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

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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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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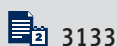
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Background

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]. However, FM was the only co-morbidity analyzed in MS that was proved to exert a moderate impact on physical HRQoL, being generally milder than the effect of other diseases [18].

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

diseases, relapses within 1 month prior to enrollment, and a Mini-Mental State Examination score <23 [26]. Patients with acute pain or occasional pain were also excluded. The study was approved by the ethics committee of our Foundation and informed consent was given in writing by all the patients.

All the patients underwent a structured interview to collect their clinical history, as well as MS preventive treatment intake. A neurological examination was performed by means of the Kurtzke Expanded Disability Status Scale (EDSS), with its functional systems [27]. The presence of chronic pain, which had been constant or nearly constant in the previous month, was investigated at the time of evaluation. The referred pain was further rated as neuropathic or not according to the DN4 questionnaire, consisting of both sensory descriptors and signs related to bedside sensory examination, and providing very good sensitivity (83%) and specificity (90%) for identification of chronic pain associated with a lesion in either the peripheral or central nervous system; a score of at least 4 out 10 is suggestive for neuropathic pain [28]. The patients with a score <4 were diagnosed with musculoskeletal pain to simplify the classification, even if it may include pain of mixed type caused by the complex interplay of nociceptive, neuropathic, and pathogenic mechanisms [29].

Fatigue was assessed by means of the Fatigue Severity Scale (FSS). A mean value >4 was considered to be indicative of clinically significant fatigue [30].

Depression was assessed by means of the Beck Depression Inventory II (BDI–II). The cut-off scores used were: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression [31].

A deep rheumatologic examination, as well as a wide panel of auto-antibodies, was performed by a ward rheumatologist to exclude any co-morbidity with other rheumatic diseases.

To investigate the FM co-morbidity, all the patients were assessed according to the 1990 American College of Rheumatology (ACR) diagnostic criteria [23]. For a diagnosis of FM to be made, the 1990 ACR diagnostic criteria require tenderness on pressure (tender points) in at least 11/18 specified sites, as well as the presence of widespread pain for at least 3 months [23].

HRQoL was assessed by means of the Medical Outcome 36-item Short Form Health Survey (SF-36), which analyzes physical and mental health status (PHS and MHS, respectively). The item scores range from 0 (poor health) to 100 (optimal health) [32].

Statistical analysis

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 statistical analysis between the 2 groups was performed by means of the Mann-Whitney rank sum Test or the chi-square test, as appropriate.

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 statistic al 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

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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 (35.3/64.7)		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)	0.44
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	(40.8)	
Interferon (%)	6	(50)	31	(40.8)	
Glatirameracetate (%)	2	(16.7)	10	(13.2)	0.78
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.

[NoP]) (Table 1). 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).

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

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)	
SP (%)	17 (73.9)	5 (100)	12 (66.7)	0.32
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)	
Glatirameracetate (%)	3 (13)	1 (20)	2 (11.1)	0.29
Azathioprine (%)	3 (13)	0 (0)	3 (16.7)	

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 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)	0.56
MS type				
RR (%)	16 (24.6)	1 (14.3)	15 (25.9)	
SP (%)	49 (75.4)	6 (85.7)	43 (74.1)	0.50
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)	
Glatirameracetate (%)	9 (13.8)	1 (14.3)	8 (13.8)	0.98
Azathioprine (%)	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.

differ in any demographic and clinical characteristics, and were grouped together for further statistical analysis (Table 3). The other 65/133 (48.9%) MS patients with chronic pain, not fulfilling the 1990 ACR criteria for FM, were considered to have
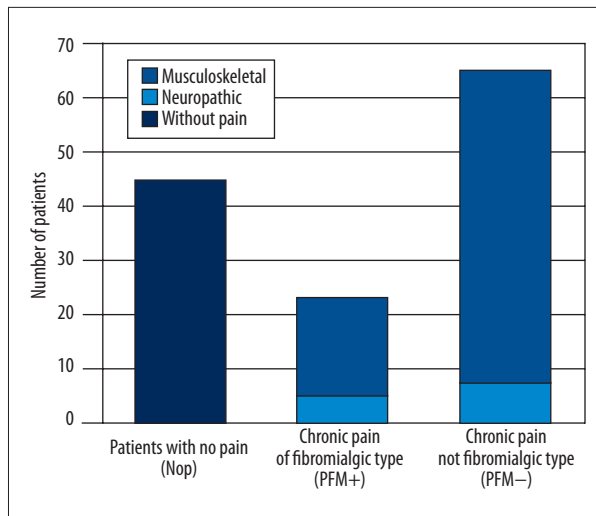
Figure 1. Distribution of our MS patients according to the presence of pain and types of pain, as assessed by means of the DN4 questionnaire and the 1990 ACR criteria for fibromyalgia.

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 sub-groups 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).

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

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).

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 (%)	19	(42.2)	5	(21.7)	16	(24.6)	
SP (%)	24	(53.3)	17	(73.9)	49	(75.4)	0.08
PP (%)	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 (%)	20	(44.4)	10	(43.5)	25	(38.5)	
Interferon (%)	21	(46.7)	7	(30.4)	30	(46.2)	0.18
Glatirameracetate (%)	2	(4.4)	3	(13)	9	(13.8)	
Azathioprine (%)	2	(4.4)	3	(13)	1	(1.5)	

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 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)	18	(78.3)	52	(80.0)	0.54
FSS	4.7	(1.1)	4.5	(1.1)	5.0	(1.1)	4.7	(1.0)	0.19
DBI-II	17.0	(11.7)	12.2	(10.4)	23.7	(10.9)#	17.9	(11.7)	0.002
Absent/mild depression (%)	87	(65.4)	37	(82.2)	9	(39.2)	40	(61.5)	0.01
Moderate/severe depression (%)	46	(34.6)	8	(17.8)	14	(60.8)	25	(38.4)	
PHS	39.1	(10.1)	42.7	(9.1)	32.2	(7.2)*	39.0	(10.4)	<0.01
MHS	43.5	(9.3)	44.8	(8.9)	36.1	(10.0)*	45.2	(8.2)	<0.01

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. # Indicates that PFM+ is significantly different from No Pain group, by means of the Dunn's post test. DBI-II – Beck sepression 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.

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 co-morbidity 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 various co-morbidities by means of a self-reported validated questionnaire in an American MS population, FM was reported by 4.9% of the patients [18]. It is known that the validity of self-reported diagnoses varies depending on the co-morbidity investigated. Indeed, it is very accurate for common disorders such as hypertension and diabetes, but is less accurate for uncommon disorders such as arthritis and FM [17]. 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−).

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

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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.

Acknowledgments

References:

1. Nick ST, Roberts C, Billiodeaux S et al. Multiple sclerosis and pain. Neurol Res, 2012; 34(9): 829–41

2. Clifford DB, Trotter JL: Pain in multiple sclerosis. Arch Neurol, 1984; 41(12): 1270–72

3. Stenager E, Knudsen L, Jensen K: Acute and chronic pain syndromes in multiple sclerosis. A 5-year follow-up study. Ital J Neurol Sci, 1995; 16(9): 629–32

4. O'Connor AB, Schwid SR, Herrmann DN et al: Pain associated with multiple sclerosis: systematic review and proposed classification. Pain, 2008; 137(1): 96–111

5. Desmeules JA, Cedraschi C, Rapiti E et al: Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum, 2003; 48(5): 1420–29

6. Gracely RH, Petzke F, Wolf JM, Clauw DJ: Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum, 2002; 46(5): 1333–43

7. Giesecke T, Gracely RH, Grant MA et al: Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum, 2004; 50(2): 613–23

8. Giesecke T, Gracely RH, Williams DA et al: The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. Arthritis Rheum, 2005; 52(5): 1577–84

9. Diatchenko L, Anderson AD, Slade GD et al: Three major haplotypes of the beta2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder. Am J Med Genet B Neuropsychiatr Gene, 2006; 141B(5): 449–62

10. Yunus MB: Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. Semin Arthritis Rheum, 2008; 37(6): 339–52

11. Henry DE, Chiodo AE, Yang W: Central nervous system reorganization in a variety of chronic pain states: a review. PM R, 2011; 3(12): 1116–25

12. Bellato E, Marini E, Castoldi F et al: Fibromyalgia syndrome: etiology, pathogenesis, diagnosis, and treatment. Pain Res Treat, 2012; 2012: 426130

13. Smith HS, Harris R, Clauw D: Fibromyalgia: an afferent processing disorder leading to a complex pain generalized syndrome. Pain Physician, 2011; 14(2): E217–45

14. Branco JC, Bannwarth B, Failde I et al: Prevalence of fibromyalgia: a survey in five European countries. Sem Arthritis Rheu, 2010; 39(6): 448–53

15. Yunus MB: The prevalence of fibromyalgia in other chronic pain conditions. Pain research and treatment. 2012; 2012: 584573

16. Turpin KV, Carroll LJ, Cassidy JD, Hader WJ: Deterioration in the health-related quality of life of persons with multiple sclerosis: the possible warning signs. Mult Scler, 2007; 13(8): 1038–45

17. Marrie R, Horwitz R, Cutter G et al: Comorbidity, socioeconomic status and multiple sclerosis. Mult Scler, 2008; 14(8): 1091–98

18. Marrie RA, Horwitz R, Cutter G, Tyry T: Cumulative impact of comorbidity on quality of life in MS. Acta Neurol Scand, 2012; 125(3): 180–86

19. Grasso MG, Clemenzi A, Tonini A et al: Pain in multiple sclerosis: a clinical and instrumental approach. Mult Scler, 2008; 14(4): 506–13

20. Thimineur M, Kitaj M, Kravitz E et al: Functional abnormalities of the cervical cord and lower medulla and their effect on pain: observations in chronic pain patients with incidental mild Chiari I malformation and moderate to severe cervical cord compression. Clin J Pain, 2002; 18(3): 171–79

21. Munce SE, Stewart DE: Gender differences in depression and chronic pain conditions in a national epidemiologic survey. Psychosomatics, 2007; 48(5): 394–99

22. Greer JM, McCombe PA: Role of gender in multiple sclerosis: clinical effects and potential molecular mechanisms. J Neuroimmunol, 2011; 234(1–2): 7–18

23. Wolfe F, Smythe HA, Yunus MB et al: The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum, 1990; 33(2): 160–72

24. Salaffi F, Sarzi-Puttini P, Girolimetti R et al: Health-related quality of life in fibromyalgia patients: a comparison with rheumatoid arthritis patients and the general population using the SF-36 health survey. Clinical Exp Rheumatol, 2009; 27(5 Suppl.56): S67–74

25. Polman CH, Reingold SC, Banwell B et al: Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol, 2011; 69(2): 292–302

26. Folstein MF, Folstein SE, McHugh PR: «Mini-mental state». A practical method for grading the cognitive state of patients for the clinician. J Psychiatric Res, 1975; 12(3): 189–98

27. Kurtzke JF: Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology, 1983; 33(11): 1444–52

28. Bouhassira D, Attal N, Alchaar H et al: Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain, 2005; 114(1–2): 29–36

29. Vellucci R: Heterogeneity of chronic pain. Clin Drug Investig, 2012; 32(Suppl.1): 3–10

30. Kaynak H, Altintas A, Kaynak D et al: Fatigue and sleep disturbance in multiple sclerosis. Eur J Neurol, 2006; 13(12): 1333–39

31. Smarr KL, Keefer AL: Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). Arthritis Care Res, 2011; 63(Suppl.11): S454–66

32. Ware JE Jr: SF-36 health survey update. Spine, 2000; 25(24): 3130–39

33. Svendsen KB, Jensen TS, Overvad K et al: Pain in patients with multiple sclerosis: a population-based study. Arch Neurol, 2003; 60(8): 1089–94

34. Archibald CJ, McGrath PJ, Ritvo PG et al: Pain prevalence, severity and impact in a clinic sample of multiple sclerosis patients. Pain, 1994; 58(1): 89–93

35. Beiske AG, Pedersen ED, Czujko B, Myhr KM: Pain and sensory complaints in multiple sclerosis. Eur J Neurol, 2004; 11(7): 479–82

36. Wolfe F, Clauw DJ, Fitzcharles MA et al: The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res, 2010; 62(5): 600–10

37. Wolfe F, Michaud K: Severe rheumatoid arthritis (RA), worse outcomes, comorbid illness, and sociodemographic disadvantage characterize ra patients with fibromyalgia. J Rheumatology, 2004; 31(4): 695–700

38. Davis JA, Robinson RL, Le TK, Xie J: Incidence and impact of pain conditions and comorbid illnesses. J Pain Res, 2011; 4: 331–45

39. Foley PL, Vesterinen HM, Laird BJ et al: Prevalence and natural history of pain in adults with multiple sclerosis: Systematic review and meta-analysis. Pain, 2013; 154(5): 632–42

40. Hauser W, Kuhn-Becker H, von Wilmoswky H et al: Demographic and clinical features of patients with fibromyalgia syndrome of different settings: a gender comparison. Gend Med, 2011; 8(2): 116–25

41. Michalski D, Liebig S, Thomae E et al: Pain in patients with multiple sclerosis: a complex assessment including quantitative and qualitative measurements provides for a disease-related biopsychosocial pain model. J Pain Res, 2011; 4: 219–25

42. Grau-Lopez L, Sierra S, Martinez-Caceres E, Ramo-Tello C: Analysis of the pain in multiple sclerosis patients. Neurologia, 2011; 26(4): 208–13

43. Patten SB, Metz LM: Depression in multiple sclerosis. Psychother Psychosom, 1997; 66(6): 286–92

44. Sadovnick AD, Remick RA, Allen J et al: Depression and multiple sclerosis. Neurology, 1996; 46(3): 628–32

45. Indaco A, Iachetta C, Nappi C et al: Chronic and acute pain syndromes in patients with multiple sclerosis. Acta Neurol, 1994; 16(3): 97–102

46. Newland PK, Wipke-Tevis DD, Williams DA et al: Impact of pain on outcomes in long-term care residents with and without multiple sclerosis. J Am Geriatr Soc, 2005; 53(9): 1490–96

47. Kalia LV, O'Connor PW: Severity of chronic pain and its relationship to quality of life in multiple sclerosis. Mult Scler, 2005; 11(3): 322–27

48. Tedman BM, Young CA, Williams IR: Assessment of depression in patients with motor neuron disease and other neurologically disabling illness. J Neurol Sci, 1997; 152(Suppl.1): S75–79

49. Bradley LA: Pathophysiologic mechanisms of fibromyalgia and its related disorders. J Clin Psychiatry, 2008; 69(Suppl.2): 6–13

50. de Souza JB, Potvin S, Goffaux P et al: The deficit of pain inhibition in fibromyalgia is more pronounced in patients with comorbid depressive symptoms. Clin J Pain, 2009; 25(2): 123–27

51. Braley TJ, Chervin RD: Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. Sleep, 2010; 33(8): 1061–67

52. Finan PH, Zautra AJ: Fibromyalgia and fatigue: central processing, widespread dysfunction. PM R, 2010; 2(5): 431–37

53. Nicassio PM, Moxham EG, Schuman CE, Gevirtz RN: The contribution of pain, reported sleep quality, and depressive symptoms to fatigue in fibromyalgia. Pain, 2002; 100(3): 271–79

54. Miller DM, Allen R: Quality of life in multiple sclerosis: determinants, measurement, and use in clinical practice. Curr Neurol Neurosci Rep, 2010; 10(5): 397–406