 (IQR 2-5) in patients without FM, 6 (4-8) in patients with FM and pathological biopsy findings, and 6 (3-7) in those with normal biopsy findings. Allodynia scores were significantly higher in both FM groups than in the non-FM group (Holm-adjusted p<0.001 for both comparisons), whereas no difference was observed between the two FM groups (**Table 3**).

Allodynia, defined as a score ≥3, was present in 68 of 106 patients without FM (64.2%), 55 of 65 patients with FM and pathological biopsy findings (84.6%), and 32 of 41 patients with FM and normal biopsy findings (78.0%) (**Figure 1A**). The overall group difference was significant (χ^2=9.21, p=0.010). In pairwise comparisons, allodynia was more frequent in the pathological-biopsy group than in the non-FM group (Holm-adjusted p=0.014). The difference between the normal-biopsy FM group and the non-FM group did not remain significant after correction (Holm-adjusted p=0.237), and no difference was observed between the two FM subgroups (Holm-adjusted p=0.441).

The distribution of allodynia severity also differed across groups (χ^2=31.78, p<0.001; **Figure 1B**, **Table 3**). Severe allodynia occurred in 3 of 106 patients without FM (2.8%), 11 of 65 patients with pathological biopsy findings (16.9%), and 5 of 41 patients with normal biopsy findings (12.2%). Moderate allodynia occurred in 13.2%, 33.8%, and 39.0% of the three groups, respectively. Overall, moderate-to-severe allodynia affected 16.0% of patients without FM, compared with 50.8% of patients with pathological biopsy findings and 51.2% of those with normal biopsy findings.

Thus, the overall burden of allodynia was greater in patients with FM, whereas the similar severity observed in the two FM subgroups provided no evidence of a clear association between pathological skin biopsy findings and allodynia severity.

Among the 133 participants with both MIDAS and allodynia data available, MIDAS score was positively correlated with total allodynia score (Spearman's ρ=0.316, p<0.001). The association remained significant after adjustment for age, monthly migraine frequency, and FM status (partial ρ=0.267, p=0.002). A significant correlation was also observed within the non-FM group (ρ=0.278, p=0.004) and remained unchanged after adjustment for age and monthly migraine

Table 2. Exploratory MIDAS analyses.

Analysis/group	n	MIDAS, median (IQR)	Comparison
Paired controls	27	30.0 (13.0-60.0)	FM vs. paired controls: Wilcoxon p=0.226
Combined FM	27	38.0 (23.5-58.5)	Paired difference 6.0 (−19.5 to 29.5)
FM + pathological biopsy	16	32.5 (22.3-55.0)	FM + pathological biopsy *vs.* normal biopsy:
FM + normal biopsy	11	56.0 (24.0-75.0)	U=102.5; p=0.489
All controls	106	24.5 (8.0-49.8)	Three-group H=3.96; p=0.138
FM + pathological biopsy *vs.* all controls	16 *vs.* 106	32.5 *vs.* 24.5	U=1005.0; Holm p=0.234
FM + normal biopsy *vs.* all controls	11 *vs.* 106	56.0 *vs.* 24.5	U=765.0; Holm p=0.179

MIDAS, Migraine Disability Assessment; IQR, interquartile range; FM, fibromyalgia; U, Mann-Whitney U test; H, Kruskal-Wallis statistic. The first available numerical MIDAS score was used irrespective of biopsy date. Analyses were exploratory because MIDAS was available in a limited subset of the FM cohort.

Table 3. Cutaneous allodynia across the three study groups.

Outcome	Migraine without FM (n=106)	FM + pathological biopsy (n=65)	FM + normal biopsy (n=41)	Overall test
Allodynia score, median (IQR)	3 (2-5)	6 (4-8)	6 (3-7)	H=29.84; p<0.001; ε^2=0.133
Allodynia present, n (%)	68 (64.2)	55 (84.6)	32 (78.0)	χ^2=9.21; p=0.010
Absent, n (%)	38 (35.8)	10 (15.4)	9 (22.0)	
Mild, n (%)	51 (48.1)	22 (33.8)	11 (26.8)	
Moderate, n (%)	14 (13.2)	22 (33.8)	16 (39.0)	χ^2=31.78; p<0.001
Severe, n (%)	3 (2.8)	11 (16.9)	5 (12.2)	
Moderate-to-severe, n (%)	17 (16.0)	33 (50.8)	21 (51.2)	

FM, fibromyalgia; IQR, interquartile range; H, Kruskal-Wallis statistic; ε^2, epsilon squared; χ^2, chi-square test. Cutaneous allodynia was defined as a total score ≥3. For allodynia presence, Holm-adjusted pairwise p-values were 0.014 for pathological-biopsy FM *vs.* migraine without FM, 0.237 for normal-biopsy FM *vs.* migraine without FM, and 0.441 for pathological- *vs.* normal-biopsy FM. For total allodynia score, both FM groups differed significantly from the non-FM group (both Holm-adjusted p<0.001), whereas the two FM subgroups did not differ significantly.

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frequency (partial ρ=0.278, p=0.004). Among patients with FM, the association was in the same positive direction but did not reach statistical significance (n=27; ρ=0.252, p=0.205; adjusted partial ρ=0.211, p=0.290).

Relationship between allodynia and intraepidermal nerve fiber density. The relationship between allodynia severity and IENFD was evaluated across the entire FM cohort (n=106) (**Table 4**). Total allodynia score was not correlated with proximal IENFD (Spearman's ρ=−0.055, p=0.578) or distal IENFD (ρ=0.012, p=0.902). These findings were unchanged after adjustment for age and monthly migraine frequency (proximal IENFD: partial ρ=−0.042, p=0.670; distal IENFD: partial ρ=−0.002, p=0.986). Thus, allodynia severity was not associated with the degree of epidermal nerve fibre loss in patients with FM.

Discussion

In the present study, we investigated whether migraine characteristics, with particular focus on cutaneous allodynia, differed according to the presence of FM and SFP as assessed by skin biopsy. The migraine control group was selected to provide a comparable distribution of episodic and CM, thereby minimizing the possibility that differences in allodynia could be primarily explained by migraine chronification rather than by FM comorbidity or SFP. Nevertheless, patients with migraine and comorbid FM had significantly higher allodynia scores, independently of skin biopsy findings. The prevalence of allodynia was numerically highest among patients with peripheral small-fibre denervation and was significantly higher in this subgroup than in migraine patients without FM.

The greater burden of cutaneous allodynia observed in patients with FM is consistent with previous evidence indicating that FM comorbidity identifies a migraine phenotype characterized by enhanced central sensitization and greater sensory hypersensitivity. (28) This association may be particularly relevant in CM, in which repeated or persistent trigeminovascular activation may facilitate central sensitization. (32,33) Accordingly, assessment of cutaneous allodynia may provide clinically relevant information on sensory sensitization in migraine patients with FM.

Here we established a weak but reasonable association between allodynia and SFP in migraine patients with FM comorbidity, as a relevant number of patients with peripheral denervation presented with acute allodynia. Moreover, patients without outstanding SFP could present it in perspective, (25) so the lack of a statistically significant difference between migraine-FM patients with or without SFP at the time of the study could have a rationale. Allodynia characterizes patients with SFN, especially those with a mild level of denervation, which implies hyperfunction of residual fibers. (30) The degree of denervation is only mild in patients with FM, while they have a prominent tendency to central sensitization and allodynia, (34) so the association with SFP could enhance the expression of allodynia in FM cohorts. However, there is

Table 4. Correlations between allodynia score and IENFD in the complete FM cohort.

IENFD site	n	Spearman rho	p-value	Adjusted partial rho	Adjusted p-value
Proximal	106	−0.055	0.578	−0.042	0.670
Distal	106	0.012	0.902	−0.002	0.986

IENFD, intraepidermal nerve fibre density; FM, fibromyalgia. Adjusted partial rank correlations control for age and monthly migraine frequency.

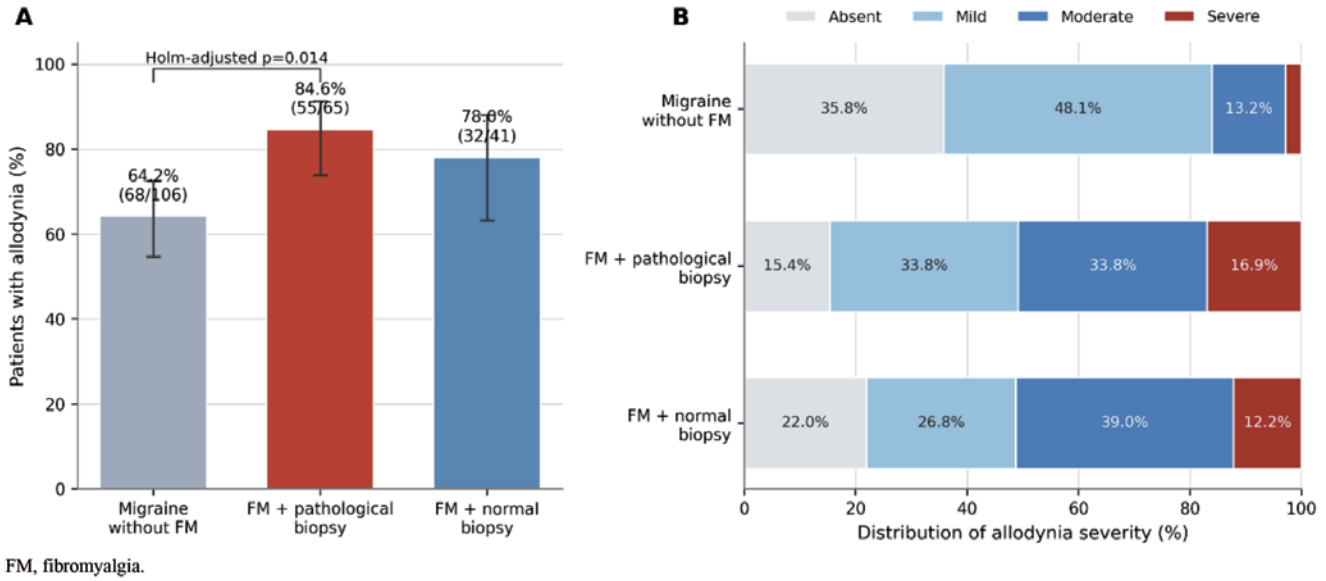


Figure 1. Cutaneous allodynia across study groups. A) Prevalence of cutaneous allodynia (score ≥3), with 95% Wilson confidence intervals. Allodynia was more frequent in both FM groups than in patients with migraine without FM, although the pairwise comparison remained significant after Holm correction only for the pathological-biopsy FM group *vs.* the non-FM group (p=0.014). No difference was observed between the two FM subgroups (p=0.441). B) Distribution of absent, mild, moderate, and severe allodynia across the three groups. The overall severity distribution differed significantly across groups (χ^2=31.78, p<0.001).

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no topographic coherence between peripheral denervation evaluated at the lower limb and acute allodynia during migraine attack. Cutaneous allodynia during migraine attacks is best explained by sensitization of central trigeminovascular neurons in the trigeminocervical complex driven by meningeal trigeminal nociceptors that include both thinly myelinated Aδ and unmyelinated C afferents, with additional evidence for a peripheral cutaneous mechanism. (35) However, the distribution of pain in FM patients with abnormal skin biopsy could imply that central sensitization causes a lack of coherence between symptoms and organic nociceptive fibers damage, without excluding the involvement of other territories different from classical length-dependent SFP. (36) In fact, in a relevant proportion of patients with FM, corneal confocal microscopy revealed denervation also in the trigeminal territory. (22,37) Apart from a more frequent representation of allodynia in FM patients with SFP, its severity was quite similar in the two FM groups, independently of skin biopsy results, and higher than in migraine without FM, as a confirmation that phenomena of central sensitization are enhanced in FM patients.

Another interesting finding that emerged in patients with FM was the prevalence of bilateral pain, which was slightly favored by SFP. The diffusion of pain on both cranial sites could be an epiphenomenon of FM clinical picture and central sensitization, probably for the tendency of headache spreading in accord to an allodynic phenomenon. Migraine pain is rarely strictly fixed to one side, and laterality can be variable as long as other features support the diagnosis. (38) The present study results could suggest that comorbidity with FM could favor bilateral headache. Moreover, associated symptoms of migraine attack, such as photophobia, were more represented in FM patients without skin biopsy evidence of SFP. Photophobia (light intolerance/visual hypersensitivity, sometimes photo-allodynia) is common in FM and is best interpreted as part of multisensory hypersensitivity from central sensitization/nociplastic pain, with human psychophysical and neuroimaging data showing lower light-discomfort thresholds and greater unpleasantness to visual stimuli than controls. (39) The reason why it prevailed in non-SFP patients does not have an obvious explanation, and deserves further confirmation in larger series. The possibility that a partial corneal denervation in patients with SFP was a protective factor against photophobia remains remote, as the prevalence of this symptom was the same also in non-FM patients. Other features of migraine attacks implying a vegetative involvement were similar in the three groups, and were not influenced by FM or the presence of SFP.

MIDAS scores were obtained in a limited proportion of patients with FM, and they were similar between FM groups and controls. The MIDAS score measures the global disability for migraine in terms of days lost from work and daily living activities. In the global number of migraine patients and in the groups of controls without FM, disability scores showed a correlation with allodynia, also after correction for headache frequency. This means that allodynia *per se* is associated with more severe migraine attacks and a greater need to avoid habitual activities. (40,41) The lack of significance of the correlation test in the FM groups is linked to the small number of FM patients with available MIDAS scores. As a matter of fact, if allodynia causes more severe disability, it is conceivable that in the FM group, especially in those patients with SFP, disability could prevail with respect to non-FM and non-SFP patients, a statement that deserves confirmation in larger series.

The present study has some limitations. First, the study had a retrospective design and was based on previously collected clinical data, which resulted in incomplete information for some variables; in particular, MIDAS scores were available for only 27 of the 106 patients with FM. Second, the study groups were derived from different sources: patients with FM belonged to a cohort that systematically underwent skin biopsy, whereas controls were retrieved from the general headache database and did not undergo skin biopsy, so that the presence of subclinical SFP in the control group cannot be excluded. Third, controls were selected non-randomly and without blinding by selecting them against the whole FM cohort with the same sex distribution and comparable age and by balancing the proportion of CM; although this procedure was intended to minimize confounding by demographic factors and migraine chronification, a selection bias cannot be ruled out. In addition, because controls were selected against the FM cohort as a whole, the subsequent stratification according to skin biopsy findings resulted in subgroups that differed in age; although the magnitude of this difference was small (ε^2=0.030) and controls were comparable in age to the combined FM group, a residual influence of age on the comparisons involving the FM subgroups cannot be completely excluded. Fourth, the size of the two FM subgroups was relatively limited, which reduced the statistical power of the secondary analyses. Moreover, structural small-fibre abnormalities were assessed by skin biopsy at the lower limb, whereas migraine-related allodynia predominantly reflects sensory processing within cephalic and trigeminal territories. This anatomical mismatch limits direct interpretation of the relationship between IENFD and cutaneous allodynia. Finally, skin biopsy provides a structural measure of small-fibre integrity but does not directly assess nociceptor function or hyperexcitability, which may be particularly relevant to positive sensory phenomena such as allodynia.

Conclusions

The present results confirm that migraine patients with FM comorbidity have a major expression of allodynia as a central sensitization biomarker. The influence of SFP weakly influenced this clinical feature, with a higher number of allodynic patients. Considering that the allodynic profile is linked to major migraine-related disability, also independent of headache frequency, checking for FM comorbidity is useful in migraine assessment. The role of SFP in favoring signs of central sensitization in the cranial district could be confirmed in longitudinal study designs, possibly assessing also denervation in the trigeminal territories with face skin biopsy and possibly confocal microscopy.

Materials and Methods

Study design and participants. This retrospective monocentric cross-sectional study combined data from patients with migraine-FM who had undergone skin biopsy with data from a general headache database, using only the first available clinical assessment. All patients were recruited and clinically assessed at the Neurophysiopathology Unit, Policlinico General Hospital, Department of Translational Biomedicine and Neuroscience, University of Bari "Aldo Moro" (Italy). The FM cohort comprised 106 patients whose headache diagnoses were verified by the investigator. (42) The comparison cohort comprised 106 migraine patients without FM from the general headache database. The general headache database is a local institutional database of the Neurophysiopathology Unit, not publicly available, collecting demographic and clinical data of patients referred to the headache outpatient service (recruitment period: 2017-2025). In both cohorts, migraine diagnoses were established according to the *International*

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Classification of Headache Disorders, 3rd Edition (ICHD-3) criteria by G.P. and M.d.T., *i.e.*, neurologists experienced in headache disorders, who also performed the clinical assessments, including the allodynia checklist and the MIDAS questionnaire.

Three mutually exclusive groups were then defined: migraine without FM (n=106), migraine with FM and pathological skin biopsy (n=65), and migraine with FM and normal skin biopsy (n=41). FM and headache diagnoses were established according to current clinical criteria. (6,42) CM was identified from the clinical diagnosis recorded at the first visit rather than inferred from the reported number of monthly attacks.

Study procedures, informed consent, and ethics approval followed those described for the parent FM cohort (Ethics Committee approval no. 1076/CE); all participants provided written informed consent for clinical assessment, skin biopsy, and anonymous research use of their data.

Selection of controls. Potential controls were required to have a migraine diagnosis, no FM diagnosis, an available numerical allodynia score, and complete demographic and headache-related data. Records with other primary headache disorders were excluded.

Controls were selected 1:1 without replacement, with the same sex as the corresponding FM patient and the closest possible age; sex was identical in all 106 pairs, and the two groups were comparable for age. The CM proportion was also balanced across groups to minimize confounding by migraine chronification, since higher allodynia prevalence in CM could otherwise influence between-group differences independently of other factors, including peripheral small-fibre denervation. (43) The non-FM and combined FM cohorts each included 98 women and 8 men. Control selection was performed against the whole FM cohort before its stratification according to skin biopsy findings. Control selection was not randomized and was not blinded to the characteristics of the FM cohort; it was intended to obtain a control group comparable to the FM cohort for sex, age, and proportion of CM, which may influence the expression of allodynia. Accordingly, the comparison between controls and the combined FM group was considered the primary analysis, whereas the comparison between the FM subgroups with and without SFP and the correlation between allodynia and IENFD within the FM cohort were considered secondary analyses.

Clinical assessment of migraine. The analysis included age at headache onset, current monthly migraine frequency, CM diagnosis, pain quality (pulsating/throbbing; pressing/tightening), bilateral pain, photophobia, phonophobia, osmophobia, nausea, and vomiting. Monthly frequency was analyzed as a quantitative variable, not as a substitute for the ICHD-3 CM diagnosis.

Aura was considered present only when the recorded diagnosis was migraine with aura and the aura-presence variable was coded 1; individual aura symptoms (scintillating phenomena, visual spots, zig-zag lines, blurred vision, facial or limb paraesthesia) were analyzed only in this subgroup.

Skin biopsy. Patients with FM underwent 3-mm punch skin biopsy at the proximal thigh and distal leg per international recommendations, (44-46) with samples fixed, cryopreserved, sectioned at 50 µm, and immunostained for protein gene product 9.5. IENFD was quantified at the Carlo Besta Neurological Institute (Milan, Italy) by blinded investigators and compared with age- and sex-adjusted normative values; (44-46) findings were classified as normal or pathological, with pathological findings defined as reduced IENFD at the proximal site, distal site, or both.

Assessment of cutaneous allodynia. Cutaneous allodynia was assessed with a 12-item checklist covering mechanical and thermal stimuli involving the head, face, and body, each item coded 0 (absent/not applicable) or 1 (present), for a total score of 0-12, classified as absent (0-2), mild (3-5), moderate (6-8), or severe (≥9). Total allodynia score was the primary outcome; allodynia presence (score ≥3) and severity category were secondary outcomes.

The general headache database contained total allodynia scores but not individual-item responses; therefore, total score and allodynia presence were compared across all three groups, while item-level analyses were restricted to the two FM subgroups and considered exploratory.

Statistical analysis. Continuous variables are reported as median (IQR), with mean and standard deviation provided where informative; categorical variables as number and percentage. Because allodynia score and monthly migraine frequency were non-normally distributed, group comparisons used the Kruskal-Wallis test, with pairwise Mann-Whitney U tests and Holm correction. In the primary analysis, patients with migraine without FM were compared with the combined FM group using the Mann-Whitney U test for continuous variables and Fisher's exact test or the chi-square test for categorical variables; three-group comparisons and analyses within the FM cohort divided into two subgroups according to the presence or absence of small-fiber pathology were also performed.

Categorical variables were compared using the chi-square test or the Fisher-Freeman-Halton exact test when expected cell counts were small, with pairwise comparisons *via* Fisher's exact tests and Holm correction.

The Benjamini-Hochberg FDR procedure was applied to secondary headache-related outcomes; effect sizes are reported as epsilon squared for Kruskal-Wallis tests and Cramér's V for categorical comparisons.

MIDAS scores were compared across groups with the Kruskal-Wallis test and exploratory pairwise Mann-Whitney U tests (Holm correction). The MIDAS-allodynia association was assessed with Spearman's correlation overall and separately in controls and FM patients, and with a partial correlation adjusted for age, monthly frequency, and FM status (within-group analyses: age and frequency only).

All tests were two-sided, with $p<0.05$ considered significant. Analyses used Python 3.12, pandas 2.2, and SciPy 1.17.

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