Original Research Paper

Prevalence of neuropathic pain in early multiple sclerosis

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Abstract
Background: Pain is considered a frequent symptom in multiple sclerosis. Neuropathic pain is the type of pain most closely related to the pathology of multiple sclerosis and its prevalence estimates vary largely.
Objective: We prospectively assessed the prevalence of neuropathic pain in patients with early multiple sclerosis and investigated the association of neuropathic pain with other clinical parameters.
Methods: A total of 377 outpatients with multiple sclerosis at an early disease stage were included in this prospective study. Mean disease duration was 4.2 years, mean Expanded Disability Status Scale (EDSS) score was 1.6, 96.8% of patients were classified as having relapsing–remitting multiple sclerosis. Neuropathic pain was assessed using the PainDETECT questionnaire (PDQ). Depression, fatigue and cognition were assessed using the Beck Depression Inventory (BDI), the Fatigue Scale for Motor and Cognitive Functions (FSMC) and the Paced Auditory Serial Addition Test.
Results: PDQ scores indicative of neuropathic pain were found in 4.2% of patients. Regression analysis revealed EDSS, BDI and FSMC scores as strongest predictors of PDQ scores.
Conclusions: Neuropathic pain appears to be less frequent in early multiple sclerosis than expected and is significantly associated with disability, depression and fatigue. The assessment and therapy of pain in multiple sclerosis should thus take into account neuropsychiatric symptoms already at early disease stages.

Keywords: Multiple sclerosis, neuropathic pain, epidemiology

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with depression are more likely to have pain,\textsuperscript{11,13,14} and a positive relationship between severity and interference of painful symptoms with the severity of depression has been reported.\textsuperscript{15} Fatigue is one of the most frequent symptoms in MS, with prevalence estimates ranging from 60\% to 95\%.\textsuperscript{16–18} Fatigue has a strong impact on quality of life in patients with MS,\textsuperscript{19} and pain has been described as a potentially influential factor on fatigue.\textsuperscript{17,20} Depression and fatigue have been proposed to form a cluster of interdependent symptoms in MS that persists throughout the course of the disease.\textsuperscript{16,18,21} A recent study added pain to this cluster and proposed fatigue as the mediating factor between pain and depression in MS.\textsuperscript{20} However, the influence of demographic, disease-related and emotional factors on neuropathic pain in early MS has not been investigated so far.

In the present prospective study, we therefore reassessed the prevalence of neuropathic pain in a cohort with early MS using a screening tool specific for neuropathic pain. We further assessed associations of neuropathic pain in MS with demographic, disease-related and emotional factors.

**Methods**

**Patients**

A total of 377 patients (252 women and 125 men) with MS were included in the study between August 2008 and November 2014. All patients were outpatients participating in a prospective observational study of our department, which has been performed in accordance with the Declaration of Helsinki and has been approved by the ethics committee of the School of Medicine of the Technische Universität München. The purpose of the study is the establishment of prognostic markers for a rational and targeted treatment of MS. Inclusion criteria were a confirmed diagnosis of MS or related disorders, for example, clinically isolated syndrome or neuromyelitis optica, and the ability to provide consent. Each MS patient visiting our outpatient MS clinic for the first time and fulfilling the inclusion criteria has been asked to participate. However, not all patients were willing to participate and we did not systematically assess the number of patients who refused to participate and their reasons for doing so. Data from the first outpatient visit of each patient to our MS clinic with the confirmed diagnosis of MS according to the McDonald criteria were chosen for analysis. The full dataset from all 377 patients was complete at the first visit. Inpatients were included when they were followed up in the outpatient clinic. The mean age of the patients was 36 (±10.2) years, mean duration of disease was 4.2 (±5.6) years and mean Expanded Disability Status Scale (EDSS) score was 1.6 (±1.3). The disease course was relapsing–remitting in 96.8\%, secondary progressive in 2.4\% and primary progressive in 0.8\% of patients.

**Questionnaires**

Neuropathic pain was assessed using the PainDETECT questionnaire (PDQ), which is a well-established screening tool specific for neuropathic pain.\textsuperscript{22} The questionnaire was completed during the first visit to the MS outpatient clinic. The PDQ comprises three main components. The first part is a ‘gradation of pain’. This core component comprises seven descriptive items asking for neuropathic pain qualities on a 6-point rating scale ranging from 0 (‘never’) to 5 (‘very strongly’). Neuropathic pain qualities covered are ‘burning’, ‘tingling/prickling’, ‘electric shock-like attacks’, ‘numbness’, ‘sensitivity to touch’, ‘sensitivity to heat/cold’ and ‘pain triggered by light pressure’. The second part refers to the ‘pain course pattern’. Patients can choose between four graphically illustrated patterns entitled ‘persistent pain with slight fluctuations’, ‘persistent pain with attacks’, ‘pain attacks without pain between them’ and ‘pain attacks with pain between them’. For the two latter patterns an extra point is added to the score, whereas for persistent pain with slight fluctuations no point is added, and for persistent pain with pain attacks one point is subtracted from the score. The third part is a simple yes or no question asking for ‘radiating pain’. In the case of pain radiating to other regions of the body two points are added to the overall score. Adding up the three parts, a maximum score of 38 points can be obtained. Scores of 19 or greater are highly indicative of a neuropathic pain component (>90\% likely). For a score of 12 or less a neuropathic pain component is considered unlikely (<15\% likely), whereas for scores between from 13 to 18 points the result is uncertain.\textsuperscript{22}

Depressive symptoms were assessed using the Beck Depression Inventory II (BDI).\textsuperscript{23} Fatigue was assessed using the Fatigue Scale for Motor and Cognitive Functions (FSMC)\textsuperscript{24} and cognitive function was assessed using the Paced Auditory Serial Addition Test (PASAT).\textsuperscript{25}

**Statistical analysis**

Means for demographic and clinical data as well as for questionnaire scores were compared between patients with and without PDQ scores indicative of neuropathic pain using t tests for independent samples after equality of variances had been assessed by using
Levene’s test. Associations between neuropathic pain and demographic and clinical variables were assessed by correlation analyses using Pearson’s correlation coefficient. To explore further the contribution of demographic, disease-related and emotional parameters to neuropathic pain in MS patients, multiple regression analysis was performed. The PDQ score served as a dependent variable. EDSS, BDI, FSMC and PASAT scores as well as age and duration of disease were chosen as independent variables. Statistical analyses were performed using SPSS (IBM SPSS for Windows, version 23.0, Armonk, NY, USA).

Results

The prevalence of PDQ scores indicative of neuropathic pain (≥19) was 4.2% (16/377) (Figure 1). The disease course of the 16 patients was relapsing–remitting. Painful dysesthesia of the extremities was the most prevalent form of neuropathic pain (n=15/16), occurring isolated (n=6/16) as well as in combination with facial (n=5/16) or back pain (n=4/16). One patient suffered from isolated facial pain, namely trigeminal neuralgia. PDQ scores in which a neuropathic pain component was uncertain (13–18) were found in 9.5% (36/377) of patients.

Patients with PDQ scores indicative of neuropathic pain (≥19) differed significantly from patients with scores below the cut-off (<19) with regard to disability (EDSS 3.3 vs. 1.5, t=4.2, P<0.001), depression (BDI 17.5 vs. 7.25, t=5.3, P<0.0001) and fatigue (FSMC 74.3 vs. 43, P<0.001) scores. However, no significant difference was found between groups was found for age (36.4 vs. 36 years, t=0.2, P=0.87), duration of disease (6.2 vs. 4.1 years, t=1.13, P=0.26) and cognitive performance (PASAT 42.3 vs. 45.1, t=0.1, P=0.34).

PDQ scores correlated positively with levels of disability (EDSS r=0.410, P=0.001), depression (BDI r=0.428, P<0.0001) and fatigue (FSMC r=0.503, P<0.0001) (Figure 2). In addition, positive correlations were found for age (r=0.174, P<0.001) and duration of disease (r=0.183, P<0.001). However, no significant correlation was found between PDQ and PASAT scores (r=−0.07, P=0.18).

Multiple regression analysis revealed disability (EDSS β=0.249, t=4.4, P<0.0001), depression (BDI β=0.239, t=3.8, P<0.0001) and fatigue (FSMC β=0.215, t=3.1, P=0.002) as the three most powerful predictors of PDQ scores (Figure 3). For all three predictors positive regression coefficients were obtained, indicating that higher individual scores in each domain predicted higher PDQ scores. The results show that the final model including EDSS, BDI and FSMC scores explains 33% of variation in PDQ scores. Parameters without significant explanatory contribution to variance in PDQ scores were age (β=0.001, t=0.24, P=0.98), duration of disease (β=0.085, t=1.60, P=0.11) and PASAT scores (β=0.028, t=0.58, P=0.56).

Discussion

In the present prospective study, we assessed the prevalence of neuropathic pain in early MS. Our results revealed a prevalence of 4%, indicating that neuropathic pain is not very frequent in early MS. We further found that disability, depression and fatigue but not cognitive deficits are significantly associated with neuropathic pain in early MS.

Prevalence of neuropathic pain in early MS

Previous studies on the prevalence of pain in MS reported largely different rates ranging from 29% to 83%, with an average prevalence in a recent meta-analysis of 63%. The more specific assessment of neuropathic pain in MS yielded a meta-analytical prevalence of 29%. This large variability in the
prevalence rates of pain in MS in previous studies is most likely due to methodological differences.\(^1,2,5\) First, the stage of disease differs widely across study cohorts, with a tendency towards advanced disease stages. Second, the frequently used mailing questionnaires might be prone to selection bias, with patients suffering from pain having higher response rates. Third, a wide variety of screening tools for painful symptoms has been used, which, particularly in older studies, include non-specific and non-standardised tools. However, the present observation of a prevalence of neuropathic pain in MS of 4% is significantly lower than all previous findings. This might be due to the characteristics of the present study cohort, which includes outpatients at an early disease stage with an average disease duration of 4 years and an average EDSS score of 1.6. Two previous studies\(^4,5\) specifically addressed neuropathic pain in early MS, and found a point prevalence of 14% in patients with a median EDSS of 2, which is still significantly higher than the prevalence observed in the present study. This discrepancy might be due to differences in study design and the patient population. In the present study, we used a validated questionnaire, which selectively assesses neuropathic pain,\(^22\) whereas in one of the previous studies\(^4\) a questionnaire was used that might not only detect neuropathic pain but also capture other forms of pain observed in MS.\(^1,3\) In the other study,\(^5\) another neuropathic pain questionnaire was used and the sensitivity and specificity of different screening tools for neuropathic pain in multiple sclerosis is unknown. Moreover, the study included patients with a significantly longer disease duration of 8 years than the 4.2 years of the present study.

**Figure 2.** Correlations between neuropathic pain scores and disability, depression and fatigue. PDQ: PainDETECT questionnaire; EDSS: Expanded Disability Status Scale; BDI: Beck Depression Inventory; FSMC: Fatigue Scale for Motor and Cognitive Functions; PASAT: Paced Auditory Serial Addition Test.

**Figure 3.** Regression analysis with neuropathic pain as a dependent variable and disability, depression, fatigue, age, time and cognitive function as independent variables. PDQ: PainDETECT questionnaire; EDSS: Expanded Disability Status Scale; BDI: Beck Depression Inventory; FSMC: Fatigue Scale for Motor and Cognitive Functions; PASAT: Paced Auditory Serial Addition Test.
Neuropathic pain in MS is presumed to relate directly to lesions within the sensory system and is therefore considered the pain type that is most closely related to the pathology of MS. This concept is supported by studies in patients with more advanced disease, which reported an increase in the prevalence of neuropathic pain with disease progression. The low prevalence of neuropathic pain found in our patient sample with early MS lends further support to this concept of a direct causal relationship between disease progression and the prevalence of neuropathic pain. In contrast, the prevalence of pain of any type is high in early MS as well as in more advanced stages of MS. Considering the high prevalence of pain in the general population, the evaluation of pain of any type might therefore only partially reflect pain directly attributed to MS. This notion is supported by a study which found that the prevalence of pain of any type did not significantly differ between MS patients and a control population.

Influence of depression, fatigue and disability on pain in early MS
To our knowledge this is the first prospective study to examine the influence of depression, fatigue and disease-related disability on neuropathic pain in early MS. We found that patients with neuropathic pain showed significantly higher levels of depression, fatigue and disability, and regression analysis revealed these three factors as the most important predictors of neuropathic pain. Furthermore, PDQ scores significantly correlated with scores for depression and fatigue as well as disability, age and duration of disease. This suggests that neuropathic pain in MS is influenced by parameters related to the progression of the disease on the one hand and emotional factors on the other hand. The relevance of disease progression for neuropathic pain is underlined by disability being the strongest predictor for neuropathic pain and a positive correlation of age and disease duration with neuropathic pain. These results confirm previous findings and extend it to early disease stages.

A close relationship of fatigue, depression and general pain in MS has been described. Our results show that this close relationship already applies to very early disease stages. It is, however, important to note that the observed relationships do not allow us to infer the causal relationship between depression, fatigue and neuropathic pain in MS. It does, however, indicate that already at early disease stages the assessment and therapy of pain in MS should not only take into account somatic factors but also neuropsychiatric symptoms. In contrast, cognitive performance assessed by the PASAT was not related to neuropathic pain. Thus emotional rather than cognitive factors appear to be relevant for neuropathic pain in MS.

Limitations
Several limitations apply to this study. First, results from single-centre studies are not necessarily generalisable to a broader population. Second, we assessed neuropathic pain but not nociceptive and mixed pain syndromes, which are, from a patient perspective, equally important. However, the relationship of the latter pain types to the pathology of MS is less obvious than for neuropathic pain. Furthermore, due to its paroxysmal nature the Lhermitte sign that is commonly subsumed under neuropathic pain was possibly not adequately detected by the questionnaire used. However, the Lhermitte sign is considered the least burdensome and therefore clinically least relevant form of neuropathic pain in MS. Third, in 9.5% of patients with PDQ scores from 13 to 18 a neuropathic pain component remains uncertain. However, correlation analyses were performed using overall PDQ scores and even when adding the 9.5% of patients with uncertain PDQ scores the prevalence of neuropathic pain in our patient sample still remains low compared to previously published results. Fourth, the assessment of neuropathic pain was exclusively based on questionnaires without objective information on lesion location provided by magnetic resonance imaging. Fifth, psychosocial factors with a potential influence on painful symptoms in MS that have previously been described, such as anxiety and sleeping quality, were not evaluated. Moreover, the assessment of depression and fatigue using the BDI and the FSMC might have been confounded by somatic factors. Future studies might use other scales, which are less sensitive to these confounds; for example, the Hospital Anxiety and Depression Scale or the BDI-fast screen for depression. Finally, we cannot rule out that refusal of patients to participate in our study has introduced a selection bias. There is, however, no obvious reason to assume that patients willing to participate in a longitudinal observational study are less affected by neuropathic pain than patients not willing to participate.

Conclusions
Taken together, our results suggest that the prevalence of neuropathic pain as the type of pain most directly related to the pathology of MS is low in early MS. The high prevalence of pain of any type in early MS shown in previous studies might therefore partially reflect pain not directly linked to the disease. Depression and
fatigue are crucial co-factors of neuropathic pain already in early MS. As these two factors have an interdependent relationship with pain in MS and are potentially modifiable, a multimodal therapeutic approach should be used for pain therapy already in early MS.

Conflict of interest
VB has received research support from Merck Serono. DB has received compensation for activities with Bayer HealthCare, BiogenIdec, MerckSerono and Novartis; she is supported by the Abirisk Consortium. TRT has received honoraria for lecturing from and/or serves on the advisory board for Pfizer, Lilly, Grünenthal, Mundipharma, Astellas und Hexal. MM has received research support from Merck Serono and Novartis; he has received travel expenses for attending meetings from Bayer and Merck Serono; he has received honoraria for lecturing from Merck Serono; he has received investigator fees for a phase III clinical study from Biogen Idec. BH has served on scientific advisory boards for Roche, Novartis, Bayer Schering, Merck Serono, Biogen Idec, GSK, Chugai Pharmaceuticals, Micromet, Genentech and Genzyme Corporation; he serves on the international advisory board of Archives of Neurology, Multiple Sclerosis Journal and Experimental Neurology; he has received speaker honoraria from Bayer Schering, Novartis, Biogen Idec, Merck Serono, Roche and Teva Pharmaceutical Industries Ltd.; and he has received research support from Biogen Idec, Bayer Schering, Merck Serono, Five prime, Metanomics, Chugai Pharmaceuticals and Novartis; he serves as a DMC for the Tone (DFG sponsored) and the PQBirch204 trial (Bencard Allergy); he has filed a patent for the detection of antibodies and T cells against KIR4.1 in a subpopulation of MS patients and genetic determinants of neutralising antibodies to interferon-beta. The other authors declare that there is no conflict of interest.

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References


