

# Neuropathic Extremity Pain in Patients With Multiple Sclerosis: Preventive and Personalized Approach

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## Research Article

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# Abstract

## Background

Neuropathic extremity pain is a disabling symptom in patients with multiple sclerosis. The aim of this study is to evaluate the prevalence of neuropathic extremity pain among patients with multiple sclerosis and to assess its effect on quality of life.

## Methods

The present cross-sectional study included 180 patients with relapsing-remitting multiple sclerosis. Douleur Neuropathique 4 pain scale and Leeds Assessment of Neuropathic Symptoms and Signs pain scale were used to evaluate neuropathic pain. The effect of neuropathic extremity pain on quality of life was assessed by the 36-Item Short Form Survey.

## Results

The mean age and the mean disease duration were  $38.78 \pm 9.37$  and  $8.96 \pm 6.93$  years, respectively. The prevalence of neuropathic extremity pain was 38.9% in the Leeds Assessment of Neuropathic Symptoms and Signs pain scale and 47.8% in the Douleur Neuropathique 4 pain scale. The presence of neuropathic extremity pain was associated with the higher Expanded Disability Status Scale in the Leeds Assessment of Neuropathic Symptoms and Signs pain scale ( $p=0.015$ ) and the longer disease duration in the Douleur Neuropathique 4 pain scale ( $p=0.021$ ). All patients with psychiatric disorders reported neuropathic extremity pain. Lower 36-Item Short Form Survey scores were obtained in patients with neuropathic extremity pain than patients without neuropathic extremity pain in all domains of 36-Item Short Form Survey.

## Conclusions

This study suggests that neuropathic extremity pain is a common symptom among patients with multiple sclerosis. Higher disability and longer disease duration are associated with neuropathic extremity pain. The presence of pain and psychiatric disorders are related to the impairment of the quality of life.

## Relevance of the article for predictive, preventive, and personalized medicine

Questioning of pain is often neglected in multiple sclerosis practice. However, identification and treatment of pain has the potential to increase the quality of life in patients with multiple sclerosis. This article emphasizes that revealing the presence of pain might improve clinical outcome in multiple sclerosis patients providing personalized approaches to disease course.

## Introduction

Multiple sclerosis (MS) is a chronic, autoimmune, and neurodegenerative disease of the central nervous system and may lead to disability among young people [1]. Many signs and symptoms may accompany MS, such as visual loss, paresthesia, motor deficits, urinary incontinence, fatigue, cognitive impairment, and pain [2]. The definition of pain by the International Association for the Study of Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [3]. Pain is a common symptom in people with MS (pwMS); however, the prevalence is still unclear and ranges between 29% and 86% in different studies [4, 5]. The wide range in the estimated prevalence may be related to applying different rating scales to evaluate pain, retrospective data collection, small sample groups, and the lack of population-based cohorts [6, 7]. pwMS may suffer from different pain types such as neuropathic pain (NP), nociceptive pain, and headache [8, 9, 10]. NP consists of neuropathic extremity pain (NEP), Lhermitte's sign, and trigeminal neuralgia. The prevalence of NEP, a serious condition that decreases the quality of life (QOL), is estimated to be between 12% and 28% [11].

There are several screening tools to distinguish NP from nociceptive pain. Douleur Neuropathique 4 (DN4) is a health care professional-administered questionnaire consisting of 10 items. Seven items related to pain quality are based on an interview with the patient, and 3 items are based on the clinical examination, including pinprick and tactile hypoesthesia and pain to light touch [12]. Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale is another bedside assessment tool administered by clinicians to discriminate NP from nociceptive pain. LANSS comprises a 7-item pain scale, including the sensory descriptors and items for sensory examination. Five of them are symptom-related, and 2 items are examination-related [12].

Many symptoms negatively affect the QOL in pwMS. The 36-Item Short Form Survey (SF-36) is well-studied and self-reported measure of QOL in pwMS [13]. It comprises 36 questions covering 8 domains of health: physical functioning, physical role functioning, emotional role functioning, vitality, mental health, social role functioning, bodily pain, and general health perception.

NP, as a disabling symptom in MS, is related to the demyelination of spinothalamic pathways, neuroinflammation in the posterior column of the cervical spinal cord, and axonal degeneration in the trigeminal nerve root entry zone [14]. Besides the wide range in the estimated prevalence of NP, the risk factors vary among different studies. For instance, age, disability, and disease duration were associated with NP in a large, cross-sectional, multicenter Italian cohort [15]; however, other studies did not show similar results [16, 17]. The prevalence of NEP has been evaluated in some previous studies. However, the effect of NEP on QOL has not been well-studied.

Therefore, the aim of this cross-sectional study was to assess the relationship between NEP and QOL, as well as risk factors related to NEP, then evaluate the association of NEP with MS treatments.

## Materials And Methods

In this study, we included 230 patients with relapsing-remitting MS (RRMS) who were fulfilling McDonald 2010 criteria [18] from an academic MS clinic. Patients were collected prospectively between July 2019 and August 2020. The inclusion criteria were the diagnosis of RRMS and being older than 18-years old. We excluded MS patients with diabetes mellitus, pregnancy, head trauma, major musculoskeletal disorder, history of spinal cord surgery, and other disorders affecting the central or peripheral nervous system. Finally, we enrolled 180 pwMS to assess NEP in our study. The clinical and demographic data, including MS treatments, were recorded. Patients underwent neurological examination, consisting of a detailed sensorial and motor function assessment, and the Expanded Disability Status Scale (EDSS) was performed to evaluate the disability status. A blind neurologist applied LANSS and DN4 screening tools. LANSS scale score  $\geq 12$  and DN4 scale score  $\geq 4$  were classified as NEP. We also performed SF-36 to evaluate the effect of NEP on QOL in pwMS. The study was approved by the local ethics committee of İzmir Katip Çelebi University. It was conducted in accordance with the Helsinki Declaration, and informed consent was provided by all the participants.

## Statistical Analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program was used to analyze the variables. Descriptive statistics were employed to calculate percentages, and data regarding continuous variables were summarized as means and standard deviations (SD). The Shapiro-Wilk test was used for the normal distribution of data. Independent sample t-test was used for group comparisons. The variables were examined at 95% confidence level, and *the p*-value was accepted significant less than 0,05.

## Results

One hundred and eighty pwMS (120 female, 67%) were enrolled in this study. The mean age and the mean disease duration were  $38.78 \pm 9.37$  and  $8.96 \pm 6.93$  years, respectively. The annual relapse rate (ARR) of pwMS was  $0.31 \pm 0.13$ , and the mean EDSS was  $1.15 \pm 1.56$ . The prevalence of NEP was 38.9% in the LANSS scale and 47.8% in the DN4 scale. The psychiatric comorbidities and the current treatments of the participants were listed in Table 1. We evaluated the relationship between NEP, disability, and disease duration.

The presence of NEP was associated with the higher EDSS in the LANSS scale ( $p = 0.015$ ) and the longer disease duration in the DN4 scale ( $p = 0.021$ ) (Table 2). However, the presence of NEP did not differ between males and females ( $p = 0.192$ ). In addition, we examined the influence of psychiatric comorbidities on NEP. MS patients with depression and anxiety disorder showed significantly higher rates of NEP ( $p < 0.01$ ). Our national population data [19] served as a control group in the present study. In all domains of SF-36, pwMS showed significantly lower scores according to the normal population except mental health domain in male patients ( $p = 0.0652$ ), as shown in Table 3. We obtained significantly lower SF-36 scores in patients with NEP than patients without NEP in all domains of SF-36 (Table 4). No

significant association was observed between MS treatments and the presence of NEP (LANSS  $p = 0.336$ , DN4  $p = 0.236$ ).

## Discussion

In this cross-sectional study, the prevalence of NEP among all pwMS was about 40%. Higher EDSS and longer disease duration caused increased incidence of NEP. The results of our study did not indicate a possible relationship between NEP and MS therapies since all of the patients described NEP before the onset of treatments. However, patients with comorbid-psychiatric disorders had significantly higher rates of NEP.

Several studies showed that pain is a disabling symptom in MS, and the prevalence of pain in pwMS was reported to be between 29–86% [20, 21]. The wide range of the estimated prevalence of pain may be related to study methodologies, evaluation of different types of pain, application of various questionnaires, and structured interview methods [22]. Likewise, the prevalence of NP varies across studies due to the involvement of pwMS at different stages, non-specific and non-standard assessment tools, and patients suffering from other types of pain [23]. LANSS and DN4 scales are reliable tools to assess NP and have over 80% sensitivity and specificity. Therefore, we used both LANSS and DN4 scales to distinguish NP from nociceptive pain. Several studies based on DN4 have examined a potential association between NEP and MS; some of them found an association between these two conditions. According to those studies, the overall incidence of NEP in pwMS ranges from 6–28% [4, 11, 20]. From our data, it appears that the frequency of NEP in pwMS (40%) is compatible with other studies [9, 15].

NP can be provoked by several risk factors in MS, but the exact mechanism is still unknown. Several studies reported that age, female gender, longer disease duration, progressive course of the disease, and higher EDSS score seemed to increase the risk of NP. In a cross-sectional multicenter study, a multivariate analysis showed that age, EDSS, gender, and disease duration were significantly associated with NP. They also reported that EDSS is an independent risk factor to precipitate NP compared to nociceptive pain [15].

In 2012, Truini et al. investigated the neurophysiological findings and pain mechanisms in pwMS. Patients with relapsing-remitting course had less frequent NP according to patients with progressive disease. Older age and longer disease duration were associated with pain; in addition, EDSS was the only significant factor related to NP [24]. These results were not consistent with data from other studies [15, 25]. For instance, in a French study conducted by a postal survey, 51% of the participants reported NP; however, sex, age, and disease duration were not associated with NP [26]. In accordance with the previous study, Labuz-Roszak et al. found no significant relationship between disease duration and NP [27].

During the natural course of MS, multiple demyelinating lesions may accumulate in the central nervous system affecting the somatosensory pathways. The migration of T-cells and the activated microglia induce tissue damage in spinothalamic pathways over time [28]; therefore, longer disease duration and higher disability due to increased lesion load may accompany NEP [4, 16]. From our data, it also appears

that patients with NEP had a longer disease duration and a higher EDSS score. Although those patients had low disability status, we observed that patients with NEP had almost 2 times higher EDSS levels than those without NEP.

Disease-modifying treatments (DMTs) have several side effects. The majority of side effects of DMTs are not associated with pain; although, interferons may induce flu-like symptoms, joint pain, myalgia, and headache. In contrast, Doolen et al. reported that fingolimod might reduce NP in a mouse model by reversing central sensitization in the dorsal column of the spinal cord [29]. Also, glatiramer acetate was found effective in preventing long-term allodynia and hyperalgesia by reducing the expression of the chemotactic fractalkine chemokine in the dorsal horn [30]. In this study, we had the exceptional opportunity of observing NP whether it was induced by the use of all MS therapies in a relatively large group. As consistent with data from previous studies, we also have not seen a relationship between NP and DMTs [26, 27, 30].

Population-based prevalence studies demonstrate that about 14–54% of pwMS suffer from psychiatric disorders such as depression and anxiety, and this rate is 2 or 3-times higher than the normal population. The reason for this kind of wide range is due to differences in definitions, study designs, and diagnostic criteria, like in pain frequency [31, 32]. Disability, pain, and perception of chronic disease can trigger the emergence of depression and anxiety as well as structural or immunological factors in MS [31, 32, 33]. In our study, depression was detected in 6.6% of the patients and anxiety in 10% of the patients. All those pwMS with psychiatric disorders reported the presence of NEP. However, more data are needed to claim that psychiatric disorders cause NEP or pain reveals as a result of depression and anxiety.

QOL is the general well-being of individuals. In addition to depression and anxiety, many symptoms, including pain, disability status, sleep quality, and fatigue, can reduce the QOL in pwMS [34]. In a recent study, Zhang et al. reported that depression, pain, fatigue, and anxiety are the major comorbidities affecting the QOL in pwMS. Besides, pain was strongly associated with "The Assessment of Quality of Life with Eight Dimensions" (AQoL-8D) physical domain and had the second-largest impact on the overall AQoL-8D [35]. In the present study, we applied SF-36 to evaluate the QOL in pwMS. All domains of SF-36, except mental health in male patients, were significantly reduced compared to the normal population. In addition, we observed that QOL was more prominently affected in patients with NEP and psychiatric disorders. A longitudinal study revealed that treating both pain and depression is more effective than targeting either depression or pain [36]. For this reason, treatment of NEP and psychiatric comorbidities together is essential to improve the QOL.

This cross-sectional study has several limitations. First, we do not have a control group consisting of healthy participants. Second, all participants were RRMS patients, and the study did not include MS patients with progressive course. Third, the range of EDSS was too narrow, and we did not evaluate the patients with high disability. Fourth, we did not evaluate the pain intensity.

## Conclusion

In conclusion, our study suggests that NEP is a common symptom among pwMS. Higher disability and longer disease duration are associated with NEP. The presence of NEP and psychiatric disorders are related to the impairment of the QOL.

### **Expert recommendations**

Neuropathic pain is one of the most disabling and medically refractory symptoms of MS, and it can have a major impact on quality of life in MS patients. However, physicians often do not question the presence and severity of pain, and this is an unmet need of most pwMS.

Due to neuropathic pain's high prevalence and proven disability for sufferers, pain scales should be applied in clinical practice. This is crucial and relevant for predictive and personalized medicine.

## **Declarations**

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Conflicts of interest/Competing interests: Authors declare no conflict of interest

Availability of data and material: The authors confirm that the data supporting findings of this study are available within the article

Code availability: Not applicable

Ethics approval: The study was approved by the local ethics committee of İzmir Katip Çelebi University.

Author's contributions: Concept: CU, GY; Design: CU, YB; Supervision: YB; Materials: CU, GY; Data collection and processing: CU, GY; Analysis: CU, GY, YB; Writing: CU, YB

Consent to participate: The participants have consented to the submission to the journal

Consent for publication: The participants gave permission of their data to publish in the journal

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## Tables

Table 1  
Clinical and demographic data of the patients

Demographics	Patients (n = 180)
Age, mean±SD (range)	38.78±9.37 (23–62)
Females /Male n (%)	120 (66.7%) / 60 (33.3%)
Disease duration, years, mean±SD (range)	8.96±6.93 (1–26)
ARR, mean±SD	0.31±0.13
EDSS, mean±SD (range)	1.15±1.56 (0–8)
LANSS, mean±SD	8.62±7.98 (0–25)
DN4, mean±SD	4.49±3.12 (0–10)
Presence of neuropathic pain based on LANSS	70 (38.9%)
Presence of neuropathic pain based on DN4	86 (47.8%)
Current Treatments	
Fingolimod	60 (33.3%)
Dimethyl fumarate	28 (15.6%)
Teriflunamide	28 (15.6%)
Ocrelizumab	26 (14.4%)
Glatiramer asetate	26 (14.4%)
Interferon beta 1a	8 (4.4%)
Interferon beta 1b	2 (1.1)
Alemtuzumab	2 (1.1)
Presence of depression and anxiety disorder	
Depression	12 (6.6%)
Anxiety disorder	18 (10.0%)
ARR: Annual relapse rate, EDSS: Expanded Disability Status Scale, LANSS: The Leeds Assessment of Neuropathic Symptoms & Signs Pain Scale, DN4: Douleur Neuropathique en 4 questions	

Table 2  
The relationship between neuropathic pain, disability, and disease duration

<b>LANSS</b>	<b>Neuropathic Pain</b>	<b>n</b>	<b>Mean</b>	<b>Std. Deviation</b>	<b>Std. Error Mean</b>	<b>p</b>
EDSS	Not present	110	0.84	1.36	0.18	0.015
	Present	70	1.66	1.76	0.30	
Disease duration	Not present	110	94.06	61.32	9.72	0.138
	Present	70	116.09	72.11	10.37	
DN4						
EDSS	Not present	94	0.91	1.41	0.21	0.129
	Present	86	1.42	1.70	0.26	
Disease duration	Not present	94	90.23	59.59	9.09	0.021
	Present	86	123.34	73.02	10.65	
EDSS: Expanded Disability Status Scale, LANSS: The Leeds Assessment of Neuropathic Symptoms & Signs Pain Scale, DN4: Douleur Neuropathique en 4 questions						

Table 3  
Subgroup analysis of SF-36 according to norm values of Turkish cohort

SF-36	Gender	n	Mean	Std. Deviation	Std. Error Mean	p
Physical functioning	female	120	71,42	28,00	3,61	0,0138
	male	60	69,67	33,47	6,11	0,0076
Physical role functioning	female	120	55,00	44,58	5,76	0,0001
	male	60	60,83	40,83	7,46	0,0005
Emotional role functioning	female	120	51,11	44,03	5,68	0,0001
	male	60	56,67	43,90	8,01	0,0001
Vitality	female	120	50,08	26,22	3,39	0,0003
	male	60	54,33	27,78	5,07	0,0328
Mental health	female	120	57,93	21,25	2,74	0,0001
	male	60	63,60	21,15	3,86	0,0652
Social role functioning	female	120	68,13	26,18	3,38	0,0001
	male	60	69,58	27,21	4,97	0,0001
Bodily pain	female	120	64,96	26,99	3,48	0,0001
	male	60	68,08	28,74	5,25	0,0030
General health perception	female	120	53,08	25,21	3,25	0,0001
	male	60	55,00	24,64	4,50	0,0003

Table 4  
 Comparison of patients with and without neuropathic pain in terms of  
 quality of life

SF-36	Neuropathic Pain		p
	Present (n = 86)	Non present (n = 94)	
Physical functioning	68,26 ± 30,04	72,94 ± 29,65	0,03
Physical role functioning	54,34 ± 44,77	60,09 ± 41,02	0,02
Emotional role functioning	50,65 ± 44,87	59,88 ± 41,73	0,01
Vitality	49,94 ± 27,34	57,21 ± 26,92	0,02
Mental health	56,77 ± 21,23	65,56 ± 20,79	0,03
Social role functioning	65,34 ± 27,44	74,54 ± 26,12	0,01
Bodily pain	62,33 ± 27,48	70,06 ± 28,22	0,01
General health perception	48,37 ± 26,66	61,23 ± 25,67	0,001