Neurología. 2011;**26(4)**:208-213

NEUROLOGÍA

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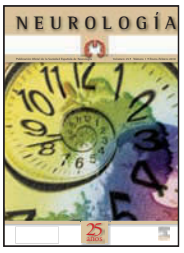

ORIGINAL ARTICLE

Analysis of the pain in multiple sclerosis patients

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Received on 25th January 2010; accepted on 21st April 2010

KEYWORDS
Multiple sclerosis;
Pain;
Spinal cord

Abstract
Introduction: Despite pain being a disabling symptom in patients with multiple sclerosis (MS), its prevalence and characteristics are not well established. The aim of this study is to describe the characteristics and prevalence of pain in patients with MS, and to assess the associated clinical variables and radiological findings.
Methods: We prospectively studied patients with MS. A structured questionnaire which evaluated depression symptoms, type of pain, location, intensity (defined according to a visual analogue scale (VAS) as severe (VAS 7-10), moderate (VAS 4-6) and mild (VAS 0-4), and pain therapy was recorded in patients who referred to pain at the time of interview. Protocol variables were demographic data, MS clinical forms (remitting-relapsing, progressive-secondary and progressive-primary), neurological dysfunction (defined according to EDSS scale), symptoms at onset, attack frequency, illness duration, disease modifying treatment, fatigue, spasticity, oligoclonal bands in CSF, visual evoked potentials, depression symptoms (Hamilton test) and presence of lesions in spinal cord MRI.
Results: A total of 134 MS patients were included, and MRI was performed on 105 of them. Pain was reported by 74 (55%) patients and was most frequently neuropathic, located in limbs, severe and burning/spiky. Of these 28 (38%) received therapy for their pain, based predominantly in anti-inflammatory drugs. Patients with pain had a worse functional state (EDSS score, 4.5 [3-6] vs 1.5 [1-2], $p<0.001$), higher number of relapses (7.13±3.4 vs 3.75±2.9, $p<0.001$), progressive forms of MS (86.7% vs 13.3%, $p<0.001$), depression (91.9% vs 8.1%, $p<0.001$), spinal cord involvement at onset (79.2% vs 20.8%, $p=0.009$), spinal cord lesions by MRI (84.3% vs 15.7%, $p<0.001$) and longer duration of disease (14.6±7.8 vs 8.43±5.9 months, $p<0.001$). In a logistic regression model, the presence of lesions in spinal cord MRI (OR 3.5 [1.5-24.5]) and higher EDSS score (OR 1.7 [1.1-2.7]) were independently associated with pain.
Conclusions: Pain is a frequent disabling symptom in MS and is associated with disability and spinal cord lesions.

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PALABRAS CLAVE
Esclerosis múltiple;
Dolor;
Resonancia medular

Análisis del dolor en pacientes con esclerosis múltiple

Resumen
Introducción: El dolor es un síntoma común en la esclerosis múltiple (EM) pero su prevalencia y características no están bien definidas. El objetivo de este trabajo fue describir la prevalencia, las características del dolor en pacientes con EM y determinar variables clínicas y radiológicas asociadas.
Métodos: Se realizó un estudio prospectivo y descriptivo de pacientes con EM. Se evaluó la presencia de dolor en el momento de inclusión. A aquellos pacientes que referían dolor se les analizó el tipo (neuropático, nociceptivo o ambos), la localización y la intensidad (medida por la escala visual analógica) del dolor, así como la analgesia recibida. Se recogieron variables demográficas, tipo de EM, disfunción neurológica (EDSS), frecuencia de brotes, años de evolución, síntomas depresivos (evaluados por el test de Hamilton), tratamiento inmunomodulador, fatiga, espasticidad, presencia de lesiones en resonancia medular y un test de calidad de vida.
Resultados: Se incluyeron 134 pacientes. Se realizó resonancia medular en 105. El 55% (74) presentaron dolor. Mayoritariamente fue neuropático, urente, en las extremidades y percibido como grave. De ellos recibió analgesia el 38% Los pacientes con dolor presentaban mayor discapacidad (EDSS 4,5 [3-6] frente a 1,5 [1-2]; $p < 0,001$), mayor número de brotes (7,13 ± 3,4 frente a 3,75 ± 2,9; $p < 0,001$), mayor tiempo de evolución (14,6 ± 7,8 frente a 8,43 ± 5,9 meses; $p < 0,001$), formas progresivas (86,7% frente a 13,3%; $p < 0,001$), depresión (91,9%frente a 8,1%; $p < 0,001$) y mayor presencia de lesiones en la resonancia medular (84,3%frente a 15,7%; $p < 0,001$). En el análisis multivariante las lesiones en resonancia medular (OR: 3,5 [1,5-24,5]; $p = 0,001$) y la discapacidad (OR: 1,7 [1,1-2,7]; $p = 0,014$) se asociaron de forma independiente con dolor.
Conclusiones: El dolor en la EM es frecuente y percibido como grave. Se asocia con la presencia de lesiones en la resonancia medular y con mayor discapacidad.

Introduction

Pain is currently recognised as a common symptom in multiple sclerosis (MS) directly related to the disease and its consequences.

The World Health Organization classifies pain syndromes into nociceptive and neurogenic (or neuropathic). Patients with MS can present both types: neuropathic or neurogenic pain, which is directly related to the disruption of myelin in the central nervous system; and nociceptive pain, which is secondary to musculoskeletal changes that take place in patients, such as weakness or spasticity.[1]

The number of studies evaluating pain in patients with MS has increased in recent years. Those that study the prevalence of this symptom differ significantly, with ranges oscillating between 30%and 90%.[2-4] These studies agree that the presence of pain has a negative impact on the quality of life of patients.[5,6] However, there are no conclusive results regarding its relationship with other clinical variables of disease (disability, duration, number and location of outbreaks, etc.)[7-9] or with radiological lesions. Despite the importance of spinal pathways in the transmission of pain, the presence of spinal cord lesions on MRI has not been studied in patients suffering MS and pain.

The objectives of our study were to determine the prevalence of pain in a cohort of patients with MS and its impact on their quality of life. In addition, we analysed the characteristics of this symptom and its relation with clinical and spinal imaging variables and evaluated the treatment received by patients and their opinion of its effectiveness.

Patients and methods

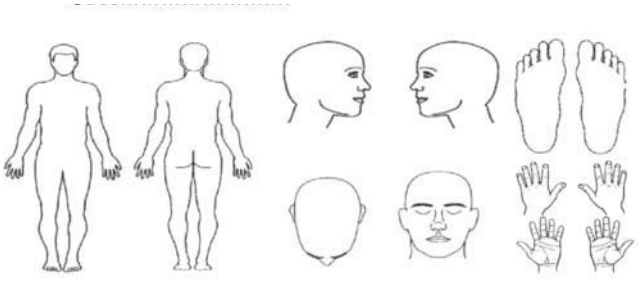
We performed a descriptive, prospective and transversal study in patients with MS (defined according to the Poser[10] and/or McDonald[11] criteria). We included consecutive patients who attended consultations at the MS Unit at the Hospital Universitari Germans Trias i Pujol in Badalona. Two groups of patients were established based on the presence or absence of pain. Those who presented this symptom at the time of inclusion, with a minimum of one week duration, completed a structured questionnaire (fig. 1) assessing the type of pain (nociceptive, neuropathic), its location, intensity (measured by a visual analogue scale [VAS] as mild [from 0 to 3], moderate [4 to 7] and severe [8 to 10]), analgesic treatment received and their opinion of its effectiveness. This survey was conducted by the same examiner, after having explained the purpose of the survey and its confidentiality and obtaining informed consent from the patient.

The clinical, radiological and quality-of-life variables of patients who presented pain were compared with the variables of those who did not report this symptom. The

study included demographic data (gender, age), clinical forms of MS (defined by Lublin[12] as relapsing-remitting MS [RRMS], secondary progressive [SPMS] and primary progressive [PPMS]), neurological disability (measured according to the Kurtzke disability scale[13]), years of evolution of the disease, the number of outbreaks since the onset of symptoms, presence or absence of spasticity

1. Have you suffered pain in the last week?
   a. Yes
   b. No

2. Underline the part of your body where you suffer pain.
   a. thigh, leg, foot
   b. arm, forearm, hand
   c. head
   d. thorax
   e. back (cervical, thoracic, lumbar)
   f. generalised
   Others ……..



3. Pain is (mark more than one if necessary)
   a. constant
   b. not constant
   c. with crises of pain
   d. without crises of pain

4. Does pain wake you up at night?
   a. yes
   b. no

5. How would you define the pain you suffer?
   a. oppressive (as if something squeezed you)
   b. stinging
   c. spasms/ramp
   d. electrical current
   e. numbness
   f. burning
   g. hypoesthesia (there is a part of my body that I do not feel or that I feel less than normal)
   h. others ……..

6. Do you suffer from Lhermitte's sign? (feeling of electrical current down your back when you flex your neck or lumbar column)
   a. yes
   b. no

7. Visual analogue scale to evaluate pain. Mark with a cross the number that best defines the intensity of your pain (0 corresponds to "no pain" and 10 to "the maximum pain imaginable"

No pain ---------- Insufferable
0 1 2 3 4 5 6 7 8 9 10

Figure 1 Questionnaire used to evaluate the characteristics of pain in patients with MS.

8. Do you receive treatment for your pain?
   a. yes
   b. no

9. What treatment do you receive?
   a. anti-inflammatory drugs (ibuprofen, naproxen, diclofenac, etc.)
   b. Nolotil®
   c. Rivotril®
   d. Neurontin®
   e. Lioresal®
   f. Cannabis
   g. Homeopathy ……..
   h. Physiotherapy
   i. Massage
   j. Chiropractic
   k. Others ……..

(Mark with a cross one or various options if necessary)

10. How frequently do you take treatment for pain?
   a. daily
   b. >3 times per week
   c. <3 times per week
   d. occasionally
   e. almost never
   f. never

11. Does the treatment calm your pain?
   a. 0%-20%
   b. 20%-40%
   c. 40%-60%
   d. 60%-80%
   e. 80%-100%

Figure 1 *(Continued)*

(measured by the Ashworth scale, considering it present with values above 2), depressive symptoms (assessed according to the Hamilton test,[14] considering positive test values higher than 51), fatigue (assessed according to the Krupp Fatigue Severity Scale[15] considering positive scale averages above 3), immunomodulatory treatment and quality of life (measured by EuroQol). Radiological variables studied were the presence and location of lesions in the spinal cord displayed on a spinal resonance. We evaluated the lesions visualised in the sagittal sections of T2 and FLAIR sequences. Resonances evaluated were those that had been obtained in the 6 months prior to admission into the study. After patient inclusion in the study, spinal images were requested for the patients for whom none were available.

The data were collected and analysed using SPSS package version 15.0. We performed descriptive statistics (mean, standard deviation, median, range, frequency tables) of the main variables (age, gender, Expanded Disability Status Scale (EDSS), years of evolution, clinical symptoms, presence, type and intensity of pain, fatigue and mood alterations and the presence and location of lesions on spinal MRI). We used the chi square test or Fisher exact test to compare categorical variables (presence or absence of pain in patients with RRMS, SPMS or PPMS in patients with demyelinating lesions in the spinal MRI, in patients with fatigue and/or alteration of mood). We used the Student t test or Mann-Whitney U test for categorical variables when comparing two groups (ratio of age, EDSS, years of evolution, number of outbreaks with the presence or absence of pain). Statistical significance was accepted for $P<.05$.

Table 1 Variables associated with pain in MS

	Total (n)	Pain (56%) n=74	No pain (44%) n=60	*P*
Female gender	134	59%(56)	41%(38)	NS
Clinical forms				
RRMS	82	36.6%(30)	63.4%(52)	
SPMS	45	86.7%(39)	13.3%(6)	0.02
PPMS	7	71%(5)	28.6%(2)	
EDSS	134	4.5 (3-8)	1.5 (1-3)	<0.001
Number of outbreaks	134	7.13±3.4	6.75±2.9	NS
Duration of disease (years)	134	14.6±7.8	8.43±5.9	<0.001
Fatigue	134	42.9%(21)	57.1%(28)	NS
Spasticity	134	56.9%(30)	29.1%(21)	NS
Depressive symptoms	134	91.9%(34)	8.1%(3)	0.01
Immunomodulatory treatment (yes)	134	64.8%(35)	35.2%(19)	NS
Spinal lesions	105	89.4%(59)	28.9%(11)	< 0.001
Location of lesions (cervical)	105	35%(26)	29%(17)	NS
Quality of life (EuroQol)	134	30±8	60±9	0.03

We performed univariate analysis to analyse the variables significantly associated with pain. We performed logistic regression analysis to assess the independent effect of each of the clinical or radiological variables on the presence of pain in patients with MS. We included in the model those variables associated, with statistical significance, to the presence of pain in the bivariate analysis.

Results

We included 134 consecutive patients who attended consultations at the MS Unit of the Hospital Universitari Germans Trias i Pujol in Badalona during a period of 6 months.

For all patients included, mean age was 42±11 years; 70% of the sample were female, and the mean period of disease progression was 11±7 years. A total of 61% suffered RRMS, 33% suffered SPMS and 5% suffered PPMS. The median disability measured by the EDSS scale was 3.5 (2.5-4.5). Pain was present in 74 (55%) patients. A total of 37% suffered mood disorders and 36.6% reported fatigue. The spinal resonance was evaluated in 105 patients, with lesions being observed in 67.3% of them. Upon analysing the demyelinating lesions in the spinal resonance, we observed that 56% were located at the cervical level, 28% at the dorsal level and 24% at the lumbar level.

To avoid bias when assessing the prevalence of pain, patients who refused to participate in the study were asked by telephone about the presence of pain. It was observed that the prevalence remained at approximately the same values (52%).

The patients who reported pain completed a specific questionnaire (fig. 1) to asses its characteristics. It was noted that 75% of patients with pain suffered it in various locations throughout the body; the most frequent were the lower limbs (42%), particularly the thighs, followed by the cervical area (39%) and the head (33%; this included trigeminal neuralgia). Upon questioning about the type of pain, we found that 58% of our patients presented neuropathic features, the most frequent being referred as stinging (41%), followed by painful spasms (33%), numbness (23%) electrical currents (21%), tightness (12%) or burning (9%). Lhermitte's sign, a very characteristic symptom of MS patients, was reported by 40% of the sample. Up to 22% of patients presented nociceptive pain, the most frequent being pain in the lumbar area; 20% of the patients suffered both neurogenic and nociceptive pain at the same time. In addition, a high percentage of patients (53%) also suffered pain constantly and persistently. When assessing pain intensity, 55% of patients described it as severe (VAS 8-10), 32% as moderate (VAS 4-7) and 13% as mild (VAS 1-3).

After the questionnaire, we evaluated the treatment that patients received for pain. It was noticed that only 38% of patients affected received treatment for this symptom. The most commonly used analgesics were NSAIDs (42%), followed by anticonvulsants (27%) and 7% of patients used homeopathic treatments. The majority of patients (51%) received analgesic drugs daily. A total of 61% of patients felt that the prescribed treatment relieved them from the presence of pain by less than 40%

Subsequently, we assessed whether there were any significant differences in demographic, clinical and radiographic variables between patients suffering pain and those without this symptom (table 1).

We observed no significant differences between genders or age groups. Neither did we find that patients who reported fatigue or spasticity in the physical examination reported more pain. Furthermore, there was no relationship between the location of demyelinating lesions in the spinal cord and the presence of this symptom. Due to the fact that currently-available treatment for MS is intramuscular or subcutaneous administration of immunomodulatory drugs, which can cause flu-like syndrome, we analysed the

Table 2 Independent predictors of pain in MS

Variables	OR	95%CI	P
Clinical forms	1.09	0.05 to 8.4	0.66
EDSS	1.7	1.1 to 2.7	0.014
Disease duration	0.92	0.85 to 2.01	0.3
Depression	1.04	0.74 to 2.69	0.09
Spinal lesions	3.5	1.5 to 24.5	0.001
Quality of life	2.1	0.8 to5.2	0.1

relationship between pain and treatment; no significant association was found.

Patients with pain presented greater disability (EDSS 4.5 [3-8] versus 1.5 [1-3]; *P*<.001), a longer period of evolution (14.6±7.8 versus 8.43±5.9 years; *P*<.001), progressive forms (86.7% versus 13.3%; *P*<.001), depression (91.9% versus 8.1%; *P*<.001) and a greater presence of spinal cord injuries in MRI images (84.3% versus 15.7%; *P*<.001). Moreover, patients with pain had lower scores on the quality of life test (EuroQol) than patients without pain (30±8 versus 60±9; *P*=.03). In a logistic regression analysis, the presence of lesions in spinal MRI (OR: 3.5 [1.5-24.5]; *P*=.001) and greater disability as measured by EDSS (OR 1.7 [1.1-2.7]; *P*=.014) were independently associated with pain (table 2).

Discussion

This study shows that a large percentage of patients (55%) diagnosed with MS report pain at the time of the interview. This figure is similar to that reported in other studies also describing a high prevalence of this symptom in patients with MS.[2,7] Our study, given its transversal nature, evaluated the presence of pain at the time of inclusion; however, if we had evaluated the painful symptoms that occurred at some point in the evolution of the disease, the percentage of patients with this symptom would have been much higher, as has been observed in other studies.[3,16,17]

In assessing the type of pain suffered by patients, we found that the most frequent was neuropathic (58%), more specifically pain described as stinging, and constant or persistent. Other studies support our findings.[18,19] The reason for the predominance of neurogenic pain over nociceptive pain could be justified in that the former occurs when there is an alteration of myelin such as that which appears in the earliest phases of the disease in all patients with MS. However, nociceptive pain is usually secondary to paresis or abnormal postures, which only appear in some patients and at later stages of MS.

It is important to identify not only how the patient physically perceives the pain, but also the location where the person feels this symptom. In our study we noted that most patients (75%) presented pain symptoms in more than one location. We also noted that the majority of patients in our study (55%) described their pain as severe (according to a VAS).

Since pain was perceived as severe by most patients and in various locations of the body constantly, it is logical to think that it should have an impact on everyday life. Our study, like others conducted previously,[6,20] demonstrated that patients with pain had a greater loss of quality of life (as measured by the EuroQol test) compared to those who did not report this symptom.

Other investigations[21] have shown that anxiety and depression in MS significantly affect the perception of pain. These data were corroborated in our study, where we found that patients with depression (as measured by the Hamilton test) reported more pain symptoms.

When evaluating other clinical characteristics associated with pain in MS, we observed that patients with progressive forms and more disability as measured by the EDSS scale reported pain symptoms in a significantly higher percentage than patients with a lesser neurological impairment. This may be because the patients who were most affected had a greater physical disruption of myelin in their central nervous systems and a higher probability of paresis, spasticity and abnormal postures, so they were more likely to suffer both neuropathic and nociceptive pain.

One of the newest findings of this study is the relationship discovered between the presence of demyelinating lesions in the spinal cord and the onset of pain. Our study showed that patients with a higher number of spinal injuries, regardless of their location, were more likely to present this symptom. Numerous studies have addressed the relationship between spinal cord injuries of various aetiologies (especially with a traumatic origin) and neuropathic pain (reviewed in Yezierski RP[22]). These studies conclude that such injuries can cause changes in the survival, function and excitability of the pathways involved in the transmission of sensitivity (spinothalamic tract and posterior columns) secondary to the decrease in inhibitory neurotransmitters such as glutamate and GABA and to the release of inflammatory mediators such as free radicals, nitric oxide and proinflammatory cytokines. These changes would make an environment conducive to the development of pain at different levels possible.

One limitation of our study is the lack of analysis of the relationship between pain and lesion load at the level of the brain. However, other studies[7] have not found a relationship between these two variables. This could be explained by the fact that nociceptive pathways act at the spinal cord level, thus being more likely to be affected when there are demyelinating lesions in the spine.

As we have shown, pain is a symptom of great importance in patients with MS and one that has an impact on quality of life. However, in evaluating the treatment received to relieve pain, we noted that only 38% of patients received analgesics and that these were insufficient to control their pain. This finding is consistent with other studies that also observed that pain is a symptom scarcely evaluated and treated.[7,8] Moreover, we also noted that the drugs prescribed were unsuitable, since the vast majority received NSAIDs despite neuropathic pain being the most common. Numerous studies have shown that antiepileptic drugs such as carbamazepine, gabapentin or levetiracetam are the most effective for the treatment of neurogenic pain in patients with MS.[23,24] The reasons why pain did not receive an optimal treatment in patients with MS are unclear. One possibility is that the drugs available do not offer the full effectiveness

that the patients expected and after testing these drugs for a while, the patients decided to stop taking them due to their side effects. We believe the solution could lie in the multidisciplinary care of patients with MS, so they would be cared for not only by neurologists, but also at Pain Units that could provide optimal treatment for their pain symptoms.

In conclusion, pain is a prevalent, although underestimated, symptom in patients with MS. Consequently, it requires greater attention for its detection and a specific treatment to provide a better quality of life for patients.

Conflict of interest

This work was partly financed by Fundació La Marato from TV3 with code 07/2410 to Eva Martínez Cáceres.

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