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Original Article

The Relationship Between Pain and Clinical Features in Multiple Sclerosis

Multipl Sklerozda Ağrı ve Klinik Özelliklerle İlişkisi

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Summary

Objective: Multiple sclerosis (MS) is an autoimmune-neurodegenerative disease of the central nervous system. The prevalence of pain is between 29% and 86% and besides neuropathic pain, somatic pain types may also emerge together or separately. In this study we aimed to analyze the relationship between pain and other clinical features in MS.

Materials and Methods: One-hundred cases who were followed in MS clinic and who have complaints of pain, were included in this study. We evaluated pain type and localization during patients were filling in the forms. We applied Visual Pain Scale (VPS), Ashworth Spasticity Scale (ASS) and Beck Depression Scale (BDS).

Results: When female and male patients were compared, there were no statistical differences between age, disease duration and EDDS scores. Seventy seven percent of cases complained of neuropathic pain, 21% of cases had Lhermitte symptoms. Trigeminal neuralgia has been observed in 1% of cases and 55% of neuropathic extremity pain. In 60% of the cases nociceptive pains, in 12% of the cases joint-extremity-muscle pain, in 47% headache and in 1% painful tonic spasms were present. Pain depending on the treatment was observed only in 2% of the cases. The pain score was high in patients with spasticity and depression. Although there was reasonable positive correlation between age, EDDS score and VPS, poor correlation was obtained between disease period and number of attacks.

Conclusion: These findings indicate that MS pain is related with spasticity, disability and depression and these clinical findings should be taken into account during pain treatment. (Turkish Journal of Neurology 2014; 20:79-83)

Key Words: Multiple sclerosis, pain, neuropathic pain, headache, trigeminal neuralgia

Özet

Amaç: Multipl Skleroz (MS), santral sinir sisteminin otoimmün-nörodejeneratif bir hastalığıdır. Ağrı prevalansının %29-%86 arasında değiştiği bu hastalıkta nöropatik, somatik ağrı tipleri bir arada veya tek olarak ortaya çıkabilir. Bu çalışmada MS'te ağrı ve diğer klinik özellikler arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya MS polikliniğinde takip edilen ve ağrı şikayeti olan 100 olguyu dahil ettik. Olgulara hazırladığımız anket formunu doldurtarak ağrı tipi ve lokalizasyonunu sorguladıktan sonra Vizüel Ağrı Skalası (VAS), Ashworth Spastite Skalası (ASS) ve Beck Depresyon Ölçeği (BDÖ) uyguladık.

Bulgular: Kadın ve erkek hastalar karşılaştırıldığında yaş, hastalık süresi, atak sayısı, EDSS skorları arasında istatistiksel olarak anlamlı fark yoktu. Olguların %77'sinde nöropatik ağrı; %21'inde Lhermitte belirtisi, %1'inde trigeminal nevralji, %55'inde nöropatik ekstremite ağrısı vardı. Olguların %60'ında nosiseptif ağrı; %12'sinde yaygın eklem-ekstremite kas ağrısı, %47'sinde baş ağrısı, %1'inde ağrılı tonik spazm mevcuttu. Olguların sadece %2'sinde tedaviye bağlı ağrı vardı. Ağrı skoru, spastisitesi ve depresyonu olanlarda anlamlı derecede yüksekti. Yaş ve EDSS skoru ile VAS arasında orta derecede pozitif korelasyon varken, hastalık süresi ve atak sayısı ile zayıf korelasyon mevcuttu.

Sonuç: Bu bulgular MS'te görülen ağrının spastisite, özürlülük, depresyon ile ilişkili olduğunu, bu klinik bulguların ağrı tedavisinde göz önünde tutulması ve bunların da tedavi edilmesi gerektiğini göstermektedir. (Türk Nöroloji Dergisi 2014; 20:79-83)

Anahtar Kelimeler: Multipl skleroz, ağrı, nöropatik ağrı, baş ağrısı, trigeminal nevralji

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Introduction

Multiple sclerosis (MS), is a multifactorial, neuroinflammatory and neurodegenerative disease with unknown etiology, primarily affecting young adults (1,2). Depending on the involved areas pain is frequently seen in this disease that targets central nervous system (CNS) especially white matter. Pain is a vital signal that our nervous system produces in order to warn us of possible tissue damage. The pain, associated with real or potential tissue damage, is an undesirable sensory and emotional experience and has psychological and social components. It does not receive adequate attention in the context of MS, which is a chronical disease with remitting and relapsing characteristics. Different studies report the prevalence of pain in this disease between 29 and 86% (3,4). The difference in these reports can be explained by the differences in the methods and pain classifications used in the studies (5,6). Numerous pain classifications are in use. The pain seen in MS can broadly be classified as neurological and non-neurological. It can be examined as acute, sub-acute and chronic or in a mechanism-dependent manner, such as central/neuropathic or peripheral/somatic (7). The mechanism-dependent classification proposed by Truini et al. is the most explanatory one:

1. MS related pain: Trigeminal neuralgia, Lhermitte phenomenon: Dependent on the ectopic stimulation along the primary afferents,

2. Ongoing extremity pain: Deafferentation pain secondary to lesion in the spino-thalamo-cortical pathways,

3. Painful tonic spasms and spasticity pain: mixed pains secondary to lesions in the central motor pathways,

4. Musculoskeletal pains: Arising from postural abnormalities secondary to motor disorders,

5. Pain associated with optic neuritis: Nerve trunk pain originating from nervi nervorum,

6. Headache: secondary to midbrain lesions,

7. Treatment-induced pains: Due to interferone etc. use (8).

The pain mechanisms in MS are not well known and the effective factors are still debated. There are different reports concerning disease type, duration, the patient's age, debility level and accompanying diseases such as depression (8,9). The most frequently reported finding is the relationship between disease duration and debility scores, and pain intensity (4). In this study, we investigated the properties of pain and its relationship with the clinical properties of MS.

Materials and Methods

The study included 100 patients who were being followed at the neurology clinic, MS policlinic, and who were diagnosed with certain MS according to McDonalds criteria (10). After obtaining approval from the local ethical board (08.18.2011, number 6641/09), the study started by asking the patients who successively came to the policlinic during their remission if they had any pain. The ones with systemic disorders that might cause pain and those who are having attacks were excluded from the study. The patients with pain complaints were included after giving informed consent. Following the neurological examination, he pain localizations and types were determined using the surveys we prepared. The pains they described were divided into subgroups as neuropathic, nociceptive, mixed and treatment-related. All patients completed visual analogue scale (VAS), Beck depression inventory (BDI) and those with spasticity also completed Ashworth spasticity scale (ASS). People who scored higher than 19 in BDI was considered as depressed. This was later verified in a psychiatry consultation. Expanded disability status scale (EDSS) scores were also obtained (11). Bladder functions of the patients were asked and marked as normal/dysfunctioning. According to the clinical forms, patients were categorized into 3 groups as relapsing-remitting (RRMS), primary progressive (PPMS) and secondary progressive (SPMS). Lesions in the saggital T2-weighted and FLAIR magnetic resonance imaging (MRI) sequences acquired earlier were investigated. Cranial and/or spinal lesions were detected. The patients were divided as spinal lesion exist/absent.

The scales filled by the patients were as follows:

VAS: It is often a 10 cm long linear line with "No pain" on one end and "Intense pain" on the other. The patient points at the appropriate location on the line to indicate the severity of the pain. The distance in centimeters between the "No pain" end and the pointed location is recorded. We applied this procedure to all patients.

BDI: Beck depression inventory has four options for 21 symptom categories. Each item gets scored between 0 and 3. The maximum score is 63. The magnitude of the score indicates the severity of depression. We asked the patients to circle the sentence that best describes how they felt within the past week including the testing day.

ASS:

0 : No increase in muscle tonus.

1 : Mild increase in muscle tonus, minimal resistance at the end of free movement.

1+: Mild increase in muscle tonus, rigidity at first, minimal resistance during the rest of the movement.

2 : Resistance in most of the movement range but the affected parts can easily be manipulated.

3 : Significant increase in muscle tonus, passive movement is difficult.

4 : Affected regions are rigid during flexion and extension.

This evaluation was applied to all cases. Spasticity was recorded as present/absent and the scores of those with spasticity were averaged.

Statistical Analysis

The data was analyzed in SPSS-16 software. The fit of the data to normal distribution was assessed by Kolmogorov-Smirnov test. Descriptive statistics were given as mean ± standart deviation or median (interquartile range: IQR: 3rd quartile-1st quartile values). For the differences between the two groups, independent samples t-test was used for the parametric distributions and Mann-Whitney U test was used for the non-parametric distribution. For multiple group comparisons, the non-parametric numerical values were compared using Kruskal-Wallis test. Post-hoc analyses following Kruskal-Wallis were made using Mann-Whitney U and p values were corrected using Bonferroni correction. Categorical values were compared using chi-square (χ^2) test. Spearman's test of linearity was used to assess linear relationship between nonparametric data. $P<0.05$ was accepted as statistically significant.

Results

Seventy six of the patients included in the study were female and 24 of them were male. Eighty two patients had RRMS, 12 had SPMS, and 6 had PPMS. All cases were in remission and their age was 34.78±9.76 with mean disease duration was 6.00 years (IQR: 3.00-10.00), mean number of attacks was 4.00 (IQR: 3.00-7.00), mean EDSS was 3.00 (IQR: 2.00-4.00), mean VAS was 5.00 (IQR: 3.00-6.00), and mean ASS was 3.00 (IQR: 2.00-3.00) (Table 1). Mean age for women was 34.71±9.61 and mean age for men was 35.00±10.44 with no statistically significant difference between the groups (p=0.9). Between women and men disease duration [6.00 (IQR: 3.00-8); 7.50 (IQR: 3.00-12.75) respectively], number of attacks [4.00 (IQR: 3.00-7.00); 4.50 (IQR 3.00-6.75) respectively], EDSS means [3.00 (IQR; 2.00-4.00); 3.00 (IQR: 2.25-4.75) respectively] were not significantly different.

In 39% of the cases, plaques in cervical medulla spinalis in addition to intracerebral plaques were detected. Seventy seven percent of the cases had neurpathic pain, 21% had Lhermitte sign, 2% had trigerminal neuralgia, and 55% had ongoing dysesthetic extremity pain. Nineteen percent of the patients with neuropathic pain had two different pain types at the same time. There was nociceptive pain in 60%, wide-spread limb-extremity-muscle pain in 12% and headache in 47%. Only 2 patients with headaches met the migraine criteria. Only 2% of the cases had treatment related haedaches. One percent of the cases had painful tonic spasms. Thirty seven percent of the cases had neuropathic and nociceptive pains at the same time. Fifty four percent of the patients had depression, 36% had spasticity and 40% had bladder dysfunction (Table 2). The median VAS scores of those with spasticity, medulla spinalis involvement, bladder dysfunction and depression was significantly higher than those who did not have those conditions (Table 3). There was a medium-strength, positive linear relationship between age, and EDSS and VAS scores, and a a weak-strength positive linear relationship between disease duration and attack duration, and VAS scores (Table 4). In terms of pain tyes, median VAS score was significantly higher for those with ongoing dysestetic extremity pain compared to those who have nociceptive pain only (p=0.001) (Table 3). Fourty four patients who were on modifying treatment (interferon) had a smaller median VAS score than those who were not (p=0.004). When 3 different forms of MS (RR, PP and SP) were compared, there was no difference in terms of VAS scores (Table 4).

Table 1. Patient demographics and clinical properties

	n	Mean
All patients (age)	100	34.78±9.76
Female	76	34.71±9.61
Male	24	35.00±10.44
EDSS score (median)	100	3.00 (IQR: 2.00-4.00)
Attack count (median)	100	4.00 (IQR: 3.00-7.00)
Disease duration (median)	100	6.00 (IQR: 3:00-10.00)
VAS (median)	100	5.00 (IQR: 3.00-6.00)
ASS	36	3.00 (IQR: 2.00-3.00)

EDSS: Expanded disability status scale, VAS: Visual analogue scale, ASS: Ashworth spasticity scale, IQR: interquartile range

Table 2. Pain types seen in multiple sclerosis patients and their percentages

Pain types	n	Prevalence (%)
Neuropathic pain	77	77
Lhermitte sign	21	21
Trigeminal neuralgia	1	1
Extermity pain	55	55
Nociceptive pain	62	62
Muscoskeletal pain	12	12
Headaches	47	47
Migraine	2	2
Other	45	45
Tonic spasms	1	1
Treatment-induced pain	2	2

Discussion

Multiple sclerosis is a multifactorial neurodegenerative disease of demyelinating nature which has a genetic background (1,2). In addition to the motor, sensory, visual and cerebellar involvement, clinical signs indicating CNS involvement such as cognitive dysfunctions, psychiatric disorders, sleep disorders and seizures are often frequently seen (3,4,12). Pain inflicts a great deal of strain on daily activities and quality of life towards the advanced stages of the disease but it might also present as the first symptom (7). Pain in MS is often seen in various types, much like its other clinical symptoms. It is classified as acute, subacute and chronic in addition to being investigated as neurological and non-neurological pain. While inflammation is held accountable for neurological pain, conditions like spasticity, osteoporosis, bladder dysfunction and infections can be the cause of non-neurological pain (13). These pains are mostly muscle and joint pains. The reported pain types, much like their prevalences, show a great deal of variety. Truini et al.'s study reports trigeminal neuralgia with 2-5%, Lhermitte finding with 15%, extremity pain with 12-18%, painful tonic spasms with 6-12%, tension type headaches with 21%, migraine with 34% and treatment related pain with ?% (unknown) prevalence (8). There are various other reports (4,12-14).

Neuropathic pain prevalence in MS changes between 50% and 80% (8). In 1-2% of the cases, it is seen as the first symptom (14). The neuropathic pain seen in MS can be investigated in 3 sections: Lhermitte sign, trigeminal neuralgia and ongoing dysesthetic extremity pain. Being a subgroup of neuropathic pains, Lhermitte sign is seen in 15% of MS patients and it is more commonly seen as dorsal cord involvement in the cervical medulla (12). This pain is caused by ectopic intraaxial high-frequency stimuli. Spontaneous discharge of demyelinating axolemma causes this (15,16). Especially the demyelination of non-nociceptive Aβ-fiber axons and the involvement of neighboring nociceptive bundles are held responsible. Its paroxysmal property compared to trigeminal

Table 3. The effect of clinical findings on pain score (VAS)

	Present (n/medyan VAS)	Absent (n/ medyan VAS)	z / p
Spasticity	36/6.00 (5.00-8.00)	64/4.00 (3.00-5.75)	p=0.001
Bladder dysfunction	40/6.00 (4.00-8.00)	60/4.00 (3.00-6.00)	p=0.001
Depression	54/6.00 (4.00-7.00)	56/4.00 (2.75-5.25)	p=0.008
Medulla spinalis involvement	39/6.00 (4.00-7.25)	61/4.00 (3.00-6.00)	p=0.001
Interferon use	44/4.00 (3.00-6.00)	56/5.00 (4.00-7.00)	p=0.004
Neuropathic extremity pain	55/6 (4.00-6.00)	45/ 4 (2.00-6.00)	p=0.001

p<0.05 there were statistically significant differences between patients who had clinical symptoms and those who do not, in terms of pain score.

Table 4. Linear relationships between pain scale and related conditions.

Patient variables	VAS	
	r	p
Age	0.391.	.010
Disease duration	0.301.	.002
Attack count	0.231.	.045
EDSS score	0.520.	.010
Spasticity score	0.719.	0.010
Clinical types	3.792.	0.150

p<0.05 is accepted as statistically significant.

neuralgia is lower and it spontaneously in a few weeks. Thirty nine percent of our patients had cervical medulla spinalis involvement and 16% had Lhermitte's sign. Even though Lhermitte commonly appears during the attacks and disappears in response to treatment, it was present in all of our sample which was in remission.

Trigeminal neuralgia, an acute neuropathic pain, is seen 20 times more in MS compared to normal population and its prevalence is estimated as 3.8% (2-5%) (4,12,17,18,19). It is often seen in young patients and it affects ophthalmic branch to a lesser extent. Its mechanisms are still debated and some neuroimaging studies mention demyelinating plaques in the pons of the patients with neuralgia (20). Meaney et al. argued that this could be coincidental (21). Pichiecchio et al., on the other hand, put it down to peripheral involvement (22). In our patients, 2% had trigeminal neuralgia and both had brain stem plaques in their MRI.

Ongoing dysesthetic extremity pains were reported in 12-18% of MS patients (8). For us, this ratio was 55%. These patients reported the most intense pains (p=0.02). This pain type is usually categorized under chronic pain and it is typically bilateral. It may affect hands and feet and it is especially strong during night time (18). The physiopathology of this pain is usually thought to be caused by the spinothalamic tract lesions and the subsequent deafferentation of the thalamic nuclei (7). The channelopathy developing on the affected nerves was shown as the cause of that. It is more frequently seen in PPMS and RPMS and those with cervical and thoracic cord lesions (12).

Nociceptive pain existed in 60% of our patients. A pain type in this group is the non-specific muscle joint pain. Muscle weakness and postural abnormalities in patients can cause overloading on certain joint, ligament and muscle and produce muscoskeletal pain. There is no study on the prevalence of the widespread muscoskeletal pain but back pain resulting from these mechanisms is seen in 10-16%. In our study, 12% showed widespread muscoskeletal pain.

Even though its nature is unclear, there is a relationship between MS and headaches. Some studies report the lifetime prevalence of headaches in MS as 4-64% (23,24,25,26). Attacks starting with headaches were also reported (23). A meta-analysis suggested migraine without aura as 34% and tension type headache as 21% but there are views asserting that this could be coincidental (24). The prevalence rates reported above show that headaches are 3 times more likely in MS compared to general population. There was no relationship between the presence of headaches, and MS types, disease duration and debilitation score. However, there was a relationship between the pain type and MS types. Migraine was more frequent in RR and tension type was more frequent in SP, more commonly seen in female patients (26). When MS patients without headaches, MS patients with migraines and non-MS patients with migraines were compared in terms of their MRI findings, MS patients with migraine were seen so have high lesion load in the periaqueductal area (an important region for antinociceptive control) (27). There was headache in 47% of our cases and 2 of them were migraine, 2 were induced by interferon, and the rest were tension type. Attacks starting with headaches were reported in one patient. A relationship between migraine and MS was reported half a century ago (25). Some studies suggested migraine is more commonly seen in secondary progressive form whereas some suggested it is more frequent in RR form. It is known that migraine is come frequent during attacks. Since we did not have a lot of patients with migraines, drawing conclusions was difficult.

Painful tonic spasms seen in one patient aremotion or emotion-triggered contractions lasting for a few minutes, frequently seen in PPMS or SPMS, constituting 16% or 1/3rd of MS patients (28). It is often seen in capsula interna, basal ganglion, medulla oblongata and cerebral peduncle lesions. The reason why we encountered a smaller number of those was possibly because of the small number of PP and SP patients included in the study.

Neuropathic and nociceptive pain was seen concurrently in 37 of the MS patients. Another noteworthy finding of our study is the statistically meaningful relationship of attack count, EDSS score, disease duration, depression and spasticity, with pain score. While the correlation between attack count and disease duration, and pain was weaker, EDSS score, depression and medulla spinalis involvement, and pain was stronger. The high EDSS score can suggest that spasticity can produce more pain but also the system contractions causing high EDSS can also affect pain-related pathways. Spasticity and pain co-occurrence was reported as 28-60% (29). Spasticity generally causes non-specific muscle joint pain. Thirty six percent of the MS patients included in the study

had spasticity and their pain score was higher than the group without spasticity (p=0.001).

Depression is seen in 19-54% of MS patients (30). This prevalence is due to both the nature of the disease and the modifying treatment, especially interferon. Depression and pain co-occurrence is also commonly reported. Thirteen percent of the cases with pain had depression. Tarsuslu et al. reported 4 times increased physical debilitation in depressed patients (31). Pain and depression use the same pathways and neurotransmitters. The key neurotransmitters in the downstream inhibitory pain pathways are serotonin and noradrenaline (26,31). The pain itself and the restrictions it brings may cause depression. In 54% of our patients we found depression and their median VAS values were higher than those without depression.

The strong linear relationship between medulla spinalis involvement and pain is possibly in line with neuropathic pain mechanism. There is an increase in the expressions of inflammatory cytokines such as necrotizing factor and tumors in the medulla spinalis dorsal root ganglia in the neuropathic pain seen in MS. Bladder dysfunction can also increase the pain score due to inflammation and infection. Some studies report decrease in pain scores of SPMS patients who use interferon. In our study, 44% used interferon and their median VAS values were significantly different than those who did not. Another variable of out study was the duration but patients failed to indicate when the pain exactly started.

Results

Pain seen in MS can show a great variety due to the sophisticated underlying mechanisms. Furthermore, disease complications and the functional systems involved can increase this variety and hinder its treatment. In addition to treating the symptoms that contribute to pain, such as spasticity, depression and bladder dysfunction, determining the type of pain and planning a suitable treatment would increase the quality of life for patients.

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