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RESEARCH ARTICLE

Investigation of Neuropathic Pain Distribution and Related Factors in People with Multiple Sclerosis

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Abstract

Objective: The primary aim of the study was to examine the distribution of neuropathic pain according to body areas in people with multiple sclerosis (pwMS) with neuropathic pain. The secondary aim was to examine the relationship between neuropathic pain and psychosocial (fatigue, sleepiness, anxiety, and depression levels) parameters in pwMS.

Materials and Methods: This study analyzed 70 pwMS. The PainDETECT questionnaire was used to assess neuropathic pain. Psychosocial parameters such as fatigue, sleepiness, anxiety, and depression were assessed.

Results: The most frequently reported neuropathic pain areas were the neck (58.6%), foot/ankle (50%), and knee (48.6%). In addition, in every 1-point increase in the depression survey, the likelihood of having neuropathic pain increases 0.66 times, and in every 1-point increase in the psychosocial parameter of the fatigue survey, the likelihood of having neuropathic pain increases 2.12 times ($p<0.05$).

Conclusion: The results of this study reveal that neuropathic pain is frequently seen in the neck, foot/ankle, and knee areas in pwMS. In addition, the psychosocial parameter of fatigue and depression increases the likelihood of having neuropathic pain in pwMS.

Keywords: Multiple sclerosis, neuropathic pain, depression, fatigue

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, progressive neurological disease of the central nervous system that is usually seen in young adults aged 20-40 years (1). Common symptoms in people with MS (pwMS) include decreased muscle strength, balance and coordination disorders, deterioration in gait patterns, pain, paresthesia, monocular vision loss, dizziness, and vertigo (2). Other accompanying symptoms and signs may include fatigue, spasticity, ataxia, sensation loss, urinary incontinence, depression, cognitive dysfunction, and many others (3). These symptoms and findings affect the health of pwMS holistically and cause physical, cognitive, and psychosocial deficiencies (4). Gait disturbances, fatigue, and pain are among the most common symptoms in MS (5).

PwMS show a wide range of pain symptoms, from chronic pain symptoms that may occur in conditions such as postural disorders and spasticity to acute pain (6). Pain is an important symptom of MS and is often associated with disability (7). In a systematic review study (17 studies, 5,319 pwMS), the prevalence of pain was 63% (8). In another study, pain was reported as the first symptom in pwMS with a prevalence of 11-23% (7).

Pain in MS is classified according to its duration, severity, and underlying mechanisms. The mechanisms underlying pain in MS are still unclear. However, two separate pain classifications have been proposed according to pathophysiology (7,9). Despite differences between the two classification systems, the classification of pain as neuropathic, nociceptive, and mixed type remains.

In a descriptive study, pain characteristics were investigated in 842 pwMS with chronic pain, and 42% of the patients had nociceptive pain, 27% had mixed type pain, and 32% had neuropathic pain (10). Neuropathic pain is defined by the

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International Association for the Study of Pain as pain resulting from a lesion or dysfunction in the central nervous system (11). Neuropathic pain in MS is directly related to the demyelination process of the disease (12). In a study examining the relationship between pain complaints and plaque formation in MS, lesions in the pons, periventricular gray matter, cerebellum, corpus callosum, thalamus, and medulla oblongata were found to be associated with pain (13).

Two key mechanisms are thought to cause neuropathic pain in MS (12):

1- The occurrence of ectopic stimuli in demyelinating lesions in response to neural damage.

2- Interruption of inhibitory impulses from the brain and absence of inhibitory impulses from the brain, which eliminates the modulation of the afferent A-delta and C pain pathways and leads to central sensitization. As a result, decreased pain thresholds occur after discharges, which increase spontaneous activity.

Neuropathic pain is one of the most common symptoms in pwMS. However, the distribution of neuropathic pain by body areas is unclear. Examining the distribution of neuropathic pain according to body areas may help diversify area-specific rehabilitation approaches. The primary aim of the study was to examine the distribution of neuropathic pain according to body areas in pwMS with neuropathic pain. The secondary aim was to examine the relationship between neuropathic pain and psychosocial (fatigue, sleepiness, anxiety, and depression levels) parameters in pwMS.

Materials and Methods

Participants and Procedures

The study protocol was approved by the Ethics Board of Dokuz Eylul University (decision number: 2022/29-02, date: 14.09.2022). This study included data from 70 definitively diagnosed pwMS with neuropathic pain from the outpatient MS clinic of Dokuz Eylül University Hospital, Izmir, Turkey (14). People with a definite diagnosis of MS according to the 2017 McDonald criteria were included (14). Participants with a PainDETECT Questionnaire (PD-Q) score of ≥13 were considered to have neuropathic pain and were included in the study (15). Participants with musculoskeletal, cardiovascular, pulmonary, metabolic, or other diseases severe enough to preclude participation in the study; participants with conditions other than MS that can cause pain, such as cancer, diabetes, overt osteoarthritis, or rheumatoid arthritis based on laboratory or imaging findings; participants with severe cognitive impairment; and pregnancy as determined by the neurologist were excluded from the study.

Outcome Measures

Neurological examinations of all participants were performed by the neurologist, and the Expanded Disability Status Scale (EDSS) scores were calculated.

The PD-Q has an accuracy rate of 80% compared with expert judgment in identifying neuropathic pain (16). The Turkish version of the PD-Q was also found to be valid and reliable (17). A PD-Q score of ≥13 was considered neuropathic pain. In our study, PD-Q was determined as the primary outcome measure. Participants with a PD-Q score of ≥13 were considered to have neuropathic pain and were included in the study. Participants were asked to mark the areas with neuropathic pain on the body diagram in PD-Q and indicate with an arrow if their pain radiates to other body parts.

The Hospital Anxiety and Depression Scale (HADS) was used to assess the anxiety and depression levels of the participants. HADS is a two-way self-assessment scale used to assess depression (HADS-D) and anxiety (HADS-A) (18). The Turkish version of the questionnaire was found to be also valid and reliable (19).

The Modified Fatigue Impact Scale (MFIS) is frequently used in clinical and experimental studies to determine the level of fatigue (20). The MFIS consists of a total of 21 questions that evaluate the physical (MFIS-physical), cognitive (MFIS-cognitive), and psychosocial (MFIS-psychosocial) effects of fatigue. Each item is given a score of 0-4, and a low score indicates a low level of fatigue. The Turkish version of the MFIS was found to be valid and reliable (21).

Epworth sleepiness scale (ESS) evaluates the daytime sleepiness of the participants (22). It consists of eight items. The score of each item varies between 0 and 3, and the total score varies between 0 and 24. The higher the total score, the higher the participant's degree of daytime sleepiness. The Turkish version of the ESS was found to be valid and reliable (23).

Sample Size and Statistical Analysis

For the primary aim of the study, the required sample size was calculated using the OpenEpi program (Version 3.01), assuming that 2,000 pwMS were followed in our unit, and the default pain percentage frequency in the population was calculated as 80%+/−5, with a 95% confidence level, as 220 pwMS (24). In a study evaluating the relationship between pain and fatigue level in pwMS with pain, the variance (R2) was 0.57 (25). In this context, the smallest sample size to be included in the study was calculated using G*Power (version 3.1), which required at least 22 pwMS, with variance (R2) =0.57, power =95%, error probability =0.05, and predictor number =9.

The normal distribution of data was checked using the Kolmogorov-Smirnov test and histograms. Descriptive analyses were presented by giving the mean and standard deviation for continuous variables and numbers and percentages for categorical variables. Hierarchical multivariate linear regression

for continuous variables and numbers and percentages for categorical variables. Hierarchical multivariate linear regression models were structured to explain the relationship between neuropathic pain and EDSS, disease duration, age, daytime sleepiness, anxiety and depression, and fatigue. Significance was set at $p<0.05$. Data were analyzed using the IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA)

Results

The most frequently reported neuropathic pain areas were the neck (58.6%), foot/ankle (50%), and knee (48.6%) (Figure 1). Table 1 presents the demographic and clinical characteristics of the participants. Table 2 provides two hierarchical multivariate linear regression models to assess the influence of EDSS, disease duration, age, ESS, HAD-A, HAD-D, and MFIS on the severity of neuropathic pain. Although there was no risk factor in step 1, HAD-D and MFIS-Psychosocial subparameter were risk factors of neuropathic pain in step 2. The results revealed that in every 1-point increase in the depression survey, the likelihood of having neuropathic pain increases 0.66 times, and every 1-point increase in the psychosocial parameter of the fatigue survey, the likelihood of having neuropathic pain increases 2.12 times ($p<0.05$).

Discussion

As the main findings of this study, neuropathic pain was the most common in the neck (58.6%), foot/ankle (50%), and knee (48.6%) areas in pwMS. In addition, the psychosocial parameter of fatigue and depression increases the likelihood of having neuropathic pain in pwMS. In this study, we collected data by the online survey method. In a study investigating chronic pain phenotypes in pwMS across the country, data were collected using an online questionnaire, similar to our research method (10).

Considering the results of previous studies, no association was found between pain and clinical and demographic characteristics of pwMS such as EDSS, disease duration, age, and sex (13,15,26,27). According to our results, no significant relationship exists between pain and sex, disease duration, age, and EDSS. We hypothesized that these mixed results could indicate the nature of pain. Since it is a subjective symptom, it varies among patients, and the definition of pain may be different (28).

Neuropathic pain in pwMS is persistent, and one of the most common bothersome symptoms that occur even in the early stages of the disease (7,29). PwMS complain of various neuropathic pain symptoms. The most common neuropathic

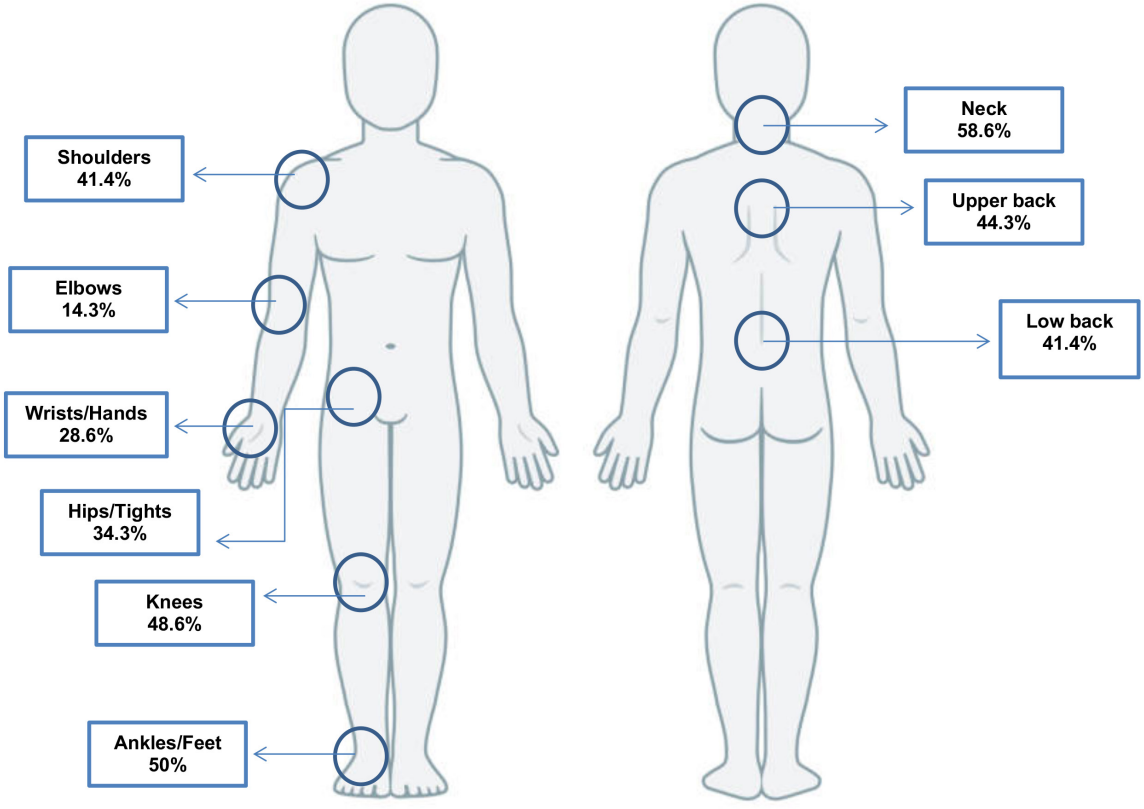

Figure 1. Neuropathic pain among body areas in patients with multiple sclerosis

pain conditions associated with MS include dysesthetic pain and paroxysmal pain (L'hermitte phenomenon and trigeminal neuralgia) (7,30,31). Neuropathic pain types appear to be more common in pwMS than in the general population (32). The most common type of neuropathic pain seen in pwMS is dysesthetic limb pain, with a prevalence of 12-28% (33,34). Common examples of dysesthetic pain in MS include tingling, burning, and pain, mostly in the feet and legs, which is usually aggravated at night and with physical activity (7,31,35). Chronic dysesthesias are typically less intense, but their permanent nature can be challenging for the patient (36). When the distribution of neuropathic pain according to body areas was examined, 50% of neuropathic pain was reported in the foot and ankle area and 48.6% in the knee area. The foot/ankle and knee areas ranked second and third as the most common neuropathic pain areas reported by the participants. Frequent reporting of neuropathic pain in the lower extremities by the participants is thought to be associated with dysesthetic pain.

Table 1. Demographic and clinical characteristics of the participants (n=70)

Age (years)	36.9 (30.55-46.0)
Sex	
Female	53 (75.7%)
Male	17 (24.3%)
Level of education	
Secondary school	7 (10%)
High school	20 (28.6%)
University	36 (51.4%)
Marital status	
Married	53 (75.7%)
Single	15 (21.4%)
Divorced/widowed	2 (2.9%)
Employment status	
Unemployed	19 (27.1%)
Employed	43 (61.4%)
Retired	5 (7.1%)
Student	3 (4.3%)
EDSS	1.5 (1.0-2.5)
Disease duration (years)	9.0 (3.0-14.25)
ESS	7.0 (4.0-10.0)
HADS-A	12.5 (10.0-14.0)
HADS-D	9.0 (7.25-10.0)
MFIS-Cognitive	4.0 (3.0-5.0)
MFIS-Physical	5.0 (3.0-6.0)
MFIS-Psychosocial	2.0 (1.0-3.0)
MFIS-Total	11.0 (7.75-14.0)

Values are presented as number and percent, except age, disease duration, EDSS, ESS, HADS-A, HADS-D, MFIS-Cognitive, MFIS-Psychosocial, MFIS-Total, which are presented as median and interquartile range.

EDSS: Expanded Disability Status Scale, ESS: Epworth sleepiness scale, HADS-A: Hospital Anxiety and Depression Scale-Anxiety, HADS-D: Hospital Anxiety and Depression Scale-Depression, MFIS: Modified Fatigue Impact Scale

The L'hermitte phenomenon is one of the most common pain symptoms examined in neuropathic pain types in pwMS. The prevalence of the phenomenon ranges from 9% to 41% in pwMS (37). The L'hermitte phenomenon is defined as a temporary, short-term paroxysmal electrical sensation that starts from the neck and spreads to the lower extremities and is usually related to neck movement. In the present study, 58.6% of neuropathic pain cases occured in the neck area. Research results suggest that neuropathic pain, which is frequently reported in the neck area, may be compatible with the L'hermitte phenomenon.

Pain affects pwMS more than other neurological conditions. Studies have shown that pain in MS is highly correlated with fatigue, depression, and anxiety (38-40). In addition, studies have stated that pain in MS negatively affects the quality of life, sleep quality, daily life activities, social functionality, and work-life of pwMS (7,41).

Depression is a common psychiatric diagnosis in people with chronic neuropathic pain and affects approximately 57% of individuals with chronic neuropathic pain (42). The prevalence of depression in the general population ranges from 4% to 8% (42). However, the risk of depression in patients with chronic pain is 2-5 times greater than that in the general population (43). Studies have found that neuropathic pain is associated with disability and depression in pwMS (44). According to our research results, in every 1-point increase in the depression survey, the likelihood of having neuropathic pain increases 0.66 times.

Limited studies have reported a significant relationship between pain and fatigue in pwMS (4,15). In addition, in the present study, similar to previous studies, every 1-point increase in the psychosocial parameter of fatigue survey increases the likelihood of having neuropathic pain 2.12 times. A previous study found that pain is associated with a higher level of sleepiness in pwMS (15). In our study, sleepiness did not significantly affect the presence of neuropathic pain. Studies with a large sample size are needed to investigate the effect of neuropathic pain on the level of sleepiness.

In this study, neuropathic pain frequently occurs in the neck, foot/ankle, and knee areas in pwMS. In addition, the psychosocial parameter of fatigue and depression increases the likelihood of having neuropathic pain in pwMS.

Study Limitations

This study has several limitations. First, given the retrospective nature of this study, the results obtained are not conclusive. Second, the presence of neuropathic pain was diagnosed by

Table 2. Risk factors on the severity of neuropathic pain

	Model 1			Model 2		
Risk Factors	**SCB**	**95% CI**	**p-value**	**SCB**	**95% CI**	**p-value**
EDSS score	0.473	-0.777 to 1.522	0.518	-0.023	-1.190 to 1.027	0.883
Disease duration	-0.049	-0.228 to 0.212	0.941	-0.006	-0.214 to 0.205	0.968
Age	-0.018	-0.130 to 0.171	0.781	-0.059	-0.166 to 0.115	0.713
ESS				-0.100	-0.357 to 0.174	0.491
HADS-A				-0.144	-0.549 to 0.188	0.329
HADS-D				0.665	0.130 to 1.199	**0.016**
MFIS-Cognitive				-0.019	-1.681 to 1.588	0.955
MFIS-Psychosocial				2.124	0.007 to 4.240	**0.025**
MFIS-Total				-0.255	-1.125 to 0.614	0.557

Significant p-values are presented in bold. EDSS: Expanded Disability Status Scale, ESS: Epworth Sleepiness Scale, HADS-A: Hospital Anxiety and Depression Scale-Anxiety, HADS-D: Hospital Anxiety and Depression Scale-Depression, MFIS: Modified Fatigue Impact Scale, CI: Confidence interval, SCB: Standardized coefficients beta

areas were not evaluated.

Conclusion

The results of this study reveal that neuropathic pain is frequently seen in the neck (58.6%), foot/ankle (50%), and knee (48.6%) areas in pwMS. In addition, the psychosocial parameter of fatigue and depression increases the likelihood of having neuropathic pain in pwMS.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Board of Dokuz Eylul University (decision number: 2022/29-02, date: 14.09.2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K., Concept: H.K., E.K., Z.A., A.T.O., Design: H.K., E.K., Z.A., A.T.O., Data Collection or Processing: H.K., E.K., Z.A., A.T.O., Analysis or Interpretation: H.K., E.K., Z.A., A.T.O., Literature Search: H.K., E.K., Z.A., A.T.O., Writing: H.K., E.K., Z.A., A.T.O.

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