The Prevalence of Pain in Adults with Multiple Sclerosis: A Multicenter Cross-Sectional Survey

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Dependent variable: presence of pain.

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Abstract

Objective. Examination of prevalence, intensity and associations of pain in persons with multiple sclerosis (MS).

Design. Multicenter, international cross-sectional survey.

Setting. Patients were recruited from seven MS centers: in Serbia (Clinic of Neurology, Clinical Center of Serbia, Belgrade; Clinic of Neurology, Military Medical Academy, Belgrade; Clinic of Neurology, Clinical Center Kragujevac; Clinic of Neurology, Clinical Center Nis; Department of Neurology, General Hospital-Uzice), in Republic of Srpska-Bosnia and Herzegovina (Clinic of Neurology, Clinical Center Banja Luka) and in Croatia (University Department of Neurology, Sestre Milosrdnice University Hospital Center, Zagreb).

Subjects. Six hundred and fifty consecutive MS patients diagnosed according to the Revised McDonald criteria (2005), from the aforementioned centers, over the period of 6 months.

Methods. A semistructured questionnaire was administered during a face-to-face interview with neurologists who also performed Expanded Disability Status Scale (EDSS), the Hamilton Rating Scale for Depression (HDRS) and Hamilton Rating Scale for Anxiety (HARS). To recognize predictive factors for the presence of pain, the linear regression analysis was used.

Results. Lifetime prevalence of pain was 66.5% (point prevalence = 44.3%). The prevalence of the comorbidity of pain and depression was 29.1%. Older age (P<0.001), primary-progressive MS (P = 0.034), higher EDSS score (P = 0.008), higher scores of HDRS (P<0.001), and HARS (P<0.001) were significantly associated with pain. Finally, in our multivariate linear regression analysis, anxiety (P<0.001) was the independent predictor of pain.
Conclusions. We confirmed high prevalence of pain, affecting approximately more than half of patients during the course of MS. Pain in MS is associated with disability, depression and, especially with anxiety, which has significant implications for treatment.

Key Words. Neurology; Pain Disorder

Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative chronic disease of the central nervous system (CNS). Pain is a common symptom in MS, which has been recently estimated to be experienced by 63% of patients [1]. Published pain prevalence in MS range widely because of significant differences in patients’ samples and study design [1–3]. Additionally, therefore the risk factors reported to be associated with greater likelihood of pain in adults with MS also differ in various studies [4]. Italian multicenter cross-sectional study as one of the largest epidemiological surveys, which included 1,672 MS patients, demonstrated that 43% of patients experienced pain and found that age, disease course, diseases duration and disability correlated with the presence of pain [2].

The WHO classifies pain as nociceptive, neuropathic and psychogenic [5]. Nociceptive pain is pain resulting from nociceptor activation by tissue-damaging stimuli. Neuropathic pain is a consequence of a lesion affecting the somatosensory system. According to classification proposed by O’Connor et al., there are three main types of MS-related pain: neuropathic pain, musculoskeletal, nociceptive pain (i.e., painful tonic spasms, pain secondary to spasticity, pain related to being wheelchair bound), and headaches [4].

The aim of this multicenter, international cross-sectional survey was to characterize, using a structured questionnaire, the prevalence and clinical characteristics of pain in a cohort of well-defined MS patients.

Material and Methods

Study Participants

Patients were recruited from seven MS centers: five in Serbia (Clinic of Neurology, Clinical Center of Serbia, Belgrade; Clinic of Neurology, Military Medical Academy, Belgrade; Clinic of Neurology, Clinical Center Krugujevac, Krugujevac; Clinic of Neurology, Clinical Center Nis, Nis; Department of Neurology, General hospital-Uzice), one in the Republic of Srpska-Bosnia and Herzegovina (Clinic of Neurology, Clinical Center Banja Luka, Banja Luka) and one in Croatia (University Department of Neurology, Sestre Milosrdnice University Hospital Center, Zagreb). A semistructured questionnaire was administered during a face-to-face interview with 650 MS patients, performed by previously trained examining neurologists. Included in the study were consecutive MS patients diagnosed according to the Revised McDonald criteria (2005) [6], diagnosed and followed in the above mentioned centers over the period of 6 months. Patients who had a relapse in the last month before the beginning of the study were excluded.

This survey was approved by Institutional Review Boards in all centers.

Measurements

The questionnaire comprised age, gender, duration and course of the disease, Expanded Disability Status Scale (EDSS) [7], and type of pain including its therapy. Pain associated with MS was classified as neuropathic pain (continuous central neuropathic pain: neuropathic extremity pain; intermittent central neuropathic pain: Lhermitte’s sign, trigeminal neuralgia), musculoskeletal, that is, nociceptive pain (low back pain and painful tonic spasms), and headache (mixed neuropathic and non-neuropathic pain) [4]. We considered pain symptoms at any point during the course of the patients’ disease and at the time of evaluation. Pain severity was assessed using 0–100 mm numerical rating scale (Visual analog scale-VAS) [8]. A higher score indicates greater pain intensity.

The severity of depressive symptoms and anxiety were quantified in all patients using the Hamilton Rating Scale for Depression (HDRS) [9] and Hamilton Rating Scale for Anxiety (HARS) [10]. Both HDRS and HARS are clinician-administered estimation scales that are conducted using a semistructured interview. The suggested cutoff values for HDRS are 0–9 (no depression), 10–13 (mild depression), 14–17 (mild to moderate depression), and >18 (moderate to severe depression) [9]. The total score of the HARS ranges from 0 to 56, in which value <17 indicates no or mild anxiety, values between 18 and 24 mild to moderate anxiety and values between 25 and 30 moderate to severe anxiety [10].

Statistical Analysis

Descriptive statistics were computed to identify the point and lifetime prevalence of pain in MS patients. Patients’ characteristics for the “pain” and “no pain” groups were compared with Chi square and Kruskal–Wallis tests for categorical and Mann–Whitney test for not normally distributed continuous variables. Additionally, we used ANOVA for evaluating differences among normally distributed continuous variables. Spearman’s correlation coefficients were used to determine the relationship between the presence of pain and both HDRS and HARS scores. To recognize predictive factors for the presence of pain among study participants, the univariate and multivariate linear regression analyses were performed. The SPSS 17.0 statistical software package (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis.
Results

Demographic and clinical data from 650 patients with diagnosis of MS were collected by questionnaires in seven MS centers (Table 1). Questionnaires were divided into pain (432; 66.5%) and no pain (218; 33.5%) group. Patients with pain were significantly older, had a higher EDSS score and also higher both HDRS and HARS scores. The pain group comprised marginally significantly ($P = 0.054$) higher proportion of persons with SP and PP disease.

According to the values of HDRS (scores $> 9$) 54.7% had depression (mild-17.9%; mild to moderate-12.9%; moderate to severe-23.9%). Out of 288 persons experiencing any pain at the time of evaluation, 189 (65.6%) met depression criteria (HDRS score $> 9$). The prevalence of the comorbidity of pain and depression is present in 29.1% of participants. HARS indicated no or mild anxiety in 79.9% patients, mild to moderate in 13.2%, and moderate to severe in 6.9%. There is significant correlation between presence of pain at the time of evaluation and both HDRS ($P < 0.001$) and anxiety, measured by HARS (standardized beta coefficient $= -0.198$, $P = 0.005$) as independent predictors of pain in this study.

Discussion

This study assessed the prevalence of pain in large cohort of well-defined MS patients from several centers.

Table 2  Prevalence of pain symptoms in persons with multiple sclerosis ($N = 650$)

<table>
<thead>
<tr>
<th>Prevalence of pain symptoms</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime prevalence</td>
<td>66.5</td>
</tr>
<tr>
<td>Point prevalence</td>
<td>44.7</td>
</tr>
<tr>
<td>Type-specific prevalence</td>
<td></td>
</tr>
<tr>
<td>Continuous central neuropathic pain</td>
<td>56.2</td>
</tr>
<tr>
<td>Intermittent central neuropathic pain</td>
<td>52.7</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>49.7</td>
</tr>
<tr>
<td>Mixed neuropathic and non-neuropathic pain</td>
<td>48.6</td>
</tr>
</tbody>
</table>
in Serbia, Croatia and the Republic of Srpska-Bosnia and Herzegovina. Lifetime prevalence of pain in our sample of 650 MS patients was 66.5%, while point prevalence was 44.3%. This lifetime prevalence is in line with heterogeneous published prevalence of pain at any point during the course of the patients with MS which ranges widely from 34% to 92% [2,4,11–13]. Recently, a systematic review and meta-analysis showed an overall pain prevalence of 63% [1].

Several types of pain are associated with MS. Criteria used to define the various types of MS-related pain are different. It is essential to adequately define the various types of pain to better understand the underlying pathophysiological mechanisms and to consequently apply the proper treatment strategy. The prevalence of various types of pain varies among numerous studies. However, neuropathic pain and headaches are the most prevalent according to the published data [3]. Our results are in accordance with those findings, as most prevalent types of pain in our survey were also neuropathic extremity pain (52.9%) and headache (39.5%). Low back pain (26.6%) was also very common in our MS patients with prevalence very similar to that reported in above mentioned systematic review [3]. Prevalence of Lhermitte’s sign (19.2%), trigeminal neuralgia (5.7%), and painful tonic spasms (9.5%) were also registered in our study. Recently, similarly, Österberg et al. found trigeminal neuralgia in 4.9% of MS patients [12], although previous studies detected less frequent occurrence of trigeminal neuralgia in MS patients of 1–2% [2,14,15].

The pain severity in MS has been described in several studies. In most of them, the average pain intensity was estimated as moderate or mild [16,17]. Similarly, according to VAS scale, in our study majority of patients had mild or moderate pain, and only about 10% reported their pain as severe.

Table 3 Univariate linear regression analyses of predictors of the presence of pain in persons with multiple sclerosis (N = 650).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized beta coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.226</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.057</td>
<td>0.146</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>-0.021</td>
<td>0.594</td>
</tr>
<tr>
<td>Primary-progressive MS</td>
<td>0.086</td>
<td>0.034</td>
</tr>
<tr>
<td>EDSS score</td>
<td>-0.115</td>
<td>0.008</td>
</tr>
<tr>
<td>HDRS score</td>
<td>-0.232</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HARS score</td>
<td>-0.269</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The majority, the risk factors for development of pain in MS patients were older age, longer disease duration, and higher EDSS, as a measure of disease severity [2,16,18]. In our study, patients with pain were also significantly older than those without pain. Additionally, median EDSS, mean HDRS and HARS scores were significantly different between our patients with or without pain.

Depression is a common and disabling symptom in MS, with a point prevalence ranging from 27 to 54% [19,20]. However, studies related to the prevalence of comorbidity of pain and depression are rather rare. Recently, Alschuler et al. emphasized that although, according to research from non-MS populations, pain and depression often co-occur and mutually impact each other, it is not clear whether the same phenomena are present for persons with MS [21]. The same authors reported that of persons experiencing any pain, 11–34% met depression criteria, and of persons meeting depression criteria, 86–100% reporting experiencing any pain [21]. Thus, they concluded, to our best knowledge in the first study reporting on the prevalence of this comorbidity, that this prevalence is 6–19%. Our results are in accordance with these previously published findings. We found the prevalence of the comorbidity of pain and depression in 29.1% of participants. Additionally, out of 288 persons experiencing any pain at the time of evaluation in our study, more than 85% met depression criteria. Regarding the difference in the comorbidity of pain and depression, in above mentioned studies, it should be mentioned that it has been previously published that comorbid pain and depression is suggested to exist in 27% of persons with neurologic conditions [22]. The significant correlations between presence of pain at the time of evaluation and both HDRS (P = 0.001) and HARS (P = 0.001) were registered. It should be emphasized that in three previously published cross-sectional studies with smaller cohorts of MS patients, association between pain and depression has been analyzed. Similar to our results, Grau-Lopez et al. found that pain was more frequent in MS patients with depression [23]. Conversely, pain was not found to be associated with depression in two remaining studies [24,25]. Finally, in our multivariate linear regression analysis, only HARS (P < 0.001) was the independent predictor of pain in MS patients. These findings are clinically relevant and warrant further study, especially related to the treatment.

Appropriate approaches to treatment of pain in MS are not well defined yet. To optimize MS-related pain treatment, it is necessary to determine the origin of pain categories. Data related to treatment of pain in MS is very limited. In our study, about half of the patients were taking pain medication. Majority has taken nonsteroid anti-inflammatory drugs, while tricyclic antidepressants, antiepileptic medications, and spasmylytics were used rarely.

Several limitations of this study require to be mentioned. This study was cross-sectional; longitudinal study which
could have followed the evolution of pain during disease would have been preferable. Additionally, it should be mentioned that possible presence of information bias could have meaningful implication in interpretation of our findings. Namely, the information regarding pain during the entire course of the disease may be wrong and consequently, possible disagreement of correct answers can arise due to memory bias. This type of bias can also occur in circumstances when patients with longer duration of MS become adapted to pain and thus might not be recognized this issue as relevant. Furthermore, investigators were not blinded, and finally there was no control group of patients without MS. Finally, HDRS and HARS were used to identify depression and anxiety.

In conclusion, we confirmed in our survey high prevalence of pain, affecting approximately more than half of patients during the course of MS. Having in mind that pain in persons with MS is associated with disability and depression, it could potentially cause additional suffering and interfere significantly with daily activities. Until now, unfortunately the evidence for treating MS-related pain is very limited. Therefore, randomized controlled trials should be conducted to examine the efficacy and safety of various pharmacological treatments as well as non-pharmacologic therapies (psychotherapy, physical and occupational therapy).

**Prevalence of Pain in Multiple Sclerosis**

**References**


