Pain in Multiple Sclerosis: Prevalence and Characteristics of Various Pain Conditions

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Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) with unpredictable course and a changeable, interindividually varying complex of symptoms with a lifelong progression which may result in disability. Since the disease is so far incurable, proper symptomatic treatment is very important in its management in addition to the disease modifying treatments.

Pain in MS is a very common symptom, with prevalence in patients ranging from 29 to 92% [1-14]. The existing research has proven pain is a key problem in patients with MS. Svendsen et al. found that pain in MS patients was reported by similar proportions of MS patients and sex and age-stratified group from the general population, however pain intensity, the need for analgetic treatment and pain interference with activities of daily living were much higher in MS patients [4]. Kalia and O'Connor compared MS patient's SF-36 bodily pain scores with those of rheumatoid arthritis and osteoarthritis finding, that all three groups had comparable levels of pain severity [15]. Ehde et al. reported severe pain (score 7-10) in 27% from 442 patients with MS [3]. Pain was the worst symptom of MS in 12% patients and 68% of patients reported dissatisfaction with the care of the physicians [16]. Also Solaro et al. reported as results of his work disruption in daily life activities, work, mood, recreation and general enjoyment of life, low satisfaction with treatment [5]. Brochet et al. found out that 73.5% of patients had pain at the onset of their MS and in 44% of patients pain significantly interfered with daily activities [12]. In an article by Marchettini et al. several cases were presented with pain as an initial sign of MS. Most of these patients reported pain as their only symptom for some time before further signs of MS began to appear [17].

Several different types of pain can be identified in patients with MS, including continuous or intermittent central neuropathic, nociceptive pain and mixed neuropathic and non-neuropathic pain. Pain in MS patients is classified according to causal mechanism in order to facilitate mechanism-tailored treatment strategies [18]. This mechanism-based classification of pain in MS distinguishes nine types of MS-related pain: trigeminal neuralgia and Lhermitte's phenomenon (paroxysmal neuralgiform pain due to ectoric impulse generation along primary afferents), on-going extremity pain (deafferentation pain secondary to lesion in the spinal-thalamo-cortical pathways), painful tonic spasms and spasticity pain (mixed pains secondary to lesions in the central motor pathways but mediated by muscle nociceptors), pain associated with optic neuritis (nerve trunk pain originating from nerve window), musculoskeletal pain (nociceptive pain arising from postural abnormalities secondary to motor disorders), migraine (nociceptive pain favored by predisposing factors or secondary to midbrain lesions) and treatment-induced pain.

Pain in MS stemming from the disease itself includes acute pain syndrome (trigeminal neuralgia, Lhermitte's sign, painful tonic seizures, segmental burning dysesthesia, neuralgia, migraine) or chronic pain syndrome (chronic dyesthetic pain, painful leg spasms, and optic
In many patients, pain results from disability, immobility, poor posture, decubital ulcer, peripheral nerve lesions due to chronic pressure, e.g. from poorly fitted braces, or MS treatment. In our study we tried to better understand the epidemiology of pain in MS, which could potentially improve pain management in MS patients. Details from the study on prevalence of central pain in MS was analysed in detail in a separate study.

**Patients and Methods**

The analysed group consisted of 307 patients (225 female and 82 male) aged 21 to 69 (with the average age of 37) with definitive MS in the patient register at the Department of Neurology of the University Hospital in Bratislava, Slovakia. The patients were sent a questionnaire focusing on basic demographic characteristics (age, sex), disease specifics (onset of first MS symptoms, the year of diagnosis confirmation, form of the disease course, and disability score) and pain. They also filled in a standardized health-related quality of life questionnaire, SF-36v2 [19]. Questions relating to pain experiencing during the course of the disease were created on the basis of existing literature sources and our own clinical experiences. Responders were asked, if they had suffered from such types and qualities of pain as follows: headache (tension, migraneous), back or neck pain, trigeminal neuralgia, Lhermitte’s sign, unpleasant painful sensations in upper legs, lower legs or other parts of the body (burning, cramping, stabbing, pressing, picking, stiffness, coldness) and secondary pain (due to urinary tract infection, spasticity, immobility, decubitus). Pain was measured by using the pain intensity and interference items from the Bodily Pain Scale of the SF-36 [20,21]. Participants were asked about pain intensity by rating how much bodily pain they experienced during the past 4 weeks ranging from 1 (none) to 6 (very severe). They also rated how much pain interfered with normal work, including both work outside the home and housework, on a scale ranging from 1 (not at all) to 6 (extremely). Questionnaire replies received along with patient’s informed consent were included in the study patient database and revised. All patients with unclear pain history were interviewed by telephone or examined at the outpatient clinic. All patients with unpleasant painful sensations in extremities and trunk were examined with aim to diagnose central or peripheral neuropathic-peripheral neuropathy or radiculopathy [22] and nociceptive pain. Patients with dementia or psychiatric conditions were excluded from the study. Back pain, spasticity pain, headache were considered as nociceptive pain in our study. Trigeminal neuralgia et Lhermitte sign were considered as type of central pain. Non-painful paresthesias of central etiology were not considered as central pain. A control group could not be formed for too low a number of painless MS patients participating in the study.

**Statistical Analysis**

The patient's data was subsequently evaluated and interpreted using descriptive and inductive statistics methods. Data normality was checked graphically and by the Shapiro-Wilk test. Each set of data was summarized in contingency tables and displayed graphically in bar and pie charts. To test significance of proportions, binomial tests were used for univariate analysis and chi-squared tests for bivariate analysis. In case of numerical calculability, exact tests were applied. Significance of medians was tested using the Mann-Whitney test. The differences are presented along with the 95% Confidence Interval (95% CI). To establish association between variables, we used corresponding bivariate or multivariate regression analysis methods. Chi-squared tests were used to determine the dependence between qualitative variables. The strength of the relationship was assessed using the Goodman-Kruskal gamma correlation coefficient. Significance of expected or published predictors of the incidence of central pain was tested by bivariate and multivariate logistic regression and it is quoted with corresponding odds ratio (OR) and the 95% confidence intervals. For all statistical analyses, we used the significance level alpha=5%. All analyses were conducted using Microsoft Office Excel 2003 (Microsoft Corporation) and StatsDirect 2.6.6 (Stats Direct Ltd., Cheshire, UK) software.

**Results**

Demographic data of the analyzed group of patients are presented in Table 1. The questionnaire was sent in by significantly less males than females (p<0.0001), 95% CI (21.50 to 33.66%). The age or disability score were not substantially different between respondents and non-respondents. Both groups had rather lower scores on the Expanded Disability Status Scale (EDSS), which indicates a higher representation of less disabled persons in our study. Both groups featured significantly more patients with relapsing-remitting MS (p<0.0001). The average disease duration (in our study time since diagnose) was similar in both groups (8 years for respondents, 10 years for non-respondents).

**Prevalence of Pain in MS Patients**

Out of 220 respondents 203 (92%) reported at least one type of pain or unpleasant pain sensation. Prevalence of pain in case of excluding headache from analyse was 90.45%. The results of our study show males to be significantly less susceptible to pain than females (Fisher’s exact test, p=0.0011, 95% CI (0.04 to 0.55). Pain was significantly more frequent in relapsing-remitting form of MS than in secondary progressive MS (p<0.0001), 95% CI (0.64 to 0.77).

Prevalence of pain does not correlate with the age of the patient. The highest incidence of pain was found in MS patients in their 40s and 50s, and then it progressively decreased (Table 2). The total chi-square test shows a statistically non-significant (P=0.052) association between the gender (i.e., between the counts of male and female patients with pain) and age decade, however, this association is plausible, since the age category is ordered and we have found a significant linear trend (P=0.042).

Our study found, that 87.2% patients reported two and more and 31.05% reported three and more concurrent pain locations (i.e. including all types of pain) and the total number of pain locations.

**Table 1:** Demographic characteristics.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Age at examination</th>
<th>EDSS</th>
<th>Disease duration (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number</td>
<td>%</td>
<td>W</td>
</tr>
<tr>
<td>Responders</td>
<td></td>
<td>220</td>
<td>71</td>
<td>160</td>
</tr>
<tr>
<td>Nonresponders</td>
<td></td>
<td>87</td>
<td>29</td>
<td>65</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td>307</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

**Course of multiple sclerosis**

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>SCHP</th>
<th>PCHP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td></td>
<td>72.00%</td>
<td>26.60%</td>
</tr>
<tr>
<td>Nonresponders</td>
<td></td>
<td>85.00%</td>
<td>15.00%</td>
</tr>
</tbody>
</table>

EDSS: Expanded Disability Status Scale; RR: Relapsing-Remitting; SCHP: Secondary Progressive; PCHP: Primary Progressive
significantly increases with disease duration (p<0.0001), 95% CI (from 0.15 to 0.32). Significantly more concurrent pain locations per patient were found in females than males–Fisher-Freeman-Halton exact test (p<0.0001), 95% CI (from -0.69 to -0.24).

**Prevalence of Different Types of Pain in MS Patients**

(Table 3)

**Headache (Neuropathic, nociceptive, psychogenic pain)**

In our study, we found headache in 51.4% of patients. Out of them 46.8% suffered from at least one another type of pain. Headache was the only painful symptom of MS in four (1.8%) patients. The results show that headache is significantly less frequent in males than females (p=0.016, OR=0.26). Our results confirmed there is no association between headache and EDSS (p=0.53). The same finding was obtained for disease duration (p=0.54). In our study headache occurred significantly more frequent in patients with relapsing-remitting form of MS compared to other forms of MS (p=0.081).

<table>
<thead>
<tr>
<th>Location of unpleasant painful sensations</th>
<th>Number of patients</th>
<th>% of patients</th>
<th>W</th>
<th>%</th>
<th>M</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>112</td>
<td>51.38</td>
<td>86</td>
<td>76.78</td>
<td>26</td>
<td>23.21</td>
</tr>
<tr>
<td>Back pain</td>
<td>124</td>
<td>57.94</td>
<td>101</td>
<td>81.45</td>
<td>23</td>
<td>18.55</td>
</tr>
<tr>
<td>Secondary pain (Due to urinary tract infection, spasticity, immobility, decubitus)</td>
<td>69</td>
<td>31.8</td>
<td>58</td>
<td>84.05</td>
<td>11</td>
<td>15.94</td>
</tr>
<tr>
<td>Lhermitte’s sign</td>
<td>74</td>
<td>34.26</td>
<td>57</td>
<td>77.03</td>
<td>17</td>
<td>22.97</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>13</td>
<td>5.91</td>
<td>11</td>
<td>84.62</td>
<td>2</td>
<td>15.38</td>
</tr>
<tr>
<td>Unpleasant painful sensations in lower legs</td>
<td>185</td>
<td>84.09</td>
<td>142</td>
<td>76.76</td>
<td>43</td>
<td>23.24</td>
</tr>
<tr>
<td>Unpleasant painful sensations in upper legs</td>
<td>134</td>
<td>61.19</td>
<td>101</td>
<td>75.37</td>
<td>33</td>
<td>24.63</td>
</tr>
<tr>
<td>Unpleasant painful sensations</td>
<td>81</td>
<td>37.85</td>
<td>67</td>
<td>82.12</td>
<td>14</td>
<td>17.28</td>
</tr>
<tr>
<td>Unpleasant painful sensations</td>
<td>65</td>
<td>30.09</td>
<td>54</td>
<td>83.08</td>
<td>11</td>
<td>16.92</td>
</tr>
</tbody>
</table>

**Table 2:** Age decades of MS patients with pain in years.

**Table 3:** Prevalence of individual types of pain in MS patients.

<table>
<thead>
<tr>
<th>Location of unpleasant painful sensations</th>
<th>n/resp</th>
<th>% out of resp</th>
<th>n/W</th>
<th>n/M</th>
<th>%/W</th>
<th>%/M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower extremity</td>
<td>220</td>
<td>84.09</td>
<td>185</td>
<td>35</td>
<td>70.71</td>
<td>13.38</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>219</td>
<td>61.19</td>
<td>134</td>
<td>85</td>
<td>37.44</td>
<td>23.75</td>
</tr>
<tr>
<td>Half of the body</td>
<td>214</td>
<td>37.85</td>
<td>81</td>
<td>133</td>
<td>14.33</td>
<td>23.52</td>
</tr>
<tr>
<td>Trunk</td>
<td>216</td>
<td>30.09</td>
<td>65</td>
<td>151</td>
<td>9.05</td>
<td>21.04</td>
</tr>
</tbody>
</table>

**Table 4:** Quantitative analysis of unpleasant painful sensations occurring concurrently in patients.

**Back pain (Nociceptive pain)**

Cervical or lumbar back pain was found in 57.94% of patients. The results of our study show that females suffer from back pain significantly more than males (p=0.0028), 95% CI (from 0.20 to 0.69). The prevalence of back pain significantly increase with the EDSS score (p=0.078). This condition was significantly more frequent in patients with relapsing-remitting form of MS (p=0.013). The presence of back pain was not associated with disease duration (p=0.7).

**Secondary pain (Nociceptive pain)**

Secondary pain was found in 31.8 of our patients (84% female). The results indicate that males are less susceptible to secondary nociceptive pain than females (OR=0.37).

The prevalence of secondary pain significantly increase with the EDSS score (p=0.0085). This condition was not associated with disease duration (p=0.82). The same finding was obtained in types of multiple sclerosis (p=0.18).

**Trigeminal neuralgia (Central neuropathic pain)**

The prevalence of trigeminal neuralgia in our study is 5.91%. The risk of this condition to occur was found to be equal in males and females (OR=0.45).

**Lhermitte’s sign (Central neuropathic pain)**

The prevalence of Lhermitte’s sign in our study is 34.26%.
This condition was found equally frequent in males and females (OR=0.45).

Neuropathic extremity and trunk pain (Central neuropathic pain)

Out of 220 respondents, central neuropathic extremity and trunk pain was found in 40.91%. Female were significantly more affected than male (p<0.0001).

Peripheral neuropathic pain

Five respondents reported peripheral neuropathic pain, which represents the prevalence of 2.4%.

Trigeminal neuralgia, Lhermitte's sign, Neuropathic extremity and trunk pain as a central neuropathic pain were analyzed in detail in upcoming separate study.

Lower extremities were the most common location of unpleasant pain sensations (84.09%, Table 4). The commonest pain quality in all the mentioned body locations (upper and lower extremities and the trunk) was stiffness (Table 5). On the trunk, it was mostly manifested as "girdling" around the body.

Evaluation Subgroups "Bodily Pain" of the SF-36v2

Verbal pain intensity scale has shown that during the past 4 weeks (before the completion of a questionnaire) 55.6% of patients experienced mild to moderate pain and 10% severe to very severe pain.

Within the 5-point verbal scale, which assesses the extent to which pain limits the patient's activities of daily living; we found moderate degree of limitation in 34% and severe degree of limitation in 27.5% of patients.

Discussion

According to available literature sources, there have been several studies looking into different pain conditions accompanying MS, but a thorough differentiation between nociceptive, peripheral and central neuropathic pain – which is essential for the appropriate treatment of patients–has, to our knowledge, been reported in only one study [6].

Representativeness of sample

Based on the assumption that in our analysis of 200 patients (approx. 5% of the MS population in Slovakia), there is an even distribution of characteristics within the population, our sample might be considered as representative. Regarding proportional representation by age our set of patients is consistent with epidemiological data on MS [23]. Regarding proportional representation by gender, it correlates with epidemiological data concerning MS [24,25]. Finally, from the viewpoint of proportional representation of patients stratified by MS forms, we found our sample to be just as consistent with epidemiological data [23].

Prevalence of pain

There are significant differences in the prevalence of pain in MS. They result from geographical and demographic factors of the prevalence of MS itself as well as from different classifications of pain conditions, various sets of patients and control groups, and methodological differences.

The prevalence of pain in our set of patients is 92%, which is not significantly different from other published studies [4,11,26]. Compared to other findings however [3-6,10], the prevalence of pain in our study turned out to be higher. We supposed that important factor in high prevalence of pain found in our study might have been headache, since headache was previously excluded from most studies and according to literature sources prevalence of primary headache in MS patients is higher than in the general population [28], headache may develop as a consequence of MS [29, 30] and can be a treatment induced [18,27,28,31,32].

To assessing the impact of headache on the overall prevalence of pain in patients with MS we decided to analysed the data excluding headache. The obtained result has not confirmed our assumption, because despite the exclusion of headache prevalence was too high. Based on these results MS specific treatment (interferon-beta, glatiramer acetat) and antidepressants probably has not fundamentally influenced the overall prevalence of pain in MS, since existing studies have confirmed their effect mainly on headache.

The high prevalence in our set of patients might have been caused by other factors.

Probably the most important factor is that the questionnaires might have mostly been filled in and returned by more motivated MS patients (experiencing pain). This hypothesis is supported by the fact that the questionnaires were sent in by significantly less male than female patients, which is in line with our finding that pain is more significant in females than males. Also, the results of demographic data analysis showed that we had significantly more patients with relapsing-remitting MS, which was found to be accompanied with pain significantly more frequently than other forms of MS [27,35].

Another factor that must have played a role in high prevalence of pain was the inclusion secondary pain to the study.

As our study found, the prevalence of pain in MS does not correlate with the age of the patient, which is consistent with the study by Østerberg et al. but inconsistent with findings by Clifford et al. or Moulin et al. who reported pain in MS patients to increase with the age. This could be explained by predominance relapsing-remitting MS form associated with pain in our study as well as the fact that relapsing-remitting MS form is more common in younger patients. According to our study, the prevalence of pain is significantly higher in females than males, which is also consistent with literature report [6,15,33,34].

We found pain to be significantly more frequent in relapsing-remitting MS, which can possibly be explained by a higher incidence of headache and paroxysmal pain symptoms during relapses in this form of MS. This could also be consistent with Pöllmann et al. [27] and study by Togha et al. who has shown that headaches are more common during a relapse [35].

Furthermore, our study confirms that MS patients have concurrent pain in many locations of the body on average [7,36]. Our results show that the total number of pain locations (i.e., including all types of pain) in MS patients significantly increases with disease duration, with significantly more pain locations being present in females. To our knowledge, none of such results have so far been reported in literature. According to literature lower extremities are the commonest location of unpleasant pain sensations. The commonest pain quality in our study was found to be painful stiffness and then cramping pain, which may be present in the form of acute or chronic complaints. On the one hand, it may be manifested as nociceptive pain, for instance due to spasticity, muscle pain arising from an abnormal body position, or pain caused by arthropathies. On the other hand, it may be manifested as central pain, includes painful spasms, cramps or tightness such as “feeling like a belt” around the leg, or possibly as peripheral neuropathic pain. Often it is a combination of more than one mechanism.
Prevalence of individual types of pain

The incidence of headache (as based on IHS Classification and diagnostic criteria for headache disorders) in patients with MS is higher than in general population, several (mostly prospective) studies show. Variable frequencies ranging from 4 to 61.8% have been reported in the prevalence of headache in MS [14,35,37-39]. Our study found the prevalence of headache to be 51.38%, which is within the mentioned range. Prevalence of headache was significantly higher in relapsing-remitting form of MS, which is in agreement with the results of several studies. [28,35,43,44]. Headache is a unique clinical problem that must be discussed in any review of MS-related pain, because there appears that the process of demyelination may be a factor in headache production, but there is still limited evidence about it. A little data is also on MS related treatment, comorbidities and MS disability on headaches, especially migraine.

In many MS patients, pain is not directly related to the process of the disease; rather, it results from the consequences of their disability. Frequently occurring back pain and lumbar sciatic syndrome are mostly stemming from wrong posture in patients with paresis, spasticity, dyscoordination of movements, and osteoporosis due to immobility and corticoid therapy. In our sample of patients, we found cervical or lumbar back pain in 57.94%, which is not very much different from the prevalence of 50% as reported by Bashir and Whitaker [40], but higher as 20% reported by Foley et al. [14]. Significantly higher prevalence of back pain in relapsing-remitting form of MS in our study could support the clinical suspicion that back pain is not only consequent to spondyloarthrits, but could be in some cases related to inflammatory episodes involving the meninges or to meningeal reaction to underlying myelitis. Chronic nociceptive pain may also be caused by bedsores, chronic uroinfection, tendonitis, and arthralgias. In our study, these were present in 31.8% of patients and significantly increase with the EDSS score. Females were significantly more susceptible to chronic nociceptive pain than males. The same was found to be true about back pain.

The prevalence of peripheral neuropathic pain (polyneuropathy, peripheral nerve lesion, e.g. as part of chronic pressure due to poorly fitted braces, or isthmus syndrome due to using crutches, etc.) in patients with MS has so far been examined in detail only in the study by Österberg et al. [6] (with all the investigated patients having undergone EMG examination) who reported the prevalence of 2%. In our study, peripheral neuropathic pain was found in five patients, which corresponds to the prevalence of 2.4%.

Unlike nociceptive pain, which was found to be significantly more present in female patients, Lhermitte’s sign and trigeminal neuralgia occur equally frequently in males and females, according to our study. Lhermitte’s sign was present in 34.7% of our patients. In literature, data on the prevalence of this disorder vary considerably from 9 to 41% [5,14,41]. Our results showed trigeminal neuralgia to be present in 5.91% of MS patients, which is consistent with the published data reporting the prevalence frequencies ranging from 1.6 to 18% [4,5,6,38,42]. Our research found central neuropathic extremity pain in 90 patients (40.91%), which is more than reffed Truini et al. [18] or Foley et al. [14], but comparable with study reported by Österberg et al. [6].

Effects on quality of life of patients pain

A comprehensive evaluation of the SF-36v2 in order to assess the proportion of pain on quality of life of MS patients in this study could not be implemented for very small control group of patients without pain. Be able to evaluate a subset of the questionnaire “bodily pain”. In this respect, our results in line with other literature confirm that the majority of patients (55%) felt the intensity of mild to moderate pain that 60% of patients with moderately to severely limit their daily activities [3,4,12].

 Replies to questions related to bodily pain in the health-related quality of life questionnaire showed that pain intensity is moderate to severe in 55.6% patients, while in 60% pain interferes with normal work moderately to “quite a bit”, which is not very different from data reporting moderate or higher intensity of bodily pain within the prior 4 weeks in 69% of the sample and 71% reporting pain-related interference that was moderate or greater [11].

Conclusion

Our study confirms high prevalence of pain in MS, significantly more frequent in relapsing-remitting MS and being significantly higher in females, includes several pain syndromes and number of pain locations which significantly increases with disease duration and female gender and confirms too, that pain is an important symptom influences quality of life of the patients.

Appropriate treatment of MS patients experiencing pain requires a thorough differentiation between nociceptive, peripheral neuropathic and central neuropathic pain. Each type of simultaneously occurring pain must be paid special attention to. Many types of pain in MS are often unrecognised by clinicians, because of difficulties for many people with MS with finding the right words to describe the painful sensations they experience. In taking a medical history, we must actively communicate with the patient and ask questions about the presence of pain or unpleasant pain sensations in order to determine the right treatment strategy.

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References


