Original Investigation / Özgün Araştırma

Neuropathic Pain in Patients with Multiple Sclerosis: Its Association with Clinical Variables and Its Impact on Quality of Life

Multipl Sklerozlu Hastalarda Nöropatik Ağrı: Klinik Değişkenlerle İlişkisi ve Yaşam Kalitesi Üzerine Etkisi

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ABSTRACT

Objective: In our study, we aimed to investigate presence of neuropathic pain in multiple sclerosis (MS) patients by using PainDETECT Questionnaire (PDQ), to assess its association with clinical parameters such as clinical course, disease severity and disease duration and as well as to determine its impact on quality of life (QoL).

Methods: A total of 32 MS patients and 32 age and sex-matched healthy controls were included in the study. Presence of neuropathic pain was assessed by PDQ. Severity of pain was measured by using 10 cm Visual Analog Scale (VAS). Disease severity was evaluated by Expanded Disability Status Scale (EDSS) and QoL by Nottingham Health Profile (NHP).

Results: According to PDQ, neuropathic pain was observed in 59.38% of the patients and 6.25% of the controls. The rate of neuropathic pain was higher in MS patients when compared with controls (Odds ratio (OR) = 21.92 confidence interval (CI) 95% (4.45-108.13)) ($p<0.0001$). There was no relation between presence of neuropathic pain and clinical course. Patients with neuropathic pain scored significantly higher in pain subgroup of NHP ($p<0.05$). There was no statistically significant difference in scores of EDSS and physical mobility, energy, sleep, social isolation and emotional reaction subgroups of NHP among the groups ($p>0.05$).

Conclusion: Because of the fact that neuropathic and non-neuropathic pain require different treatment approaches; diagnosis of neuropathic pain is critically important. Awareness of neuropathic pain in MS will help us develop new treatment methods and provide a better QoL.

Keywords: Multiple sclerosis, neuropathic pain, quality of life

ÖZET

Amaç: Çalışmamızda multipl skleroz (MS) hastalarında PainDETECT anketi (PainDETECT Questionnaire (PDQ)) kullanarak nöropatik ağrı varlığını araştırmayı, klinik seyir, hastalık şiddeti ve hastalık süresi gibi klinik parametrelerle ilişkisini değerlendirmeyi ve bunun yanında yaşam kalitesi (quality of life (QoL)) üzerine etkisini saptamayı amaçladık.

Yöntemler: Çalışmaya toplam 32 MS hastası ve yaş ve cinsiyet uyumlu 32 sağlıklı kontrol dahil edildi. Nöropatik ağrı varlığı PDQ ile değerlendirildi. Ağrı şiddeti 10 cm Görsel Analog Skala (Visual Analog Scale (VAS)) ile ölçüldü. Hastalık şiddeti Genişletilmiş Özürlülük Durum Skalası (Expanded Disability Status Scale (EDSS)) ve yaşam kalitesi ise Nottingham Sağlık Profili (Nottingham Health Profile (NHP)) ile değerlendirildi.

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Bulgular: PDQ'ya göre hastaların %59.38'inde ve kontrollerin %6,25'inde nöropatik ağrı gözlendi. Nöropatik ağrı oranı MS hastalarında kontrollerle kıyaslandığında daha yüksekti (Odds oranı (Odds ratio (OR)) = 21.92, güven aralığı (confidence interval (CI)) 95% (4.45-108.13)) (p<0.0001). Nöropatik ağrı varlığı ile klinik seyir arasında ilişki yoktu. Nöropatik ağrısı olan hastalar NHP ağrı alt grubunda belirgin olarak yüksek skor elde ettiler (p<0.05). Gruplar arasında EDSS ve NHP fiziksel mobilite, enerji, uyku, sosyal izolasyon ve emosyonel reaksiyon alt gruplarında istatistiksel olarak anlamlı fark yoktu (p>0.05).

Sonuçlar: Nöropatik ağrı ve non-nöropatik ağrı tedavisi farklı tedavi yaklaşımları gerektirdiğinden dolayı, nöropatik ağrının tanısı son derece önemlidir. MS'de nöropatik ağrı farkındalığı, yeni tedavi yöntemleri geliştirme ve daha iyi bir yaşam kalitesi sağlamada bize yardımcı olacaktır.

Anahtar sözcükler: Multipl skleroz, nöropatik ağrı, yaşam kalitesi

Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system of an unknown etiology, which is characterized by demyelination and neurodegeneration. Main symptoms are motion, visual and sensory disturbances, cerebellar symptoms and sphincter dysfunctions (1, 2). Pain is currently accepted as a common symptom in MS, directly related to the disease and its consequences (3) and can be classified as nociceptive or neuropathic (1).

Neuropathic pain is defined as "pain caused by a primary lesion or dysfunction in the nervous system" by International Association for the Study of Pain (IASP) (4). Neuropathic pain is common in the patients with MS. Previous studies have shown that the prevalence of neuropathic pain in the patients with MS is around 30% (5). The most frequent types of NP which have been described in the patients with MS are 'dysesthetic extremity pain' and Lhermitte's phenomenon. Dysesthetic extremity pain is a continuous burning pain which affects lower extremities bilaterally (6). Lhermitte's phenomenon is described as an electrical-like sensation radiating down the back and the limbs with neck motions (7).

Since neuropathic and non-neuropathic pain need different treatment approaches, diagnosis of neuropathic pain becomes more of an issue for optimal treatment. Various screening tools have been designed for the distinction between neuropathic and nociceptive pain (8). The most commonly used ones are Leeds Assessment of Neuropathic Symptoms and Signs (LANNS) (9), Douleur Neuropathique 4 (DN4) questionnaire (10) and Pain*DETECT* Questionnaire (PDQ) (11).

PDQ is a simple screening tool, which was developed to differentiate neuropathic pain from non- neuropathic pain by evaluating neuropathic signs and symptoms without physical examination. It was developed by Freynhagen et al. (11) to examine neuropathic components in the patients with back pain. Its adaptation to Turkish language and validation were proven by Alkan et al. (12).

Neuropathic pain is not a single disease, but a syndrome caused by wide range of diseases and lesions, which has a significant negative impact on individuals' well-being and quality of life (QoL) (12). In the present study, we aimed to investigate neuropathic pain in Turkish patients with MS using PDQ, to assess its relationship with clinical variables including clinical course, disease severity, disease duration and to evaluate its effect on QoL in terms of functional status, social and emotional functioning. To our knowledge, this is the first study to use PDQ for assessing neuropathic pain in MS patients.

Patients and Methods

The study included a total of 32 patients diagnosed with clinically definite MS according to 2010 Mc Donald criteria (13) who were admitted to our outpatient neurology clinic between January and May 2015. Control group included 32 age and sex-matched healthy subjects. Exclusion criteria were other neurological diseases such as cerebrovascular disorders, Parkinson disease and peripheral neuropathy; endocrine diseases such as diabetes mellitus and thyroid disorders and concomitant autoimmune inflammatory disease such as rheumatoid arthritis. Informed consent form was obtained from each patient. The study protocol was approved by Medical Research Ethics Committee of Medical Faculty. The study conforms to the provisions of the World Medical Association's Declaration of Helsinki.

Patient data including age, gender, clinical course of the disease (relapsing-remitting, primary progressive or secondary progressive), disease duration and medication were recorded. Expanded Disability Status Scale (EDSS) (14) was used for determining severity of MS. Severity of pain was measured by using 10 cm Visual Analog Scale-pain (VAS-pain) (15). QoL was evaluated by using Nottingham Health Profile (NHP) (16).

Assessment of Neuropathic Pain

Presence of neuropathic pain was determined by PDQ (12). PDQ is a simple screening questionnaire which has been designed to assess neuropathic pain

components in the patients with chronic pain. It includes four categories. The first category evaluates intensity of pain at the moment, the average and the maximum pain intensity during the past 4 weeks (0 = no pain, 10 = maximum pain) which diagnose the presence of pain. In the second category, patients are asked to point out one of the four diagrams which define their pain course patterns: persistent pain with slight fluctuations (0 points), persistent pain with pain attacks (-1 point), pain attacks without pain between them (1 point), and pain attacks with pain between them (1 point). In the third category, patients are asked to mark painful area on a homunculus and show the direction of radiating pain with an arrow. In the fourth category there are seven questions about the following sensations: burning, tingling or prickling, allodynia, pain attacks, temperature-evoked pain, numbness, and pressure-evoked pain. The severity of these sensations are scored as following (0 = never, 1 = hardly noticed, 2 = slightly, 3 = moderately, 4 = strongly, 5 = very strongly). This category provides scores between 0 and 35 points. The final score is obtained summing up the scores of the last three sections with a total score of -1 to 38. Scores ≤12 indicate that a neuropathic pain component is doubtful. Scores ≥19 are evidence for neuropathic pain. Scores between 12 and 19 indicate unclarity (12).

Statistical Analysis

Descriptive statistics (mean, median, SD (Standard deviation), minimum, maximum and frequencies) were used for assessing the demographics and clinical parameters. Differences among groups were assessed using Mann-Whitney U test. Chi-square test was used to compare groups of categorical variables. The presence of correlation was evaluated by Spearman's correlation coefficients. A value of $p<0.05$ was considered statistically significant. All analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) for Windows, Version 21.0 (Armonk, New York, USA).

Results

Study Sample Characteristics

32 patients (23 women, 9 men) and 32 controls (23 women, 9 men) were included in the study. Mean age was 44.94±9.84 (25-67 years) in the patient group and 43.21±13.14 (25-66 years) in the control group. Age did not significantly differ among the groups (p=0.556). 19 patients suffered from relapsing-remitting MS and 13 patients from secondary progressive MS. Mean VAS-pain score was 4.09±3.48. Scores of EDSS, NHP subgroups (pain, physical mobility, energy, sleep, social isolation, and emotional reactions) and demographics and clinical data are summarized in Table 1.

Medications

30 patients (93.75%) were under medical therapy. Of all the patients, 34.38% (11 patients) were under beta interferon 1 a therapy, 34.38 % (11 patients) under beta interferon 1 b therapy, 12.5% (4 patients) under glatiramer acetate therapy, 6.25% (2 patients) under fingolimab therapy and 6.25% (2 patients) under natalizumab therapy.

Neuropathic Pain Scores

The mean PDQ score was 22.69±12.82 (median: 23.5) in the MS group and 7.18±6.48 (median: 6) in the control group. PDQ score was significantly higher in the

Table 1. Demographic and clinical patient data.

	Minimum	Maximum	Mean	Standard deviation
Age (year)	25.00	67.00	44.94	9.84
Disease duration (year)	1.00	36.00	11.28	7.69
VAS-pain	0.00	9.00	4.09	3.48
PDQ	-1.00	38.00	22.69	12.82
EDDS	0.00	8.00	3.25	2.57
NHP-pain	0.00	100.00	32.11	30.13
NHP-physical mobility	0.00	100.00	44.14	29.95
NHP- energy	0.00	100.00	67.19	37.26
NHP- sleep	0.00	100.00	26.25	27.09
NHP-social isolation	0.00	100.00	35.00	40.64
NHP-emotional reactions	0.00	100.00	41.02	33.93

VAS-pain: *Visual Analog Scale-pain,* ***PDQ:*** *PainDETECT Questionnaire,* ***EDSS:*** *Expanded Disability Status Scale,* ***NHP:*** *Nottingham Health Profile*

MS group, when compared with the controls (p<0.0001). PDQ was found to be ≥19 in 19 patients with MS (59.38%). According to PDQ, the prevalence of neuropathic pain was 59.38% in the patients and 6.25% in the controls. The prevalence of neuropathic pain was higher in the patients with MS (Odds ratio (OR) = 21.92 confidence interval (CI) 95% (4.45-108.13)) (p<0.0001) compared with controls.

According to Chi-square test, there was no relation between presence of neuropathic pain and clinical course (Pearson X^2(df) =1.587(1)) (Table 2). Patients with neuropathic pain scored significantly higher in pain subgroup of NHP (p<0.05). There was no statistically significant difference in scores of EDSS and physical mobility, energy, sleep, social isolation and emotional reaction subgroups of NHP among the groups (p>0.05) (Table 3). Relations between PDQ and clinical parameters are shown in Table 4.

Discussion

Epidemiological studies have shown that 26-58% of the patients with MS suffer from neuropathic pain (6). The discrepancy between results can be explained by research design (screening tools used or the description of NP). Multiple sclerosis-related NP results directly or indirectly from demyelinating lesions in the brain and spinal cord (17). Neuropathic pain occurs in MS patients as 3 types including Lhermitte's phenomenon, dysesthetic extremity pain and trigeminal neuralgia (2). There are possible mechanisms that can explain these types of neuropathic pain. Lhermitte's sign results from high-frequency ectopic impulse resulting from demyelinating plaques located in posterior column of cervical cord (18). Dysesthetic extremity pain is explained by deafferentation pain derived from the injury in the spino-thalamo-cortical pathways (6). And lastly, ectopic discharges generated by intra-axial inflammatory and extra-axial mechanical demyelination of trigeminal primary afferents cause trigeminal neuralgia (2).

In a study from Turkey, performed in 100 patients with MS, frequency of NP was found as 77% (19). Of the patients, 55% had dysesthetic extremity pain, 21% Lhermitte's sign and 1% had trigeminal neuralgia. In a recent study which was conducted in 302 Italian MS patients, frequency of neuropathic pain was reported as 14% (6). They assessed neuropathic pain by clinical examination and DN4 questionnaire. In a multi-center study from Italy (20), which was conducted in 1,672 MS patients, it was found that 18.1% had dysesthetic extremity pain, 9% had Lhermitte's phenomenon, and 2% had trigeminal neuralgia. In another study from Italy, Martinelli Boneschi et al. (21) reported the lifetime prevalence of NP as 28% and rates of NP components as follows: 20.5% for Lhermitte's sign, 12% for dysesthetic extremity pain and 4% for trigeminal neuralgia. On the other hand, Vidovic et al. (22) reported the rate of neuropathic pain in Croatian MS patients as 23%. In our study, we found the rate of neuropathic pain as 59.38%. To our knowledge, this study is the first to investigate neuropathic pain in Turkish patients with MS by using a neuropathic pain screening tool. We used PDQ, which is a simple tool which can differentiate neuropathic pain from nociceptive pain despite the classification of neuropathic pain into dysesthetic extremity pain, Lhermitte's phenomenon and trigeminal neuralgia.

Table 2. The relation between presence of neuropathic pain and clinical course.

		Neuropathic pain			p value
		present	absent	total	
Clinical course	relapsing-remitting	13	6	19	0.208
	secondary progressive	6	7	13	
	total	19	13	32	

Pearson X^2(df)=1.587(1), p <0.05 (significant)

Table 3. Comparison of the patients with/without neuropathic pain in terms of clinical parameters.

	NP		
	Present (n=19) median	Absent (n=13) median	p value
Disease duration	10	12	0.323
EDSS	2	3	0.136
NHP-pain	42.8	14.2	0.010*
NHP-physical mobility	37.5	37.5	0.850
NHP- energy	50	100	0.970
NHP- sleep	20	20	0.472
NHP-social isolation	0	20	0.570
NHP-emotional reactions	37.5	50	0.970

***EDSS:** Expanded Disability Status Scale, **FSS:** Fatigue Severity Scale, **BDS:** Beck Depression Scale, **NHP:** Nothingham Health Profile, ***:** P < 0.05 (significant)*

Table 4. The relations of PDQ with clinical parameters.

		EDSS	Disease duration	VAS-pain
PDQ	r	-0.062	-0.031	0.807*
	p	0.734	0.867	<0.0001

***PDQ:** PainDETECT Questionnaire, **EDSS:** Expanded Disability Status Scale, ***:** P < 0.05 (significant)*

In the current study, presence of neuropathic pain was not related with disease severity, clinical course or disease duration. We did not find any statistically significant difference between the patients with/without NP in terms of clinical variables. Moreover PDQ scores were not correlated with EDSS and disease duration. Our findings were consistent with several studies in the literature. Similarly, in a study from Canada, no statistically significant difference was reported in disease duration or disease severity between MS patients with/without neuropathic pain (23). Also Beiske et al. (24) did not report a relation between MS-related pain and disease parameters such as disease duration, disease course and functional status. They suggested that pain was a disabling symptom, independent of clinical variables in MS patients. In contrast to our findings, Solaro et al. (20) showed an association between neuropathic pain and disease course and disease severity in the patients with MS. They explained the relation between neuropathic pain and disease severity by dysesthetic pain due to spinal cord involvement and back pain resulting from abnormal posturing and gait disorders. In the study of Akpinar et al. (19), EDSS scores were associated with pain scores. They suggested that spinal cord involvement associated with high EDDS scores may also cause pain by affecting pain-related pathways. On the other hand, Martinelli Boneschi et al. (21) demonstrated that neuropathic pain was related with MS disease severity in the study where 428 Italian MS patients were evaluated.

We also explored the impact of neuropathic pain on QoL. To our knowledge, the relation of neuropathic pain severity with quality of life has not been previously studied in MS patients. In our study, patients with neuropathic pain scored significantly higher in pain subgroup of NHP; however no statistically significant difference was found in scores of physical mobility, energy, sleep, social isolation and emotional reaction subgroups of NHP among the groups.

Our study has several limitations. First one is relatively small number of subjects. And second one is the lack of electrophysiological studies. Owing to the fact that subclinical neuropathy may not be detected in early stages; we used a neuropathic pain screening tool in the discrimination of neuropathic pain from non-neuropathic pain.

Since different treatment approaches are needed to manage neuropathic and non-neuropathic pain, neuropathic pain should be diagnosed by using validated screening tools. A better knowledge of pathophysiologic mechanism of neuropathic pain in MS is needed to develop new treatment approaches and provide a better QoL.

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