Chronic pain in multiple sclerosis: Is there also fibromyalgia? An observational study

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Background: Chronic pain is common in persons with multiple sclerosis (MS), but the co-morbidity of fibromyalgia (FM) has yet to be investigated in MS. Objectives of the study were to evaluate, among the various types of chronic pain, the frequency of FM in MS and its impact on MS patients' health-related quality of life (HRQoL).

Material/Methods: 133 MS patients were investigated for the presence and characterization of chronic pain within 1 month of assessment. A rheumatologist assessed the presence FM according to the 1990 ACR diagnostic criteria. Depression, fatigue, and HRQoL were also assessed by means of specific scales.

Results: Chronic pain was present in 66.2% of patients (musculoskeletal in 86.3%; neuropathic in 13.7%; absent in 33.8% [called NoP]). Pain was diagnosed with FM (PFM+) in 17.3% of our MS patients, while 48.9% of them had chronic pain not FM type (PFM–); the prevalence of neuropathic pain in these 2 sub-groups was the same. PFM+ patients were prevalently females and had a higher EDSS than NoP. The PFM+ patients had a more pronounced depression than in the NoP group, and scored the worst in both physical and mental QoL.

Conclusions: In our sample of MS patients we found a high prevalence of chronic pain, with those patients displaying a higher disability and a more severe depression. Moreover, FM frequency, significantly higher than that observed in the general population, was detected among the MS patients with chronic pain. FM occurrence was associated with a stronger impact on patients’ QoL.

MeSH Keywords: Fatigue • Quality of Life – psychology • Depression • Fibromyalgia • Multiple Sclerosis

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Background

Pain is a common and disabling symptom in persons with multiple sclerosis (MS), with a prevalence ranging widely between 29% and 86% [1–3]. Several different pain conditions are associated with MS and may be defined by location, by presumed mechanism, and by duration, ranging from paroxysmal to chronic. Restricting our focus to chronic pain, approximately 75% of MS patients report having had pain within 1 month prior to assessment [4]. One broad category of MS-related pain is central neuropathic pain, which includes dysesthetic extremity pain, a chronic form of pain described as the most common. Other chronic pain conditions are musculoskeletal pain (e.g., back pain), painful tonic spasms, and headache [4].

Fibromyalgia (FM), originally described as a psychogenic disorder or a variant of depression, has recently been considered a model of central neuropathic pain. Neurophysiologic methods able to explore the nociceptive afferent system suggest that in FM patients weak painful stimuli delivered at both tender and non-tender points induce cortical hyperactivation and lead to generalized hyperalgesia [5]. These phenomena have been confirmed by functional magnetic resonance imaging, whose findings showed a significantly greater activation in the anterior insula and the cingulate cortex in response to painful stimuli in FM patients compared to controls [6,7]. A study investigating the intensity-dependence of auditory-evoked cortical potentials found that FM patients are hypervigilant to acoustic stimuli and showed a reduced inhibition response to noxious and intense auditory stimuli. This pattern of “cortical hypervigilance” to multimodal stimuli is well known in FM patients [8–10].

Therefore, on the basis of both neurophysiological and functional magnetic resonance imaging methods [11], it has been supposed that FM is related to CNS malfunction and altered pain transmission and perception, as supported by the augmented stimulus responses transmitted by primary afferent fibers, the impairment of descending inhibitory pain pathways, and the altered release of neurotransmitters involved in pain modulation [12,13].

FM may appear alone, with a prevalence of 2.9–4.7% in the general population [14], or associated with other rheumatic diseases, such as up to 25.3% in systemic lupus erythematosus (SLE) and up to 19.8% in rheumatoid arthritis (RA) [15].

The prevalence of FM among MS patients and its impact on health-related quality of life (HRQoL) has not yet been clearly determined. The few studies available on this topic exclusively collected data from administrative records or self-reported questionnaires [16,17].

In our own experience, we have observed a high incidence of FM associated with MS, as ascribable to various factors. First, some of the pathophysiological abnormalities of each of these disorders may be shared. A previous study by our group, which evaluated the thermal and discomfort thresholds in MS patients, yielded lower values in patients than in healthy controls [19]. Similarly, FM is characterized by central sensitization, which is a disordered sensory processing in the central nervous system and is responsible for an increased perception of pain in response to low stimuli of different types [11].

Second, cervical spine involvement is frequent in both MS and FM. In particular, FM may result from a cervical myelopathy due to various causes, such as a motor vehicle accident, surgery, Arnold-Chiari malformation, spinal canal stenosis, positional cervical compression, or trauma [20].

Third, some of the predisposing risk factors to these 2 diseases, such as female sex [21,22], may be shared.

For all these reasons, we believe that the frequency of FM in MS patients is higher than in the general population and similar to that observed in other rheumatic diseases.

The primary aim of this study was to evaluate the frequency of FM in a continuous series of Italian MS patients by means of specific validated diagnostic criteria [23], regardless of the various types of chronic pain referred. The secondary aim of the study was to detect any demographic and clinical characteristics associated with FM in MS.

FM has serious repercussions on family, social, and professional life [24]. Moreover, when associated with a highly disabling disease, such as MS, it clearly exacerbates the patients’ already compromised quality of life [18]. The third objective of this study was to evaluate the possible impact of FM on MS patients’ HRQoL, regardless of the other types of chronic pain.

Material and Methods

Patient selection and evaluations

We recruited, between October 2012 and August 2013, a continuous series of patients with definite MS according to the McDonald criteria [25], from a total of 205 in- and out-patients undergoing rehabilitation for MS at the Santa Lucia Foundation, a large, free-standing, university-affiliated rehabilitation institute not dependent on an acute-care general hospital.

The exclusion criteria were age <18 years, other known neurological or rheumatic diseases, other disorders of the spine, cancer, renal diseases, diabetes mellitus, severe psychiatric...
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According to published reports, the frequency of FM is approximately 19.8% in RA and 3.8% in the general population [14,15]. For this pilot study, a sample size of at least 75 patients would provide 80% power for detecting a difference in FM frequency not below 16% between the MS group and the general population, at the 5% level of significance.

Both the epidemiological and clinical characteristics of the patients enrolled were summarized by mean and standard deviation for numerical variables, and by frequencies and percentages for categorical variables.

The Shapiro-Wilk test was used to check the normality distribution for each variable used in the study. A p<0.05 was sufficient to reject the null hypothesis that the variable was normally distributed.

Patients were divided into 3 sub-groups (1 without pain, 1 with pain not FM-type, and 1 with pain FM-type) according to the modified ACR 1990 criteria.

The nonparametric Kruskal-Wallis one-way analysis of variance followed by the Dunn’s post test was performed to compare more than 2 unmatched sub-groups.

IBM SPSS 17.0 software was used for the statistical analysis. A p value <0.05 was considered statistically significant.

Results

From October 2012 to August 2013, 205 MS in- and out-patients were admitted at our Hospital. Out of them, 72 (35.1%) fulfilled the exclusion criteria, such as diabetes mellitus (4.8%), relapses in the last month prior to enrollment (3.9%), cancer (2.4%), age <18 years (0.9%), disorders of the spine (5.8%), other rheumatic disease (7.3%), patients with acute or occasional pain (6%), as well as severe cognitive impairment (9.7%), and were excluded.

The remaining 133/205 (64.8%) MS patients were enrolled in the study; the patients’ demographic and clinical characteristics are shown in Table 1. The F/M ratio was 1.8, which is in keeping with previous reports [22]. The patients enrolled had a mean age of 51.8±12.9 years, a high disability (mean EDSS 5.5±2.6) and mean disease duration of 19.3±11.7 years. Most of the patients (67.7%) were in the secondary progressive phase of disease.

All the patients enrolled were investigated for the occurrence of chronic pain, which was referred by 88/133 (66.2%) and absent in the remaining 45/133 (33.8%) (patients with no pain...
According to the DN4 questionnaire, the pain was neuropathic in 12/88 (13.7%) patients and musculoskeletal or mixed in 76/88 (86.3%) patients. The demographic and clinical characteristics of these sub-groups did not differ significantly (Table 2).

Table 1. Demographic and clinical characteristics of the 133 MS patients enrolled.

|                          | All patients (133; 100%) | Chronic pain (88; 66.2%) | No Pain (45; 33.8%) | P  |
|--------------------------|--------------------------|--------------------------|---------------------|----|
| Age – years (SD)         | 51.8 (12.9)              | 52.7 (11.3)              | 49.2 (15.1)         | 0.13 |
| Gender M/F (%)           | 47/86 (53.5/64.7)        | 27/61 (30.7/69.3)        | 20/25 (44.4/55.6)   | 0.08 |
| Mean EDSS (SD)           | 5.5 (2.6)                | 6.0 (2.5)                | 4.6 (2.6)           | 0.004 |
| MS type                  |                          |                          |                     |     |
| RR (%)                   | 40 (30.1)                | 21 (23.9)                | 19 (42.2)           |     |
| SP (%)                   | 90 (67.7)                | 66 (75.0)                | 24 (53.3)           | 0.03 |
| PP (%)                   | 3 (2.3)                  | 1 (1.1)                  | 2 (4.4)             |     |
| MS duration – years (SD) | 19.3 (11.7)              | 19.4 (11.4)              | 19.1 (12.4)         | 0.73 |
| MS therapy              |                          |                          |                     |     |
| None (%)                 | 55 (41.4)                | 35 (39.8)                | 20 (44.4)           |     |
| Interferon (%)           | 58 (43.6)                | 37 (42)                  | 21 (46.7)           |     |
| Glatirameracetate (%)    | 14 (10.5)                | 12 (13.6)                | 2 (4.4)             |     |
| Azathioprine (%)         | 6 (4.5)                  | 4 (4.5)                  | 2 (4.4)             |     |

The patients were divided in subgroups according to the presence of pain at the clinical evaluation. The Mann-Whitney Rank Sum Test or the chi-square test were used for comparisons between subgroups, as appropriate. EDSS – expanded disability status scale; RR – relapsing remitting; SP – secondary progressive; PP – primary progressive.

Table 2. Patients with neuropathic or musculoskeletal/mixed chronic pain according to DN4 Questionnaire.

|                          | Neuropathic pain | Musculoskeletal pain | P  |
|--------------------------|------------------|----------------------|----|
| Number of patients (%)   | 12 (13.7%)       | 76 (86.3%)           | 0.005 |
| Age – years (SD)         | 59.4 (12.1)      | 52.8 (11.0)          | 0.07 |
| Gender M/F (%)           | 4/8 (33.3/66.7)  | 23/53 (30.3/69.7)    | 0.83 |
| Mean EDSS (SD)           | 6.7 (2.0)        | 5.8 (2.5)            | 0.48 |
| MS type                  |                   |                      |     |
| RR (%)                   | 1 (8.3)          | 20 (26.3)            |     |
| SP (%)                   | 11 (91.7%)       | 55 (72.4)            | 0.35 |
| PP (%)                   | 0 (0)            | 1 (1.3)              |     |
| MS duration – years (SD) | 24.0 (13.3)      | 18.7 (11.0)          | 0.18 |
| MS therapy              |                   |                      |     |
| None (%)                 | 4 (33.3)         | 31 (40.9)            |     |
| Interferon (%)           | 6 (50)           | 31 (40.8)            | 0.78 |
| Glatirameracetate (%)    | 2 (16.7)         | 10 (13.2)            |     |
| Azathioprine (%)         | 0 (0)            | 4 (5.3)              |     |

The patients were divided in subgroups according to the presence of neuoropathic or musculoskeletal/mixed pain by means of the DN4 Questionnaire. The Mann-Whitney Rank Sum Test or the chi-square test were used for comparisons between subgroups, as appropriate. EDSS – expanded disability status scale; RR – relapsing remitting; SP – secondary progressive; PP – primary progressive.

Among all the patients enrolled, 23/133 (17.3%) also fulfilled the 1990 ACR criteria for FM (PFM+ patients); out of them, 5 (21.7%) had neuropathic pain, while in the remaining 18 (78.3%) the pain was musculoskeletal (p=0.03), as determined by the DN4 questionnaire. These 2 PFM+ subgroups did not differ significantly. [NoP] (Table 1).
The fibromyalgic patients were divided in subgroups according to the presence of neuropathic or musculoskeletal/mixed pain by means of the DN4 Questionnaire. The Mann-Whitney Rank Sum Test or the chi-square test were used for comparisons between subgroups, as appropriate. EDSS – expanded disability status scale; RR – relapsing remitting; SP – secondary progressive; PP – primary progressive.

Table 3. Demographic and clinical characteristics of the fibromyalgic patients enrolled in the study.

|                         | All MSFM+ patients | MSFM+ with neuropathic pain | MSFM+ with musculoskeletal pain | P     |
|-------------------------|--------------------|-----------------------------|---------------------------------|-------|
| Number of patients (%)  | 23 (100%)          | 5 (21.7%)                   | 18 (78.3%)                      | 0.03  |
| Age – years (SD)        | 54.3 (9.1)         | 57 (9.4)                    | 53.5 (9.1)                      | 0.41  |
| Gender M/F (%)          | 3/20 (13/87)       | 0/5 (0/100)                 | 3/15 (16.7/83.3)                | 0.32  |
| Mean EDSS (SD)          | 6.5 (2.1)          | 7.1 (1.2)                   | 6.3 (2.6)                       | 0.91  |
| MS type                 |                    |                             |                                 |       |
| RR (%)                  | 5 (21.7)           | 0 (0)                       | 5 (27.8)                        | 0.32  |
| SP (%)                  | 17 (73.9)          | 15 (100)                    | 12 (66.7)                       |       |
| PP (%)                  | 1 (4.3)            | 0 (0)                       | 1 (5.6)                         |       |
| MS duration – years (SD)| 6.5 (2.1)          | 20.2 (8.9)                  | 17.3 (8.9)                      | 0.52  |
| MS therapy              |                    |                             |                                 |       |
| None (%)                | 10 (43.5)          | 1 (20)                      | 9 (50)                          |       |
| Interferon (%)          | 7 (30.4)           | 3 (60)                      | 4 (22.2)                        | 0.29  |
| Glatirameracetate (%)   | 3 (13)             | 1 (20)                      | 2 (11.1)                        |       |
| Azathioprine (%)        | 3 (13)             | 0 (0)                       | 3 (16.7)                        |       |

Table 4. Demographic and clinical characteristics of the patients with not fibromyalgic type chronic pain.

|                         | All PFM– patients | PFM– with neuropathic pain | PFM– with musculoskeletal pain | P     |
|-------------------------|-------------------|----------------------------|--------------------------------|-------|
| Number of patients (%)  | 65 (48.9%)        | 7 (10.8%)                  | 58 (89.2%)                     | 0.01  |
| Age – years (SD)        | 53.5 (12.1)       | 61.1 (14.2)                | 52.6 (11.6)                    | 0.07  |
| Gender M/F (%)          | 24/41 (36.9/63.1) | 4/3 (57.1/42.9)            | 20/38 (34.5/65.5)              | 0.24  |
| Mean EDSS (SD)          | 5.8 (2.6)         | 6.5 (2.5)                  | 5.7 (2.6)                      |       |
| MS type                 |                    |                             |                                 |       |
| RR (%)                  | 16 (24.6)         | 1 (14.3)                   | 15 (25.9)                      | 0.50  |
| SP (%)                  | 49 (75.4)         | 6 (85.7)                   | 43 (74.1)                      |       |
| PP (%)                  | 0 (0)             | 0 (0)                      | 0 (0)                          |       |
| MS duration – years (SD)| 19.9 (12.2)       | 26.7 (15.8)                | 19.1 (11.6)                    | 0.23  |
| MS therapy              |                    |                             |                                 |       |
| None (%)                | 25 (38.5)         | 3 (42.9)                   | 22 (37.9)                      |       |
| Interferon (%)          | 30 (46.2)         | 3 (42.9)                   | 27 (46.6)                      | 0.32  |
| Glatirameracetate (%)   | 1 (1.5)           | 0 (0)                      | 1 (1.7)                        |       |

The patients with chronic pain not fibromyalgic type were divided in subgroups according to the presence of neuropathic or musculoskeletal/mixed pain by means of the DN4 Questionnaire. The Mann-Whitney Rank Sum Test or the chi-square test were used for comparisons between subgroups, as appropriate. EDSS – expanded disability status scale; RR – relapsing remitting; SP – secondary progressive; PP – primary progressive.
chronic pain not FM type (PFM– patients). Out of them, 7 (10.8%) had neuropathic pain and 58 (89.2%) had musculoskeletal pain (p=0.01), as determined by means of the DN4 questionnaire. These 2 PFM– subgroups did not differ in any demographic and clinical characteristics, and were grouped together for further statistical analysis (Table 4). The distribution of our SM patients in the 3 sub-groups (NoP, PFM+ and PFM–) is shown in Figure 1. The frequency of neuropathic and musculoskeletal pain did not differ between the PFM+ and PFM– sub-groups (p=0.18).

The PFM+ patients were predominantly female (p=0.03) and had a greater EDSS than the NoP group (p=0.01), but not greater than the PFM– patients; no significant differences among PFM+, PFM–, and NoP groups emerged as regards the other demographic and clinical characteristics (Table 5).

Depression was present in 54.1% of the patients enrolled, generally displaying a mild depression (mean DBI-II 17.01±11.7). Out of the patients with chronic pain, 42 (66.7%) were diagnosed with depression, compared to 11 (31.4%) patients in the NoP group, by means of the DBI-II (p=0.007). When the subgroups were considered separately, the PFM+ patients had a more pronounced depression than the NoP group (p=0.002), mainly ranging in the moderate/severe grade (p=0.01), but did not differ from the PFM– patients (Table 6).

Fatigue, as assessed by means of the FSS, was present in 102/133 (76.7%) of our sample, but did not differ among the 3 sub-groups (Table 6).

The fibromyalgic patients were divided in subgroups according to the presence of neuropathic or musculoskeletal/mixed pain by means of the DN4 Questionnaire. The nonparametric Kruskal–Wallis one-way analysis of variance or the chi-square test were performed to compare the three unmatched sub-groups, as appropriate. * Indicates that PFM+ is significantly different from No Pain group, by means of the Dunn’s post test. EDSS – expanded disability status scale; RR – relapsing remitting; SP – secondary progressive; PP – primary progressive.

**Table 5.** Demographic and clinical characteristics of the patients enrolled, divided in subgroups according to the different types of pain.

|                      | No Pain (45; 33.8%) | PFM+ (23; 17.3%) | PFM– (65; 48.9%) | p   |
|----------------------|---------------------|------------------|------------------|-----|
| Age – years (SD)     | 49.2 (15.1)         | 54.3 (9.1)       | 53.5 (12.1)      | 0.06|
| Gender M/F (%)       | 20/25 (44.4/55.6)   | 3/20 (13/87)     | 24/41 (36.9/63.1)| 0.03|
| Mean EDSS (SD)       | 4.6 (2.6)           | 6.5 (2.1)*       | 5.8 (2.6)        | 0.01|
| MS type              | RR (%)              | SP (%)           | PP (%)           |     |
|                      | 19 (42.2)           | 5 (21.7)         | 16 (24.6)        | 0.08|
|                      | 24 (53.3)           | 17 (73.9)        | 49 (75.4)        |     |
|                      | 2 (4.4)             | 1 (4.3)          | 0 (0)            |     |
| MS duration – years (SD) | 19.1 (12.4)   | 6.5 (2.1)        | 19.9 (12.2)      | 0.78|
| MS therapy           | None (%)            | Interferon (%)   | Glatirameracetate (%) | Azathioprine (%) |
|                      | 20 (44.4)           | 21 (46.7)        | 2 (4.4)          | 2 (4.4) |
|                      | 10 (43.5)           | 3 (13)           | 3 (13)           | 3 (13) |
|                      | 25 (38.5)           | 30 (46.2)        | 9 (13.8)         | 1 (1.5) |

* Indicates that PFM+ is significantly different from No Pain group, by means of the Dunn’s post test. EDSS – expanded disability status scale; RR – relapsing remitting; SP – secondary progressive; PP – primary progressive.
The prevalence of chronic pain in MS is estimated at 53–79% in studies based on mailed survey, in-person survey, or in-person assessment, and evaluating the prevalence of pain during the month prior to assessment [33–35]. Despite the slightly different values reported in the literature, it may vary because of the heterogeneous methods and definition of pain adopted, the 66.2% prevalence of chronic pain we found in our sample may be considered in keeping with the literature.

FM was diagnosed in 17.3% of our sample. This frequency is higher than the 3.8% reported in the general population [14], and similar to those reported in other rheumatic diseases, such as RA and SLE [36,37]. Few studies have investigated the comorbidity of FM in MS. The FM prevalence in one such study, which investigated different types of chronic pain and was based on administrative claim records, was 14.06% in the MS cohort [38]. In another study, which investigated different types of chronic pain and was based on self-reported validated questionnaire in an American MS population, FM was reported by 4.9% of the patients [39]. These 2 factors may justify the low prevalence of neuropathic pain found in our sample.

When considering the PFM+ subgroup, we found a higher prevalence of females with respect to the NoP sub-group only. Female sex appears to play a critical role in the development of MS [22], and women are diagnosed as having FM approximately 7 times more often than men [40]. The fact that female sex appears to be a major risk factor for the development of both MS and FM may, at least in part, explain this comorbidity. Moreover, women are about 2 times more likely to report chronic and widespread pain, because of higher pain sensitivity [21], and this may explain the lack of difference between the 2 different sub-groups of MS patients with chronic pain (PFM+ and PFM–).

The other difference between PFM+ and NoP patients was a higher degree of disability in the former, although the EDSS was high in both groups. This finding seems to suggest that pain may have a negative effect on disability and is in line with those reported in the literature. The impact of pain on

Table 6. Physical and mental scores of quality of life, fatigue and depression results in the three sub-groups.

|                          | All patients
|--------------------------|--------------------------|
|                          | (133; 100%)             | No Pain
|                          | (45; 33.8%)             | PFM+ patients
|                          | (23; 17.3%)             | PFM–
|                          | (65;48.9%)              | P
| Fatigued patients (%)    | 102 (76.7)              | 32 (71.1) |
| FSS                      | 4.7 (1.1)               | 4.5 (1.1) |
| DBI-II                   | 17.0 (11.7)             | 12.2 (10.4) |
| Absent/mild depression (%)| 87 (65.4)             | 37 (82.2) |
| Moderate/severe depression (%)| 46 (34.6) | 8 (17.8) |
| PHS                      | 39.1 (10.1)             | 42.7 (9.1) |
| MHS                      | 43.5 (9.3)              | 44.8 (8.9) |

* Indicates that PFM+ is significantly different from both No Pain and PFM− groups, by means of the Dunn’s post test. 

The patients were divided in subgroups according to the absence of pain, the presence of FM type or not FM type chronic pain. The nonparametric Kruskal-Wallis one-way analysis of variance or the chi-square test were performed to compare the three unmatched sub-groups, as appropriate. * Indicates that PFM+ is significantly different from both No Pain and PFM− groups, by means of the Dunn’s post test. DBI-II – Beck depression inventory II; FSS – fatigue severity scale; PCS – physical health status; MHS – mental health status.

The SF-36 synthetic score results are also shown in Table 6. The PFM+ patients scored the worst in both the PHS and the MHS when compared to the PFM− and the NoP groups (p<0.01). The same scores did not differ between the PFM− and NoP groups.

Discussion

The prevalence of chronic pain in MS is estimated at 53–79% in studies based on mailed survey, in-person survey, or in-person assessment, and evaluating the prevalence of pain during the month prior to assessment [33–35]. Despite the slightly different values reported in the literature, it may vary because of the heterogeneous methods and definition of pain adopted, the 66.2% prevalence of chronic pain we found in our sample may be considered in keeping with the literature.

In our study, a ward rheumatologist performed an examination to assess the presence of co-morbid FM in our MS patients, and the differences in the diagnostic methods adopted may explain the high frequency of FM detected in our MS sample.

Of the patients with chronic pain, only 13.7% had a neuropathic pain, without significant difference between the PFM+ and PFM− sub-groups. This frequency is low if compared with other data on neuropathic pain derived from systematic review and meta-analysis, which estimate a prevalence of 28.5% in MS [39]. We identified some methodological variables in the studies included, such as deficient blinding, different study design, and varying diagnostic criteria. In our study we focused on pain lasting for no less than 1 month, excluding forms of acute and paroxysmal pain, and used the DN4 questionnaire [33]. These 2 factors may justify the low prevalence of neuropathic pain found in our sample.

When considering the PFM+ subgroup, we found a higher prevalence of females with respect to the NoP sub-group only. Female sex appears to play a critical role in the development of MS [22], and women are diagnosed as having FM approximately 7 times more often than men [40]. The fact that female sex appears to be a major risk factor for the development of both MS and FM may, at least in part, explain this comorbidity. Moreover, women are about 2 times more likely to report chronic and widespread pain, because of higher pain sensitivity [21], and this may explain the lack of difference between the 2 different sub-groups of MS patients with chronic pain (PFM+ and PFM−).
disability was found to be modest in patients with a low EDSS [41] and high in those with a high EDSS [42]. The association between pain and disability may be inter-related, with these 2 factors exacerbating each other, especially in patients with a higher degree of impairment.

Our data confirm the high prevalence of depression in MS, which is estimated at around 50% [43,44]. In addition, we found a more pronounced depression in PFM+ patients than in NoP patients, but similar to the PFM– patients. This finding seems to show a negative impact of FM, but not of other types of chronic pain, on patient mood. Findings from studies that examined the relationship between pain and depression in MS are mixed, with roughly equal numbers of studies showing a positive versus a null relationship [45–48]. Instead, the high rate of co-morbidity between FM and depression is well known. Moreover, FM and depression share a similar pathophysiology [49], with a more pronounced deficit in pain inhibition in FM patients with depressive symptoms [50].

In our study, fatigue was detected in 75% of the patients, which is in keeping with reports in the literature [51], with no difference between the 3 sub-groups. However, fatigue is also very frequent in FM, with figures ranging between 78% and 94% [52]. Fatigue in both FM and MS may arise from a range of mechanisms that have yet to be fully clarified [51,53], and the complexity of its pathophysiology may thus explain why we could not find any associations with the presence of chronic pain or FM.

The impact of FM on family, social, and professional life is well known. Patients with FM were found to have a worse QoL even than RA patients [24] and MS has a significant impact on health-related QoL at all stages of disease [54]. Thus, the co-morbidity of FM in MS clearly exacerbates the already compromised QoL [18]. In our sample, the PFM+ group scored the worst in both PHS and MHS, which points to a marked effect of FM co-morbidity on MS patient QoL. Our findings are consistent with those of previous studies, which have shown that, out of various co-morbidities, FM has a relevant impact on physical and mental HRQoL in MS patients [16,18].

Conclusions

In our series we found a prevalence of 66.2% of chronic pain, with those patients displaying mainly musculoskeletal-type pain, greater disability, and more severe depression.

In our sample, almost 1/5 of MS patients had a co-morbidity with FM, which is a significantly higher prevalence than that observed in the general population, but similar to those reported in SLE and RA.

Even if PFM+ patients were similar to PFM– patients, according to the clinical and demographic characteristics, FM occurrence was associated with a stronger impact on patient QoL. FM co-morbidity should be further investigated in MS patients, given its frequency and impact on patient quality of life.

One limitation of this study is the lack of a wider range of EDSS scores. Indeed, a larger study, including patients with lower EDSS scores, might shed more light on how frequent FM is, even in the early stage of disease.

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