Turk J Phys Med Rehab 2023;69(1):31-39
DOI: 10.5606/tftrd.2022.10524
Available online at www.turkishjournalpmr.com

Original Article

Pain in patients with multiple sclerosis

Zerrin Kasap[1], Hatice Uğurlu[2]

[1]Department of Physical Medicine and Rehabilitation, Giresun University Faculty of Medicine, Giresun, Türkiye
[2]Department of Physical Medicine and Rehabilitation, Necmettin Erbakan University Meram Faculty of Medicine, Konya, Türkiye

Received: January 20, 2022 **Accepted:** June 15, 2022 **Published online:** February 16, 2023

ABSTRACT

Objectives: This study aims to identify the factors associated with pain and neuropathic pain (NP) in patients with multiple sclerosis (MS) and to determine the relationship between pain and NP with disability, functionality, activities of daily living, fatigue, mood, and quality of life (QoL).

Patients and methods: Between July 2017 and October 2017, a total of 100 adult patients with MS (18 males, 82 females; mean age: 35.3±9.9 years; range, 19 to 71 years) were included. All patients were evaluated in terms of pain and NP. Patients with and without pain, and patients with and without NP were compared in terms of sociodemographic characteristics, disease data, disability, functionality, daily living activities, fatigue severity, mood, and QoL using various scales.

Results: A total of 62% of the patients had pain. Pain was found to be associated with low education level (p=0.014), increased fatigue (p<0.001), depressive mood (p<0.001) and lower QoL (p<0.001). A total of 29.03% of patients with pain had NP. Patients with NP had a greater pain intensity (p<0.001) and fatigue (p=0.002) and lower QoL (p=0.011). The number of patients who received the correct treatment for their symptoms was low.

Conclusion: Pain and NP should be better investigated and treated by physicians, as these symptoms are common in MS and adversely affect the QoL and social relations of affected patients and reduce their productivity.

Keywords: Multiple sclerosis, neuropathic pain, pain, quality of life.

Multiple sclerosis (MS) is a chronic neurological disease with local inflammation, gliosis, and demyelination in the central nervous system (CNS). Different symptoms can be seen depending on the affected areas in CNS. Pain is not one of the characteristic symptoms of MS, but it is quite common and may be the initial symptom for some patients.[1] The prevalence of pain in MS is about 63%[2] and neuropathic pain (NP) prevalence is about 50%.[3] Focused on underlying mechanism, nine different types of pain are defined in MS: musculoskeletal pains, ongoing extremity pain, trigeminal neuralgia and Lhermitte's phenomenon, painful tonic spasms and spasticity pain, migraine, pain associated with optic neuritis and treatment-induced pains.[4] Based on the pathophysiology, pain is classified as nociceptive or neuropathic.[5,6] While musculoskeletal abnormalities, immobility or spasticity cause nociceptive pain; trigeminal neuralgia, dysesthetic extremity pain, Lhermitte's phenomenon cause NP.[7] Understanding the underlying mechanism helps solving the source of the pain. However, for pain medication it is important to understand the neurophysiological subtype (nociceptive or neuropathic). Nociceptive and NP require different pain management strategies. Non-steroidal anti-inflammatory drugs (NSAIDs) or opioids are used for the treatment of nociceptive

Corresponding author: Zerrin Kasap, MD. Giresun Üniversitesi Tıp Fakültesi Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, 28200 Giresun, Türkiye.
E-mail: drzerrinkasap@gmail.com

Cite this article as:
Kasap Z, Uğurlu H. Pain in patients with multiple sclerosis. Turk J Phys Med Rehab 2023;69(1):31-39. doi: 10.5606/tftrd.2022.10524.

pain and anticonvulsants or antidepressants for the treatment of NP.[8]

Although pain is a common symptom in patients with MS, it may be disregarded beside the other visible symptoms such as gait disturbance, arm and hand difficulties, visual abnormalities, spasticity or bladder/bowel disfunction that affects health perception, employment, and quality of life (QoL).[9-12] Also, as the neurophysiological pain type is not fully understood, wrong or insufficient treatments may be prescribed.[13] Therefore, the social and professional lives of patients are negatively affected and their QoL decreases significantly.[14-16]

In the present study, we aimed to identify factors associated with pain and NP and to determine the relationship between pain and NP with disability, functionality, activities of daily living, fatigue, emotional state, and QoL in patients with MS. In particular, studies about NP in MS are limited in the literature and do not provide detailed data in terms of its impact on patients' lives.[6,13,17,18] Therefore, we attempted to emphasize these symptoms and their consequences.

PATIENTS AND METHODS

This single-center, cross-sectional clinical study was conducted at the Physical Medicine and Rehabilitation and Neurology Clinics of Necmettin Erbakan University, Meram Faculty of Medicine between July 2017 and October 2017. A total of 100 patients (18 males, 82 females; mean age: 35.3±9.9 years; range, 19 to 71 years) who were diagnosed with MS according to the McDonald 2010 diagnostic criteria[19] were included in the study. Patients aged under 18 years and those who were followed with a diagnosis of diabetes mellitus, had a history of head trauma, alcohol and substance addiction, and other neurological diseases were excluded from the study.

The sociodemographic characteristics of the patients including age, sex, education level, marital status, and family support were recorded. While evaluating the education level of the patients, graduating from the eighth grade and lower was accepted as low education level and graduating from the ninth grade and higher was accepted as high education level.

Comprehensive neuromusculoskeletal examinations were performed. The MS type, disease duration, and plaque locations were recorded from the patient records.

All patients were evaluated in terms of disability, ambulation status, daily living activities, fatigue, mood, and QoL using the Kurtzke Expanded Disability Status Scale (EDSS), Functional Ambulation Classification (FAC), Barthel Activities of Daily Living (ADL) Index, Fatigue Severity Scale (FSS), Beck Depression Inventory (BDI), and Nottingham Health Profile (NHP), respectively.

The patients were divided into two groups as patients with and without pain. The groups were compared in terms of sociodemographic characteristics, disease data, disability, functionality, daily living activities, fatigue severity, mood, and quality of life.

The Pain Detect Questionnaire (PDQ) was used to evaluate the neuropathic component of the pain in patients with pain and they were divided into two groups as those with and without neuropathic pain. Also, these two groups were compared in terms of sociodemographic characteristics, disease data, disability, functionality, activities of daily living, fatigue severity, mood, and quality of life.

Assessment measures

The Kurtzke EDSS: The EDSS is the most widely used scale in the assessment of disability in patients with MS. "0" corresponds to a normal neurological examination, and "10" to death from MS.[20,21]

Functional ambulation classification: The FAC was used to evaluate the ambulatory ability of the neurologically impaired patients. "0" is considered to be non-functional ambulation, "5" independent ambulatory.[22]

Barthel Activities of Daily Living Index: The Barthel ADL Index is a self-assessment scale used to evaluate the physical independence of the neurologically impaired patients in their daily lives. "0" indicates fully dependent and "100" indicates fully independent.[23,24]

Fatigue Severity Scale: The FSS was developed to evaluate fatigue in patients with MS. A high score indicates increased fatigue intensity. A score of 4 and above is considered pathological fatigue.[25,26]

Beck Depression Inventory: The BDI was used to evaluate depressive symptoms. A high score indicates greater severity of depressive symptoms. In the Turkish validity and reliability study of the scale, the appropriate cut-off point was 17 points. A score of 18 and above indicates moderate and severe depression.[27-29]

Nottingham Health Profile: The NHP is a general QoL questionnaire that evaluates patients' perception of health problems and the effects of these problems on the daily living activities of patients. Pain, emotional reactions, sleep, social isolation, physical abilities, and energy level subscales are evaluated. For each subscale, 0 points correspond to the best health profile and 100 points the worst health profile. The total NHP score is obtained by summing the scores of the subscales.[30,31]

Pain Detect Questionnaire: The PDQ was developed to evaluate the neuropathic components of pain. It consists of four parts. The first part which scores pain intensity is used to assess the presence of pain. In the second part, the pattern of the pain course is evaluated; persistent pain with slight fluctuations is evaluated as 0 points, persistent pain with pain attacks -1 point; pain attacks without pain in between, 1 point; and pain attacks with pain in between, 1 point. In the third part, the patient is asked to mark the pain areas on the figure. The presence of radiating pain is evaluated as 2 points. In the fourth and last part, the presence of burning, tingling/pricking, pain with a light touch, sudden pain attack like an electric shock, pain with hot or cold, numbness, pain with slight pressure is asked and scored between 0-5 points. The total score is obtained by summing up the scores of the last three parts. The total score is -1 to 38.[32] In the Turkish validity and reliability study of the questionnaire, the cut-off value of 14 would be appropriate, when patients with mixed pain were included.[33] In this study, 15 and above was accepted as NP.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. Assessment of normality was analyzed using the Shapiro-Wilk test. Categorical data were compared using the chi-square test or Fisher exact test. Comparison of continuous variables between the two groups was performed using the Student t-test or Mann-Whitney U test. A *p* value of <0.05 was considered statistically significant.

RESULTS

The sociodemographic characteristics of the patients included in the study are shown in Table 1. Sixty-two of the patients (62%) had pain, and thirty-eight (38%) did not.

Pain-related factors

Patients with and without pain were similar in terms of age, sex, marital status, and family support. Pain was more common in patients with a low education level, which was statistically significant (p=0.012) (Table 2).

The groups were similar in terms of MS type, disease duration and plaque location (Table 2). When

TABLE 1
Sociodemographic characteristics of participants

	n	%	Mean±SD	Median	Min-Max
Age (year)			35.3±9.9	34.5	19.0-71.0
Sex					
Female	82	82			
Male	18	18			
Education level					
Low	45	45			
High	55	55			
Marital status					
Single	33	33			
Married	60	60			
Been married before	7	7			
Family support					
Living alone	1	1			
Living with wife/husband and/or children	64	64			
Living with parents	35	35			

SD: Standard deviation.

the groups were compared in terms of EDSS, FAS, and Barthel ADL Index scores, no statistically significant difference was found. The FSS scores (p<0.001) and the BDI sores (p<0.001) were, however, statistically significantly higher in the group with pain than in the group without pain (Table 3).

The rate of patients with pathological fatigue (n=24, 38.7% *vs.* n=6, 15.8%) (p<0.001) and the percentage of patients with moderate/severe depression were higher (n=25, 40.3% *vs.* n=2, 10.5%) (p=0.001) in the group with pain, which were statistically significant.

All NHP subscale scores and NHP total scores were statistically significantly higher in the group with pain. The QoL of patients with pain was significantly lower in all respects than in those without pain (Table 3).

According to the location of pain, headache was the most common. Thirty-eight (61.35%) of the patients with pain had headache, 25 (40.3%) had diffuse lower extremity pain, 17 (27.4%) had low back pain, 16 (25.8%) had diffuse upper extremity pain, and 15 (24.2%) had neck pain. With decreasing frequency, the patients had knee (19.3%), back (19.3%), hand-wrist (16.1%), foot-ankle (16.1%), hip (11.3%), shoulder (9.7%), and elbow (4.8%) pain. Fifty-five

TABLE 2
Comparison of sociodemographic characteristics and disease data

	MS patients with pain (n=62) (100%)	MS patients without pain (n=38) (100%)	*p* value	MS patients with neuropathic pain (PDQ-positive) (n=18) (100%)	MS patients without neuropathic pain (PDQ-negative) (n=44) (100%)	*p* value
Age (year)			0.253[a]			0.532[d]
Mean±SD	36.0±9.5	34.2±10.7		34.8±11.2	36.5±8.8	
Median	35.0	32.5		34.0	35.0	
Min-Max	19.0-60.0	19.0-71.0		19-58	21-60	
Sex			0.932[b]			0.715[c]
Female	51 (82.3%)	31 (81.6%)		14 (77.8%)	37 (84.1%)	
Male	11 (17.7%)	7 (18.4%)		4 (22.2%)	7 (15.9%)	
Education level			**0.012[b]**			0.942[b]
Low	34 (54.8%)	11 (28.9%)		10 (55.6%)	24 (54.5%)	
High	28 (45.2%)	27 (71.1%)		8 (44.4%)	20 (45.6%)	
Marital status			0.863[b]			0.323[b]
Single	20 (32.3%)	13 (34.2%)		6 (33.3%)	14 (31.8%)	
Married	37 (59.7%)	23 (60.5%)		12 (66.7%)	25 (56.8%)	
Been married before	5 (8.1%)	2 (5.3%)		0 (0%)	5 (11.4%)	
Family support			0.438[b]			0.821[b]
Living alone	0 (0%)	1 (2.6%)		0 (0%)	0 (0%)	
Living with wife/husband and/or children	40 (64.5%)	24 (63.2%)		12 (66.7%)	28 (63.6%)	
Living with parents	22 (35.5%)	13 (34.2%)		6 (33.3%)	16 (36.4%)	
Disease duration			0.881[a]			0.489[a]
Mean±SD	67.3±51.5	70.8±56.1		74.2±52.3	64.5±51.5	
Median	60.0	60.0		78.0	54.0	
Min-Max	0-214.0	1.0-216.0		1-192	0-214	
MS type			0.759[b]			0.052[b]
Clinic isolated syndrome	11 (17.7%)	9 (23.7%)		1 (5.6%)	10 (22.7%)	
Relapsing remitting MS	36 (58.1%)	18 (47.4%)		14 (77.8%)	22 (50.0%)	
Progressive MS	14 (22.6%)	10 (26.3%)		2 (11.1%)	12 (27.3%)	
Benign MS	1 (1.6%)	1 (2.6%)		1 (5.6%)	0 (0%)	
Plaque locations						
Cranial	61 (98.4%)	38 (100%)	0.999[c]	18 (100%)	43 (97.7%)	0.999[c]
Brainstem	16 (25.8%)	11 (28.9%)	0.731[b]	5 (27.8%)	11 (25%)	0.999[c]
Cervical	38 (61.3%)	21 (55.3%)	0.525[b]	11 (61.1%)	27 (61.4%)	0.985[b]
Cerebellar	17 (27.4%)	7 (18.4%)	0.306[b]	6 (33.3%)	11 (25%)	0.541[c]

MS: Multiple sclerosis; PDQ: The Pain Detect Questionnaire; SD: Standard deviation; a: Mann-Whitney U test; b: Pearson's chi-square test; c: Fisher exact test; d: Student's t-test.

TABLE 3
Comparison of EDSS, FAC, Barthel ADL Index, FSS, BDI, NHP subscales and total

	MS patients with pain (n=62)	MS patients without pain (n=38)	*p* value	MS patients with neuropathic pain (PDQ-positive (n=18)	MS patients without neuropathic pain (PDQ-negative) (n=44)	*p* value
EDSS			0.452[a]			0.514[a]
Mean±SD	1.42±1.92	1.00±1.40		1.44±2.43	1.42±1.70	
Median	0	0		0	1	
Min-Max	0-9.0	0-5.0		0-9	0-7.5	
FAC			0.802[a]			0.910[a]
Mean±SD	4.85±0.65	4.81±0.83		4.82±0.72	4.86±0.63	
Median	5.0	5.00		5.00	5.00	
Min-Max	0.00-5.00	0.00-5.00		2.00-5.00	100-5.00	
Barthel ADL Index			0.306[a]			0.499[a]
Mean±SD	95.32±16.06	97.50±12.23		91.66±25.72	96.81±9.82	
Median	100.00	100.00		100	100	
Min-Max	0.00-100.00	25.00-100.00		0.00-100.00	40.00-100.00	
FSS			**<0.001**[a]			**0.002**[a]
Mean±SD	4.31±2.17	1.98±1.87		5.67±1.25	3.75±2.24	
Median	4.82	1.94		6.05	4.05	
Min-Max	0.00-7.00	0.00-6.77		2.88-7.00	0.00-7.00	
BDI			**<0.001**[a]			0.115[a]
Mean±SD	17.29±10.02	8.07±9.45		20.72±10.32	15.88±9.66	
Median	15.00	4.50		18.00	14.00	
Min-Max	1.00-47.00	0.00-40.00		10.00-47.00	1.00-43.00	
NHP pain						**0.012**[a]
Mean±SD	41.29±28.14	0		57.36±33.68	34.72±22.87	
Median	34.71	0		56.74	26.01	
Min-Max	5.83-100.00	0-0		0.00-100.00	0.00-100.00	
NHP emotional reaction			**<0.001**[a]			0.140[a]
Mean±SD	40.59±29.63	16.37±20.83		48.06±26.18	37.53±30.69	
Median	38.38	11.24		51.99	33.75	
Min-Max	0.00-100.00	0.00-100.00		7.08-86.01	0.00-100.00	
NHP sleep			**0.007**[a]			0.083[a]
Mean±SD	28.23±28.71	14.50±24.75		38.77±30.29	23.92±27.22	
Median	16.10	0.00		43.71	16.10	
Min-Max	0.00-100.00	0.00-100.00		0.00-77.63	0.00-100.00	
NHP social isolation			**0.004**[a]			0.242[a]
Mean±SD	31.37±33.18	13.42±24.72		38.76±34.91	28.35±32.36	
Median	22.01	0.00		29.05	21.07	
Min-Max	0.00-100.00	0.00-100.00		0.00-100.00	0.00-100.00	
NHP physical abilities			**<0.001**[a]			0.247[a]
Mean±SD	29.36±23.61	12.40±14.98		34.23±25.10	27.37±22.97	
Median	22.74	11.20		32.41	22.16	
Min-Max	0.00-100.00	0.00-67.16		0.00-100.00	0.00-100.00	
NHP energy level			**<0.001**[a]			0.154[a]
Mean±SD	71.23±35.46	30.21±34.55		81.77±30.27	66.92±36.82	
Median	100.00	24.00		100.00	63.20	
Min-Max	0.00-100.00	0.00-100.00		0.00-100.00	0.00-100.00	
NHP total			**<0.001**[a]			**0.012**[b]
Mean±SD	242.75±114.33	88.95±95.13		298.70±128.30	219.86±100.93	
Median	245.85	78.77		330.49	201.45	
Min-Max	29.47-553.88	0.00-452.36		29.47-553.88	57.06-452.47	

MS: Multiple sclerosis; PDQ: The Pain Detect Questionnaire; SD: Standard deviation; EDSS: Expanded Disability Status Scale; FAC: Functional Ambulation Classification; ADL: Activities of Daily Living; FSS: Fatigue Severity Scale; BDI: Beck Depression Inventory; NHP: Nottingham Health Profile; a: Mann-Whitney U test; b: Student's t-test.

(88.70%) of the patients with pain described pain in more than one area.

Neuropathic pain-related factors

Patients with pain were divided into two groups according to the PDQ as positive (with NP: PDQ score ≥15) and negative (without NP: PDQ score <15). Eighteen (29.0%) patients were in the positive group and 44 (71.0%) patients were in the negative group.

Fourteen (22.6%) of the patients with pain were using medication for NP, 11 (78.6%) of whom were using pregabalin, two (14.3%) used gabapentin, and one (7.1%) used carbamazepine. No patients were using an antidepressant group drug or combination of drugs. Of the patients using medication, four (28.57%) were in the positive group and 10 (71.43%) were in the negative group. Only four (22.22%) of the patients in the positive group were using medication for NP.

The age, sex, education level, marital status, and family support were similar between the PDQ-positive and negative groups (Table 2). The MS type, disease duration, and plaque location were also similar between the PDQ-positive and negative groups (Table 2).

No statistically significant difference was found in terms of EDSS, FAC, Barthel ADL Index, and BDI scores between the groups. The FSS score was higher in the PDQ-positive group and the difference was statistically significant (p=0.002) (Table 3).

The percentages of patients with pathological fatigue (n=16, 88.9% *vs.* n=22, 50.0%) was statistically significant higher in the PDQ-positive group (p=0.004). The percentages of patients with moderate/severe depression were similar (n=10, 55.8% *vs.* n=15, 50.0%) (p=0.157) in both groups.

The patients in the PDQ-positive group had higher mean NHP pain subscale scores (p=0.012) and total NSP scores (p=0.012), which was statistically significant. There were no statistically significant differences in emotional reaction, sleep, social isolation, physical abilities, and energy level subscales (Table 3).

When the pain intensity of the patients was evaluated over 10, the mean pain intensity at the time of evaluation (5.6±3.0 *vs.* 2.4±2.60), the mean pain intensity in the last four weeks (8.7±1.7 *vs.* 5.5±2.7) and the highest mean pain intensity in the last four weeks (6.7±2.2 *vs.* 3.6±2.3) were all statistically significantly higher in the PDQ-positive group (p<0.001).

DISCUSSION

Pain in MS is a complex symptom considering the underlying mechanisms and individual factors. Since it is not a physical symptom, it is difficult to understand how it affects patients' life without questioning. In a previous study, it is shown that the symptom that affects the MS patients' health perceptions the most is pain.[9] In this study, we draw attention to this complex, unfavorable symptom in MS by performing comparisons between patients with and without pain/NP. According to the study results, pain was found to be associated with low education level, increased fatigue, depressive mood, and lower QoL. Patients with NP had a greater pain intensity and fatigue and lower QoL. The number of patients who received the correct treatment for their symptoms was low.

In the current study, 62% of the patients had pain. When the factors associated with pain were determined, age, sex, marital status, and family support were not associated with pain. Education level was found to be associated with pain. Similar to the study by Hadjimichael et al.,[34] pain was more common in patients with low education levels. From this point of view, we believe that pain in patients with MS can be reduced with occupational therapy in the hospital and encouraging new hobbies in daily life afterwards.

Contrary to the studies in the literature[35-37] showing that pain is associated with MS type, plaque location or disease duration, no significant relationship was found between disease data and pain in the present study.

Although it is usually reported that pain increases with increasing disability,[17,18,35,36,38] in our study, similar to Svendsen et al.'s[16] study, no relationship was found between the EDSS scores and pain. In the present study, there was no significant difference in functionality and daily living activities between patients with and without pain. Fatigue and depressive mood were found to be associated with pain. The mean FSS scores were statistically significantly higher in the group with pain and the number of patients with pathological fatigue was higher. The mean BDI scores were also higher in this group. In a prospective study, the pain states of the patients after two years were related to the depression score at the onset of the disease.[39] In the study conducted by Akpınar et al.,[38] in our hospital, depression was found in 54% of patients and the pain levels of these patients were higher. In the study

conducted by Şentürk Güven et al.,[40] there was no significant difference in the severity of depression between the groups with and without pain, but the severity of fatigue was higher in patients with pain. In this study, all NHP subscales (pain, emotional reactions, sleep, social isolation, physical abilities and energy level) were affected more, negatively, and that was found to be statistically significant. The fact that pain is associated with fatigue and depression and that the QoL of the patients with pain is lower is consistent with other studies in the literature.[14-16,35,36,41]

When the patients were evaluated in terms of pain location, headache was the most common, followed by diffuse lower extremity pain, low back pain, diffuse upper extremity pain, and neck pain, respectively. Similar to the studies in the literature, the majority of patients with pain in this study described pain in more than one area.[16,35]

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system.[42] Since MS is a one of these disease, NP is quite common in MS.[6] Understanding the pain character considering the pathophysiology helps its treatment.[13] The rate of NP was 29% in this study. In terms of NP medication, the most preferred drug was pregabalin, followed by gabapentin and carbamazepine. Antidepressants and drug combinations were not preferred in any of the patients. Most of the patients who were using medication for NP were in the NP negative group. We attributed this to a significant decrease in patients' symptoms due to drugs. Only 22.2% of the patients with NP were using medication. Similar to previous studies, the use of medication for pain was quite low.[14,18,35] It indicates that pain/NP was ignored by both the physician and the patient during follow-up. It was thought that it may be due to not being a physical or life-threatening symptom.

This study was mainly focused on unspecified pain and NP in MS. However, similar to the study of Kratz et al.,[13] in this study, nociceptive pain was the most frequent pain type. Thus, nociceptive pain and treatment preferences in MS may be another topic for further studies.

When the factors associated with NP were evaluated in this study, no significant difference was found between patients with and without NP in terms of age, sex, education level, marital status, family support, MS type, disease duration, plaque location, functionality, disability, daily living activities, and depression. The EDSS score was found as the only factor associated with NP in the study by Solaro et al.;[18] however, no such difference was determined between the groups in terms of EDSS in the present study.

Similar to the study conducted by Ferraro et al.,[6] we observed that the pain intensity was higher in patients with NP. In this study, patients with NP had higher levels of fatigue; it was found that the number of patients with pathological levels of fatigue was higher in this group. In a four-year longitudinal study conducted by Heitmann et al.,[17] fatigue and depression were associated with pain and NP, and this relationship became stronger over time. In our study, no statistically significant relationship was found between NP and depression. Also, we found that the QoL of patients with NP was lower.

As a study evaluating pain in patients with MS, the main limitation of the study was the lack of questioning NSAIDs, analgesics, and also anti-spasticity medication in detail. One of the most important limitations of this study was that it was a cross-sectional study. Therefore, the duration of the pain symptoms, how pain behavior developed, how the pain symptoms changed over time, and whether it was progressive could not be evaluated. Other limitations of the study were that it was a single-center study and all patients were included in the study regardless of relapse or remission in relapsing-remitting multiple sclerosis (RRMS). Also, the definite diagnosis of NP requires confirmatory tests such as magnetic resonance imaging (MRI) and electroneuromyography (ENMG), which prove the history and clinical findings of the patients; however, only the PDQ was used for classification in the present study.

In view of the limitations of this study, pain in MS can be assessed comprehensively in terms of attacks, pain duration, nociceptive pain and treatment preferences with further studies by more objective methods such as ENMG or MRI.

In conclusion, our study results indicate that pain and NP should not be neglected due to its negative effects on patients' mood, fatigue, and QoL. We believe that with wider, further studies, pain/NP-related factors in MS can be determined more clearly and by increasing awareness, pain/NP symptoms, which negatively affect the QoL of patients, would be treated more accurately.

Acknowledgement: We are dedicating this paper to the memory of Dear Prof Dr Zehra Akpınar who contributed greatly to the design and materials of the study and unfortunately passed away while the writing process.

Ethics Committee Approval: The study protocol was approved by the Necmettin Erbakan University, Meram Faculty of Medicine Ethics Committee (Approval number/ date: 994/16.06.2017). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Concept, design, data, analyzing data, literature search, writing: Z.K.; Concept, design, supervision, writing, review: H.U.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Dilek B. Mültipl skleroz ve rehabilitasyonu. In: Beyazova M, Kutsal, YG, editör. Fiziksel Tıp ve Rehabilitasyon. Ankara: Güneş Tıp Kitabevleri; 2016. s. 2333-45.
2. Foley PL, Vesterinen HM, Laird BJ, Sena ES, Colvin LA, Chandran S, et al. Prevalence and natural history of pain in adults with multiple sclerosis: Systematic review and meta-analysis. Pain 2013;154:632-42.
3. Solaro C, Uccelli MM. Management of pain in multiple sclerosis: A pharmacological approach. Nat Rev Neurol 2011;7:519-27.
4. Truini A, Barbanti P, Pozzilli C, Cruccu G. A mechanism-based classification of pain in multiple sclerosis. J Neurol 2013;260:351-67.
5. Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron 2006;52:77-92.
6. Ferraro D, Plantone D, Morselli F, Dallari G, Simone AM, Vitetta F, et al. Systematic assessment and characterization of chronic pain in multiple sclerosis patients. Neurol Sci 2018;39:445-53.
7. Thompson AJ, Toosy AT, Ciccarelli O. Pharmacological management of symptoms in multiple sclerosis: Current approaches and future directions. Lancet Neurol 2010;9:1182-99.
8. Kim KH, Seo HJ, Abdi S, Huh B. All about pain pharmacology: What pain physicians should know. Korean J Pain 2020;33:108-20.
9. Green R, Cutter G, Friendly M, Kister I. Which symptoms contribute the most to patients' perception of health in multiple sclerosis? Mult Scler J Exp Transl Clin 2017;3:2055217317728301.
10. Barin L, Salmen A, Disanto G, Babačić H, Calabrese P, Chan A, et al. The disease burden of multiple sclerosis from the individual and population perspective: Which symptoms matter most? Mult Scler Relat Disord 2018;25:112-21.
11. Simmons RD, Tribe KL, McDonald EA. Living with multiple sclerosis: Longitudinal changes in employment and the importance of symptom management. J Neurol 2010;257:926-36.
12. Khalaf KM, Coyne KS, Globe DR, Malone DC, Armstrong EP, Patel V, et al. The impact of lower urinary tract symptoms on health-related quality of life among patients with multiple sclerosis. Neurourol Urodyn 2016;35:48-54.
13. Kratz AL, Whibley D, Alschuler KN, Ehde DM, Williams DA, Clauw DJ, et al. Characterizing chronic pain phenotypes in multiple sclerosis: A nationwide survey study. Pain 2021;162:1426-33.
14. Kalia LV, O'Connor PW. Severity of chronic pain and its relationship to quality of life in multiple sclerosis. Mult Scler 2005;11:322-7.
15. Young J, Amatya B, Galea MP, Khan F. Chronic pain in multiple sclerosis: A 10-year longitudinal study. Scand J Pain 2017;16:198-203.
16. Svendsen KB, Jensen TS, Hansen HJ, Bach FW. Sensory function and quality of life in patients with multiple sclerosis and pain. Pain 2005;114:473-81.
17. Heitmann H, Haller B, Tiemann L, Mühlau M, Berthele A, Tölle TR, et al. Longitudinal prevalence and determinants of pain in multiple sclerosis: Results from the German National Multiple Sclerosis Cohort study. Pain 2020;161:787-96.
18. Solaro C, Cella M, Signori A, Martinelli V, Radaelli M, Centonze D, et al. Identifying neuropathic pain in patients with multiple sclerosis: A cross-sectional multicenter study using highly specific criteria. J Neurol 2018;265:828-35.
19. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.
20. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 1983;33:1444-52.
21. Meyer-Moock S, Feng YS, Maeurer M, Dippel FW, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. BMC Neurol 2014;14:58.
22. Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. Phys Ther 1984;64:35-40.
23. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: A reliability study. Int Disabil Stud 1988;10:61-3.
24. Küçükdeveci AA, Yavuzer G, Tennant A, Süldür N, Sonel B, Arasil T. Adaptation of the modified Barthel Index for use in physical medicine and rehabilitation in Turkey. Scand J Rehabil Med 2000;32:87-92.
25. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. Arch Neurol 1988;45:435-7.
26. Armutlu K, Korkmaz NC, Keser I, Sumbuloglu V, Akbiyik DI, Guney Z, et al. The validity and reliability of the Fatigue Severity Scale in Turkish multiple sclerosis patients. Int J Rehabil Res 2007;30:81-5.

27. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
28. Richter P, Werner J, Heerlein A, Kraus A, Sauer H. On the validity of the Beck Depression Inventory. A review. Psychopathology 1998;31:160-8.
29. Hisli N. Beck depresyon envanterinin geçerliği üzerine bir çalışma. Psikoloji Dergisi 1988;6:118-26.
30. Essink-Bot ML, Krabbe PF, Bonsel GJ, Aaronson NK. An empirical comparison of four generic health status measures. The Nottingham Health Profile, the Medical Outcomes Study 36-item Short-Form Health Survey, the COOP/WONCA charts, and the EuroQol instrument. Med Care 1997;35:522-37.
31. Kücükdeveci AA, McKenna SP, Kutlay S, Gürsel Y, Whalley D, Arasil T. The development and psychometric assessment of the Turkish version of the Nottingham Health Profile. Int J Rehabil Res 2000;23:31-8.
32. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: A new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22:1911-20.
33. Alkan H, Ardic F, Erdogan C, Sahin F, Sarsan A, Findikoglu G. Turkish version of the painDETECT questionnaire in the assessment of neuropathic pain: A validity and reliability study. Pain Med 2013;14:1933-43.
34. Hadjimichael O, Kerns RD, Rizzo MA, Cutter G, Vollmer T. Persistent pain and uncomfortable sensations in persons with multiple sclerosis. Pain 2007;127:35-41.
35. Grau-López L, Sierra S, Martínez-Cáceres E, Ramo-Tello C. Analysis of the pain in multiple sclerosis patients. Neurologia 2011;26:208-13.
36. O'Connor AB, Schwid SR, Herrmann DN, Markman JD, Dworkin RH. Pain associated with multiple sclerosis: Systematic review and proposed classification. Pain 2008;137:96-111.
37. Osterberg A, Boivie J, Thuomas KA. Central pain in multiple sclerosis--prevalence and clinical characteristics. Eur J Pain 2005;9:531-42.
38. Akpınar Z, Tokgöz OS, Gümüş H. Multipl sklerozda ağrı ve klinik özelliklerle ilişkisi. Turk J Neurol 2014;20:79-83.
39. Brochet B, Deloire MS, Ouallet JC, Salort E, Bonnet M, Jové J, et al. Pain and quality of life in the early stages after multiple sclerosis diagnosis: A 2-year longitudinal study. Clin J Pain 2009;25:211-7.
40. Şentürk Güven Ş, Sezgin Özcan D, Aras M, Köseoğlu BF, Ak F. Multipl sklerozlu hastalarda ağrının değerlendirilmesi ve yaşam kalitesi, yorgunluk ve depresyon ile ilişkisi. Turk J Phys Med Rehab 2016;62:123-31.
41. Forbes A, While A, Mathes L, Griffiths P. Health problems and health-related quality of life in people with multiple sclerosis. Clin Rehabil 2006;20:67-78.
42. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice ASC, et al. A new definition of neuropathic pain. Pain 2011;152:2204-5.