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PAIN AND QUALITY OF LIFE IN MULTIPLE SCLEROSIS PATIENTS

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Abstract

Pain is an important disabling symptom in multiple sclerosis (MS) that is frequently overlooked in clinical practice. Previous studies have described pain prevalence figures between 30 and 60%. This study intended to evaluate the prevalence of neuropathic and musculoskeletal pain and its relation quality of life. A total of 60 patients underwent a structured interview to assess painful symptoms and completed the Beck Depression Inventory (BDI) and the MusiQoL questionnaire. The prevalence of pain was 63% and its presence was independent of patients' age, gender, years of disease, disease subtype, expanded disability status scale (EDSS) and number of relapses in the last year. BDI score was significantly different between groups (p=0,008). 13% of patients complained of neuropathic pain, 22% of musculoskeletal pain and 28% of both types of pain. In the neuropathic pain, Lhermitte's sign was the most common (56%) and in the musculoskeletal pain, muscular pain was the most prevalent (77%). Patients with pain had significantly lower MusiQoL scores that also related negatively with BDI score. Depression was the only clinical predictor of pain (R^2= 0,186 p=0.008) and the presence of pain was a strong predictor of a lower score on the MusiQoL symptoms domain (F=3,97, p=0,05). About 32% of patients with pain were doing a symptomatic medication. Pain is, therefore, a symptom that greatly impairs quality of life and is often associated with depression which further worsens quality of life and alters pain perception. The low frequency of treatment for these symptoms indicates the need for improved attention to this problem.

Key-words

Multiple sclerosis, Pain, Depression, Quality of Life, Neuropathic Pain, Musculoskeletal Pain

Resumo

A dor é um sintoma incapacitante na esclerose múltipla (EM) que é frequentemente esquecido na prática clínica. Estudos prévios descreveram valores de prevalência de dor entre 30 e 60%. Este estudo pretende avaliar a prevalência de dor neuropática e musculoesquelética e a sua relação com a qualidade de vida. Um total de 60 doentes foi entrevistado para avaliar sintomas dolorosos e preencher o inventário de depressão de Beck (BDI) e o questionário MusiQoL. A prevalência de dor encontrada foi de 63% e a sua presença foi independente da idade, género, número de anos de doença, subtipo de doença, escala expandida de status da incapacidade de Kurtzke (EDSS) e número de surtos no ano anterior. A pontuação do BDI foi significativamente diferente entre grupos (p=0,008). 13% dos doentes referiram dor neuropática, 22% dor musculoesquelética e 28% os dois tipos de dor. Na dor neuropática, o sinal de Lhermitte foi o mais comum (56%) e na dor musculoesquelética, a dor muscular foi a mais prevalente (77%). Doentes com dor tinham uma pontuação de MusiQoL significativamente menor que também se relacionava negativamente com a cotação do BDI. A depressão foi o preditor mais forte de dor (R^2=0,186, p=0,008) e a presença de dor foi um forte preditor de uma menor pontuação no domínio da sintomatologia do MusiQoL (F=3,97, p=0,05). Cerca de 32% dos doentes com dor estavam a fazer terapêutica sintomática. A dor é, portanto, um sintoma que prejudica muito a qualidade de vida e que está frequentemente associado a depressão, que piora ainda mais a qualidade de vida e altera a perceção da dor. A baixa frequência de tratamento destes sintomas indica a necessidade de maior atenção a este problema.

Palavras-chave

Esclerose múltipla, Dor, Depressão, Qualidade de Vida, Dor neuropática, Dor Musculoesquelética

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system and its hallmark lesions are sclerotic plaques in white matter[1] where the primary targets are the myelin sheath and oligodendrocytes[1]. These plaques are the end result of inflammatory, demyelinating and axonal degeneration mechanisms[2] accompanied by the presence of an inflammatory infiltrate made up of various mediators of immune response[1].

The clinical manifestations in MS are directly or indirectly related to the site of the neuronal injury and usually involve the motor, sensory, visual and autonomic systems. While most symptoms are not disease specific, some are strongly suggestive of MS, like Lhermitte's symptom and the Uhthoff phenomenon[1,2].

There are other symptoms, namely related with sensitive and motor systems, ocular and oculomotor function, autonomic nervous system, psychiatric problems and pain[3] that have been increasingly recognized in the last years and that may have a significant impact on patients' quality of life.

Pain is one of these symptoms and is frequently overlooked. This is a problem that reaches about 82% of the MS population, according to Svedsen et al[4]; in 2004 Solaro conducted a wide cross-sectional multicenter study that pointed to 86% of MS patients affected by different types of pain[5].

The mechanisms of pain in MS are still not fully understood although various explanations have been proposed. Recent evidence seems to support the theory that plaque distribution is related to pain perception[6] and also that demyelinated axons produce an abnormal impulse that causes pain[6]. Moreover, the glial inflammatory response associated with MS seems to have an important relation with pain[7] , particularly the chemokines, which seem to increase the release of neurotransmitters through Ca-modulated mechanisms[8] and also seem to function as neurotransmitters themselves, being a causative factor of neuropathic pain[7]. As

reviewed by Nurmikko et al, specific mechanisms have also been proposed for the different types of pain in MS[9]: central dysesthetic pain seems to relate to plaques in the cervical and thoracic cord and to periventricular white matter lesions and also with lesions in the thalamus; trigeminal neuralgia is associated with demyelination in the trigeminal root entry zone in the brainstem; Lhermitte's sign is related to spinothalamic tract activation due to demyelination and is also associated with lesions in the cervical cord; painful tonic spasms are caused by acute inflammation of the pyramidal or extrapyramidal tracts; lumbar pain is thought to be mechanic and not bearing any relation to CNS inflammation.

Besides acknowledging the existence of pain in these patients, it is essential to characterize it. Some researchers have categorized pain according to its temporal profile[4] and others according to their pathological mechanism[10]. The main advantage of the last approach is that it contributes for a directed treatment according the underlying pathophysiological mechanisms. As such, the classification of pain used in this work is the one proposed by O'Connor et all[10]. According to his work, pain should be divided in neuropathic and non-neuropathic. In the neuropathic pain, two types are considered: continuous central neuropathic pain (dysesthetic extremity pain) and intermittent central neuropathic pain (Lhermitte's sign and trigeminal neuralgia); in the non-neuropathic pain group is included musculoskeletal pain (painful tonic spasms, low back pain, and muscles spasms). A third group is also defined, of mixed neuropathic and non-neuropathic pain.

Our work attempts to estimate the prevalence of these types of pain in the MS population and to analyze its relation with quality of life.

Material and Methods

We collected data from 60 consecutive patients who are regularly followed at the Department of Neurology at Hospitais da Universidade de Coimbra. All patients have a definite diagnosis of MS for a period of at least 6 months according to the McDonald criteria 2005[11].Exclusion criteria were a history of neoplastic disease, nerve compression syndromes, rheumatic disease and a relapse in the last 4 weeks.

We used a face-to-face structured questionnaire which included demographic data, year of diagnosis, disease subtype, disease modifying treatment, pain therapy, presence of neuropathic pain – Lhermitte's sign, trigeminal neuralgia, dysesthetic pain -, somatic pain – back pain, muscular pain, painful tonic spasms. We did not consider headache, acute pain related to optic neuritis and other types of somatic pain. We considered symptoms present during the month previous to the interview. To access depression symptoms we used the Beck Depression Inventory[12] and to access quality of life we used the MusiQOL questionnaire[13], both validated in MS samples. The MusiQoL is a disease-specific questionnaire describing nine dimensions (activity of daily living, psychological well-being, symptoms, relationships with friends, relationships with family, relationships with health care system, sentimental and sexual life, coping and rejection) and yielding a global index score. All patients signed a consent form and to ensure the confidentiality, all patient data were recorded anonymously.

Data analyses and statistics

Values of age, disease duration and BDI score had a normal distribution and these parameters were compared between groups (patients with pain vs. patients without pain) using Student's t-test. Differences between groups relative to gender and disease subtype, were compared using Chi2 test, while difference in medians of EDSS was analyzed using the Wilcoxon-

Mann-Whitney test. A *P*-value <0,05 was considered statistically significant. A logistic regression analysis was performed in order to find clinical predictors of pain in MS patients. The analysis of covariance (ANCOVA) model was used for assessing effects of pain and its subtypes on quality of life, controlling for depression (BDI). Pearson product moment correlation was used to analyze the relationship between depression and patients' quality of life.

All analyses were conducted using SPSS for Windows version 19.0 (SPSS Inc, Chicago, IL). Logistic regression and ANCOVA models were evaluated using standard procedures to ensure that final models met the underlying assumptions required by these statistical techniques. Significance for hypothesis-testing analyses was set at p<0,05.

Results

Subject characteristics

Our entire sample consisted of 60 patients, 73,30% of whom were women. The mean age was 42,68 (+/- 11,39) years and the mean duration of disease was 9,63 years. 78,30% of patients had a relapse-remitting form of MS, 15% a secondary progressive form and 6,70% a primary progressive form of the disease. The EDSS median was 3,25 (1,0 – 7,5) and 33,30% of patients had had at least one relapse in the previous year.

Comparing the group of patients with pain with those without pain, there was no statistically significant differences with respect to age and gender, years of disease, disease subtype, EDSS and number of relapses in the last year (Table 1). The only variable that was statistically significantly different between the two groups was the BDI score, with the pain group having higher BDI (*p*=0,008).

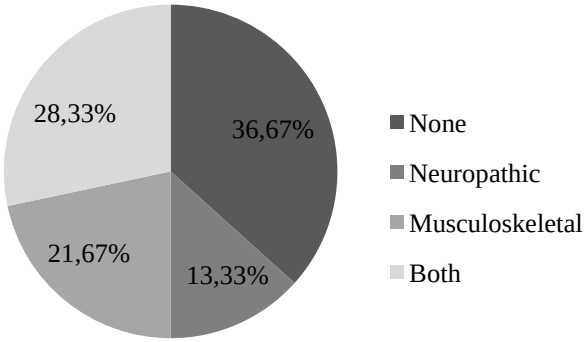
Table 1

	Entire sample (N=60)	**MS patients with pain (N=38)**	**MS patients without pain (N=22)**	***P*-Value**
Age (years), mean (SD)	42,68 (11,39)	43,24 (10,85)	41,73 (12,47)	0,63[a]
Gender (% female)	73,30%	78,90%	63,60%	0,20[b]
Disease duration (years), mean (SD)	9,63 (7,59)	8,89 (6,81)	10,91 (8,79)	0,33[a]
Disease course (%)				0,52[b]
Relapse remitting	78,30%	66,00%	34,00%	-
Secondary progressive	15,00%	53,80%	46,20%	-
Primary progressive	6,70%			
EDSS, median	3,25	2,75	3,5	0,85[c]
EDSS (minimum ; maximum)	1,0 ; 7,5	1,0 ; 6,5	1,0 ; 7,5	-
EDSS quartile 25	1,63	1,88	1,50	-
EDSS quartile 50	3,25	2,75	3,50	-
Depression (BDI score), mean (SD)	9,63 (6,75)	11,37 (7,17)	6,64 (4,73)	0,008[a]
Minimal depression (0-9)	58,30%	47,40%	77,30%	-
Mild depression (10-18)	33,30%	42,10%	18,20%	-
Moderate depression (19-29)	5,00%	5,30%	4,50%	-
Severe depression (30-63)	3,30%	5,30%	0,00%	-
QoL total, mean (SD)	68,78 (14,23)	66,00 (13,73)	73,57 (0,55)	0,05[a]
QoL activities, mean (SD)	52,86 (28,07)	47,04 (25,89)	62,93 (29,41)	0,03[a]
QoL psychological, mean (SD)	62,88 (21,02)	57,35 (22,20)	72,44 (14,90)	0,006[a]
QoL symptoms, mean (SD)	63,54 (21,59)	58,06 (19,81)	73,01 (21,68)	0,009[a]
QoL friends, mean (SD)	68,87 (21,59)	66,44 (24,63)	73,06 (27,32)	0,34[a]
QoL family, mean (SD)	83,33 (22,46)	78,72 (24,88)	91,30 (14,89)	0,04[a]
QoL relationships, mean (SD)	61,67 (36,01)	62,17 (34,69)	60,80 (39,02)	0,89[a]
QoL coping, mean (SD)	63,96 (24,58)	63,49 (22,77)	64,77 (27,99)	0,85[a]
QoL rejection, mean (SD)	74,58 (31,72)	73,68 (31,00)	74,14 (33,61)	0,78[a]
QoL health system, mean (SD)	87,30 (13,88)	87,08 (14,20)	87,68 (13,63)	0,87[a]
Relapses in last year, mean (SD)	0,53 (0,89)	0,58 (0,92)	0,45 (0,86)	0,61[a]
Relapses in last year (%)	33,30%	36,80%	27,30%	0,46[a]

[a] Two sample *t*-test.
[b] Chi-square test.
[c] Wilcoxon-Mann-Whitney rank test.

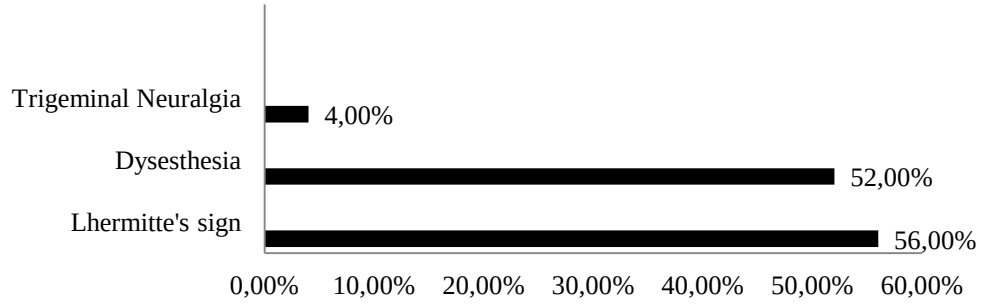
Pain description

In a sample of 60 patients, 38 (63,33%) reported feeling pain during the month previous to the interview. Most patients reported both neuropathic and musculoskeletal pain (28,33%), 13,33% of patients reported only neuropathic pain and 21,67% of patients only complained of musculoskeletal pain (Graphic 1).



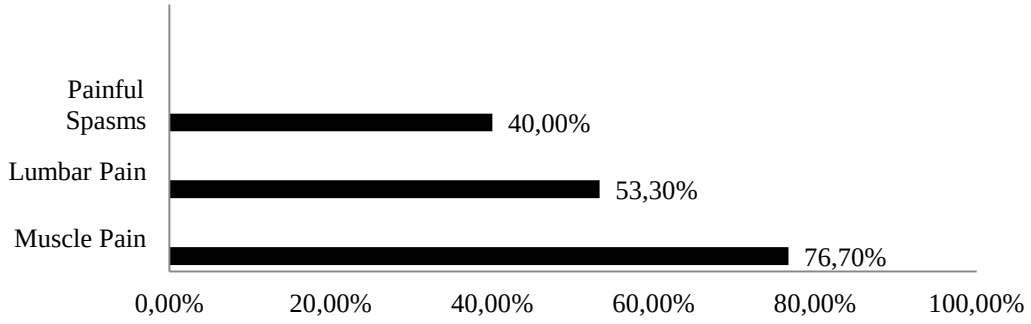
Graphic 1: Partial percentages of the prevalence of various types of pain in the study population.

Of the patients who referred neuropathic pain, the commonest complaint was Lhermitte's sign, which affected 56,00% of patients (Graphic 2), followed by dysesthetic extremity pain (52,00%). Trigeminal neuralgia was the least common type of neuropathic pain, affecting only 1 patient (4%).



Graphic 2: Prevalence of the various types of neuropathic pain in the study population.

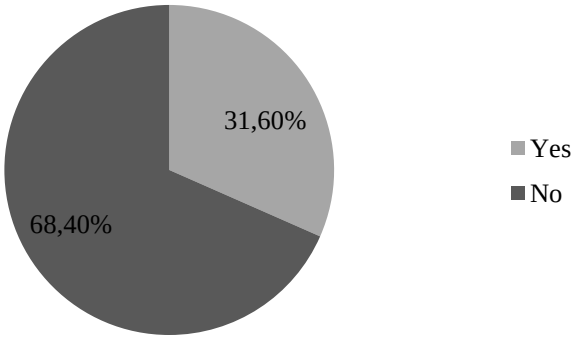
In the patients who complained of musculoskeletal pain, the commonest type was muscle pain, affecting 76,70% of patients. Lumbar pain was present in 53,30% of patients and 40,00% of patients complained of painful muscles spasms (Graphic 3).



Graphic 3: Prevalence of the various types of musculoskeletal pain in the study population.

Symptomatic therapy

In the following step we wanted to know if patients who complained of pain, whatever its type, were being treated for it. The therapeutics we considered were the ones recommended for treatment of pain and spasticity in MS, namely, gabapentin, topiramate, amitriptyline, buprenorphin and baclofen, gabapentin, respectively. As Graphic 4 shows, 31,60% of patients in the pain group were being treated for their symptoms, while 68,40% had no symptomatic treatment.



Graphic 4: Percentage of patients in the pain group treated for their symptoms.

Clinical predictors of Pain

The logistic regression model predicting the presence of pain in the MS patients, retained only the BDI score as the strongest predictor (R^2= 0,186 *p*=0.008). The other clinical variables, namely age, gender, disease duration, disease subtype, EDSS and number of relapses in the last year, were not retained in the model and therefore are not predictors of pain.

Pain and Quality of Life

MusiQoL is a questionnaire that assesses quality of life in several aspects of daily routine. In this test the higher the value, the better a patient's quality of life. We compared the mean scores of each dimension and also the global score of the MusiQoL questionnaire in both groups and found that the mean total score in the MusiQoL was significantly lower in the pain group (66,00) compared to the group of patients without pain (73,57) (*p*=0,05), which shows that patients with pain complaints have an overall lower quality of life.

When analyzing each dimension of the MusiQoL separately, we found a statistically significant difference, pain group with lower scores, in the following: activity of daily living, (47,04 vs.62,93, *p*= 0,03), symptoms (58,06 vs 73,01, *p*= 0,009), psychological well-being (57,35 vs 72,44, *p*= 0,006) and relationships with family (78,72 vs 91,30 *p*=0,04). The domains of relationships with friends, sentimental and sexual life, coping, rejection and relationships with health care system did not present differences.

In the univariate analysis, we found that the MusiQoL global score and also specific domains were significantly higher in the group of patients without pain compared to the group with pain. However, the group of patients with pain also presented significantly higher scores of depression (BDI). Therefore, we wanted to analyze if pain was an independent predictor of quality of life, after controlling for depression (BDI).

We used the ANCOVA models to assess the presence of pain and its effect on quality of life (QoL total, QoL activity of daily living, QoL psychological well-being, QoL symptoms, QoL relationships with family) controlling for BDI score. We found that, when controlling for depression, the presence of pain is an independent predictor of lower score on the QoL symptoms domain (F=3,97, *p*=0,05) but not for the other domains or the overall quality of life.

Next, we analyzed the impact of each subtype of pain (neuropathic, musculoskeletal, both) on quality of life, using the ANCOVA model. After controlling for depression, the group with both types of pain (neuropathic and musculoskeletal) had lower QoL activity of daily living than the groups without pain (b1= -18.6, p=0.024), the group with only neuropathic pain (b1= -21.8, *p*=0.038) and the group with musculoskeletal pain (b1= -20.0, *p*=0.028). The main effect comparing the groups was F= 2.74 (*p*=0.05), indicating that the subtype of pain is an independent predictor of QoL activities of daily living. The subtype of pain is also an independent predictor of QoL relationships with family (F=3.19, *p*=0.031), with the group of patients with musculoskeletal pain presenting lower scores than the group without pain (b1= -18.8, *p*=0.011).

Depression and Quality of Life

Since BDI score was significantly higher in the group of patients with pain compared to the group without pain, we decided to study the relationship between depression and quality of life. We used Pearson product moment correlation, which identified a negative relationship between BDI score and global score of MusiQoL (r=-0,69, *p*=0,00). Analyzing the specific domains of MusiQoL, we found a negative correlation that was statistically significant for all domains of MusiQoL except for the relationship with health care system (Table 2).

Table 2

	BDI Pearson Correlation	*p*
QoL symptoms	-0,47	<0,001
QoL psychological	-0,60	<0,001
QoL symptoms	-0,32	0,01
QoL friends	-0,32	0,01
QoL family	-0,42	<0,001
QoL relationships	-0,31	0,02
QoL coping	-0,35	0,01
QoL rejection	-0,53	<0,001
QoL Health system	-0,20	0,24
QoL Total	-0,69	<0,001

Discussion

In this work we intended to evaluate the prevalence of pain in the patient population of the MS clinic and to explore the relationship with their quality of life.

The overall prevalence of pain in our sample was 63,3%, which is in agreement with recent studies – 65% [14] and 68,7%[15]. It is however, higher than a Portuguese study (34%)[16], which could be due to differences between the samples studied or methods employed. When analyzing the differences between the group of patients with pain and the group without pain, we found that age, gender, disease duration, EDSS, disease subtype, and relapses in the last year were not associated with pain, similarly to previous studies[14][17]. This means that pain can affect any MS patient, regardless of its

demographic characteristics and, as such, physicians should be alert and always rule out its existence.

When analyzing the prevalence of the different types of pain, we realized that most patients in the pain group reported feeling both types of pain. In the patients that complained of musculoskeletal pain, generalized muscle pain was the most prevalent, affecting 76,70% of patients with pain. This had already been reported by other studies[14] and it has been considered that generalized muscle pain might have various causes in MS patients. The most important one is probably related to spasticity, although a central sensitization mechanism might be involved[9]. Moreover, this type of pain could also be related to the administration of immunotherapy, namely flu-like adverse events associated to interferons. In the neuropathic pain group, Lhermitte's sign was the most common, followed closely by dysesthetic pain in the extremities. Although these types of pain have different pathophysiological origins[18], they both arise from lesion in the cervical segments of the spinal cord[9][18], which could explain why their prevalence is so similar.

Concerning the analysis of BDI scores in both groups, there was a significant difference between patients with pain and those without pain, as had been noted in other studies[15][19]. The average score was higher in the pain group as was the percentage of moderately to severely depressed patients. Also, the BDI score was the only clinical predictor for the presence of pain in the logistic regression analysis. Baliki et al[20] have proposed an explanation for why depression is more prevalent in chronic pain patients. According to their work, chronic pain has a great impact on brain function, altering the default mode network (DMN), which is responsible for maintaining the brain's resting state. Using functional magnetic resonance imaging (fMRI) they compared brain function between chronic pain patients and healthy controls while executing a simple visual

attention task. They discovered that patients in the pain group showed reduced deactivation of several DMN regions that might underlie cognitive and behavioral impairments that accompany chronic pain.

Other studies[21] have hypothesized another explanation for this relationship that is based on the fact that pain and depression may be processed in the somatosensory pathways of the brain and spinal cord which can be affected in MS, becoming atrophic and demyelinated. Also, both pain and depression are processed in the limbic system which modulates pain and manifests its affective dimension[21]. The important fact to stress is that pain can occur early in the disease, being unrelated to EDSS, disease subtype, gender or age, but frequently related to depression. Therefore the physician must watch out for this possibility, rule out the existence of pain and depression and, if present, treat them appropriately.

In fact, we also assessed the prevalence of pain treatment in our sample and realized that 68,40% of patients in the pain group were not being treated for this symptom, as has been seen reported in other studies[16][17]. Symptomatic treatment especially when combined with patient rehabilitation is essential in these patients[22]. There are several options when it comes to treating these symptoms, however most of these are still "off-label" and their efficacy has yet to be proved by clinical trials[3].

In this study, we also wanted to assess the impact of pain on quality of life of MS patients. We found that patients with pain complaints had a significantly lower overall quality of life than patients without pain. Analyzing the individual domains of quality of life measured by MusiQoL, patients with pain scored lower in activities of daily living, symptoms, psychological well-being and relationships with family domains. MusiQoL scores were also negatively correlated with BDI scores, as has been described by other researchers[23]. When controlling for this important covariate, the presence of pain

seems to have a greater impact on domains of activity of daily living, symptoms and relationship with family domains. This means that, while pain and depression often coexist in MS patients, depression does not cause pain, as had been noted by other studies[17]. Since pain is not significantly related to EDSS but seems to impair quality of life, these results raise the question that EDSS is not enough to evaluate patient's disability satisfactorily.

As for the limitations of this study, the fact that it is cross-sectional limits the study of these symptoms and their relation to quality of life to one point in time and does not allow us to observe the evolution of symptoms over time. Also, the sample size of 60 patients could explain why not all sections of the MusiQoL questionnaire were positively correlated to pain; it is possible that using a wider sample could confirm other relations. Moreover, it should be noticed, that generalized muscle pain and lumbar pain could also have other causes unrelated to MS, which might mean that our results are overestimating the prevalence of these types of pain in MS.

Conclusion

This study adds to the general opinion that pain is a frequent symptom in MS patients with diverse mechanisms requiring different treatments, which greatly decreases patients' quality of life beyond its relation with depression. It is important to notice that these are problems that can affect patients from early on in the disease, which is why physicians should actively look for these possibilities. A complete patient history focusing on painful symptoms in addition to the neurological examination are essential to evaluate the presence and characteristics of painful symptoms in order to treat them according to their etiology. Moreover, a good relationship between patient and physician is particularly important in this setting to better assess the patient's needs.

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