

Evaluation of Neuropathic Extremity Pain in Patients with Multiple Sclerosis

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ABSTRACT

Introduction: Neuropathic extremity pain is one of the most common symptoms of multiple sclerosis (MS). This study was aimed to evaluate and compare the frequency and severity of neuropathic extremity pain in subtypes of MS.

Methods: Patients with the diagnosis of MS were included in the study, consecutively. Patients' demographic and clinical data were recorded. Patients' pain severity was assessed with visual analog scale (VAS). For the evaluation of neuropathic pain Leeds assessment of neuropathic symptoms and signs (LANSS) and *douleur neuropathique* 4 questions (DN4) were used. Disability was assessed with the Extended Disability Status Scale (EDSS).

Results: One hundred and three patients were included and 82.5% of

them had relapsing-remitting (RR) MS. According to LANSS and DN4, 47.6% of patients had neuropathic pain. Female patients had significantly higher pain scores. There was no significant difference between the subtypes of MS based on having neuropathic pain. Patients with secondary progressive (SP) MS had significantly higher EDSS. A significant positive correlation was detected between EDSS score and duration of disease.

Conclusion: Regardless of the MS subtype patients had neuropathic pain. Patients with SP had significantly higher disease duration and EDSS which were correlated with each other. All patients with the diagnosis of MS should be evaluated for neuropathic pain.

Keywords: Multiple sclerosis, neuropathic pain, disability

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INTRODUCTION

Multiple sclerosis (MS), as an autoimmune inflammatory demyelinating disease of the central nervous system, is one of the important causes of disability in young adults (1). MS phenotypes are mainly categorized into two groups either relapsing-remitting or progressive. MS subtypes are further classified into 4 groups as clinically isolated syndrome, relapsing-remitting (RR), secondary progressive (SP) and primary progressive MS (2). MS signs and symptoms include sensory symptoms on the face or extremities, unilateral visual loss, acute or subacute motor weakness, diplopia, gait disturbances, balance problems, Lhermitte's sign, vertigo, bladder problems and pain (1).

According to the definition of International Association for the Study of Pain (IASP), pain is an unpleasant emotional sensation originating from a particular area of the body, related to or not due to tissue destruction, about a person's past experiences (3). There are two main types of pain, nociceptive and neuropathic. Nociceptive pain is caused by somatic or visceral tissue damage. Neuropathic pain is caused by a lesion or disease in the somatosensory nervous system (4). The prevalence of neuropathic pain in MS was reported as 31% and lifetime prevalence of neuropathic extremity pain ranged between 12 and 28% (5).

This study aimed to evaluate and compare the subtypes of MS in terms of frequency and severity of neuropathic extremity pain.

METHODS

The study was approved by the local ethics committee of Acibadem University (17.05.2018/ATADEK-2018 7/28). Between July 2018 and January 2019 the study was conducted in a tertiary care center. Patients aged 18–75 years diagnosed as MS according to McDonald criteria were included in the study consecutively (6). Patients with other neurological diseases, head trauma, diabetes mellitus, and patients with a history of cranial or spinal surgery were excluded.

Demographic and clinical data of the patients were recorded. Detailed physical examination including sensory and motor examination was performed. Extended Disability Status Scale (EDSS) was used to evaluate disability in MS (7). Patients' pain severity was assessed by the Visual Analog Scale (VAS). For the assessment of neuropathic pain, the Leeds assessment of neuropathic symptoms and signs (LANSS) and *douleur neuropathique* 4 questions (DN4) were used. LANSS is composed of two parts including pain questionnaire and sensory testing. A score of 12 or more was classified as neuropathic pain in the LANSS scale (8, 9). DN4 questions contained both interview with and examination of the patient. The cut-off value for the diagnosis of neuropathic pain was 4/10 (10).

Statistical Analysis

The IBM SPSS Statistics 22 (SPSS IBM, Turkey) program was used for

Table 1. Clinical and demographical data of the patients

| | All Patients (n=103) | RR MS (n=85) | SP MS (n=18) | p | |
|---|---|-------------------------|-------------------------|---------------------|--------------------|
| Age (mean ± SD) (years) | 37.52±10.80 | 35.41±10.06 | 47.50±8.50 | 0.0001 ¹ | |
| Sex, M/F (%) | 28.2/71.8 | 29.4/70.6 | 22.2/77.8 | 0.380 ² | |
| Disease duration mean ± SD (min-max) (months) | 83.66±80.99 (1–360) | 65.54±65.58 (16–60) | 169.27±93.30 (1–360) | 0.0001 ³ | |
| VAS mean ± SD (median) | 4.31±2.62 (5) | 4.16±2.56 (4) | 5.0±2.86 (5) | 0.242 ³ | |
| LANSS mean ± SD (median) | 8.92±6.44 (8) | 8.43±6.23 (8) | 11.22±7.09 (11.5) | 0.133 ³ | |
| DN4 mean ± SD (median) | 3.88±2.75 (4) | 3.74±2.81 (4) | 4.55±2.43 (5) | 0.205 ³ | |
| Neuropathic pain in patient history (Yes/No) (%) | 85.4/15.6 | 83.5/16.5 | 94.4/5.6 | 0.233 ² | |
| Neuropathic pain based on LANSS and DN4 (Yes/No) (%) | 47.6/52.4 | 44.7/55.3 | 61.1/38.9 | 0.205 ² | |
| EDSS mean ± SD (median) | 2.90±1.96 (2.5) | 2.30±1.41 (2) | 5.72±1.71 (6.5) | 0.0001 ³ | |
| Localization of neuropathic pain (%) (n) | Unilateral upper extremity | 16.5 (17) | 18.8 (16) | 5.6 (1) | 0.200 ² |
| | Bilateral upper extremities | 9.7 (10) | 10.6 (9) | 5.6 (1) | |
| | Unilateral lower extremity | 9.7 (10) | 9.4 (8) | 11.1 (2) | |
| | Bilateral lower extremities | 22.3 (23) | 20 (17) | 33.3 (6) | |
| | All extremities | 12.6 (13) | 9.4 (8) | 27.8 (5) | |
| | Unilateral upper and lower extremities | 14.6 (15) | 15.3 (13) | 11.1 (2) | |

¹ Student t test.² Chi-square test.³ Mann-Whitney U test.

* Statistical tests performed for the comparison of RR MS and SP MS groups.

DN4, douleur neuropathique 4 questions; EDSS, extended disability status scale; LANSS, Leeds assessment of neuropathic symptoms and signs; F, female; M, male; MS, multiple sclerosis; RR, relapsing remitting; SP, secondary progressive; SD, standard deviation; VAS, visual analog scale.

statistical analysis. The normality of the parameters was assessed with the Kolmogorov-Smirnov test. Mean, median, standard deviation, minimum, maximum, and frequency were used as descriptive statistical methods. If the data normally distributed, the Student's t-test was used to make comparisons between the parameters, and the Mann-Whitney U test was used to make comparisons between the parameters that were not normally distributed. The chi-square test was used to compare qualitative data. For the analysis of the correlation between the parameters, the Pearson test was performed. Significance was assessed at $p < 0.05$ level, 95% confidence interval.

RESULTS

One hundred and three patients were included in the study and 29 were male and 74 were female. The mean duration of MS was 83.66±80.99 months. While RR MS was present in 82.5% of the patients, SP MS was present in 17.5% of all patients. Eighty-five percent of all patients complained of neuropathic pain, 42% of all patients had unilateral (unilateral upper extremity, unilateral lower extremity, and unilateral lower and upper extremity) neuropathic pain. According to LANSS (≥ 12) and DN4 (> 4), neuropathic pain was found in 47.6% of the patients (Table 1). When RR MS and SP MS were evaluated for the presence of neuropathic pain, 44.7% of RR MS and 61.1% of SP MS had neuropathic pain and this difference was not statistically significant (0.205) (Table 1).

When the demographic and clinical data of the patients according to the MS subtype were compared, the mean age and duration of MS diagnosis

Table 2. Comparison of pain and disability according to gender

| | Female (n=74) | Male (n=29) | p |
|--------------------------|----------------------|--------------------|----------|
| VAS mean ± SD (median) | 4.85±2.47 (5) | 2.93±2.53 (4) | 0.001* |
| LANSS mean ± SD (median) | 9.95±6.15 (9) | 6.27±6.52 (5) | 0.006* |
| DN4 mean ± SD (median) | 4.21±2.75 (4) | 3.03±2.63 (3) | 0.048* |
| EDSS mean ± SD (median) | 2.90±2.07 (2.5) | 2.89±1.68 (2.5) | 0.773* |

* Mann-Whitney U test.

DN4, douleur neuropathique 4 questions; EDSS, extended disability status scale;

LANSS, Leeds assessment of neuropathic symptoms and signs; VAS, visual analog scale.

were higher in patients with SP MS compared to RR MS. However, there was no statistical significance in pain scores according to VAS, DN4, and LANSS. Again, there was no significant difference between the two groups in terms of neuropathic pain anamnesis. (Table 1). On the other hand, when the pain scores were analyzed according to the gender; female patients had significantly higher VAS, LANSS and DN4 scores (Table 2).

When EDSS scores were evaluated, the median was 2 in RR MS and 6.5 in SP MS and this difference was statistically significant. EDSS scores were compared to the presence of the neuropathic pain according to the LANSS and DN4 and patients with neuropathic pain had higher EDSS scores but this difference was not statistically significant (Table 3). When the same analysis was performed for RR and SP MS as a subgroup, again there was no significant difference (Table 3). The correlation analysis was

Table 3. EDSS scores of MS types based on the presence of neuropathic pain

| | Neuropathic Pain Present (n=49) | Neuropathic Pain Not Present (n=54) | p |
|-----------------------|---------------------------------|-------------------------------------|--------|
| EDSS scores of RR MS | 2.48±1.64 | 2.15±1.20 | 0.298* |
| EDSS scores of SP MS | 6.28±0.90 | 5.36±2.03 | 0.459* |
| EDSS scores of all MS | 3.13±2.10 | 2.69±1.81 | 0.216* |

* Mann-Whitney U test.

EDSS, extended disability status scale; MS, multiple sclerosis; RR, relapsing remitting; SP, secondary progressive.

Table 4. Correlations between pain parameters, disease duration and disability

| | | Disease Duration | EDSS |
|-------|---|------------------|-------|
| VAS | r | 0.143 | 0.122 |
| | p | 0.151 | 0.220 |
| LANSS | r | 0.073 | 0.078 |
| | p | 0.463 | 0.431 |
| DN4 | r | -0.045 | 0.048 |
| | p | 0.651 | 0.632 |
| EDSS | r | 0.486 | - |
| | p | 0.0001 | - |

* Pearson test.

DN4, douleur neuropathique 4 questions; EDSS, extended disability status scale; LANSS, Leeds assessment of neuropathic symptoms and signs; VAS, visual analog scale.

performed between LANSS, DN4, duration of disease and EDSS, and only significant correlation was present between EDSS score and duration of disease, moderately ($p=0.0001$, $r=0.486$) (Table 4).

DISCUSSION

Relapsing-remitting MS was present in 82.5% of 103 patients and 47.6% of all patients had neuropathic pain according to LANSS and DN4. There was no significant difference between the frequencies of neuropathic pain according to the MS subtype. Mean age, duration of MS diagnosis, duration of neuropathic pain, and EDSS score were higher in patients with SP MS. There was a moderately significant correlation between EDSS score and duration of MS.

Pain in MS can be classified as 1) central neuropathic pain including dysesthetic extremity pain, trigeminal neuralgia, Lhermitte's sign, 2) painful tonic spasms, 3) back pain, and 4) headache (11). In a more recent classification, it was examined in 4 groups such as neuropathic pains, nociceptive pains, mixed pains, and other pains. Neuropathic pains consisted of dysesthetic extremity pain, trigeminal neuralgia, and Lhermitte's phenomenon. Dysesthetic extremity pain was defined as deafferentation pain secondary to lesions in the spino-thalamocortical pathways (5). A lesion of somatosensory brain regions or their connecting pathways is the cause of the neuropathic pain in MS (12). Prevalence of pain in MS is around 63%, and that it is composed of a variety of pain syndromes including neuropathic extremity pain (13). The prevalence of neuropathic extremity pain ranged between 12 and 28% and this type of pain is more common in patients with the primary progressive or the progressive-relapsing types of MS, and lowest in the relapsing-remitting type. Patients with this type of pain tend to be more disabled than those without pain (5). In this study, the prevalence of neuropathic pain was

47.6% and it was found higher compared to the aforementioned studies. However, in a recent study, 40.3% of 426 MS patients had neuropathic pain syndromes (14). The difference can be caused by the duration of the disease or the criteria used for the diagnosis. In that study, Solaro et al found that patients with pain had a higher EDSS score and a longer disease duration (14). In our study, although the patients with neuropathic pain had tendency to have a higher EDSS score, no significant correlation was detected. However, we detected a moderate correlation between EDSS and the duration of disease. Since MS is diagnosed at early ages (20–40 years) Conradsson et al. aimed to evaluate the changes in disability and its relation with disease severity over 10 years. Mean EDSS scores and patients' dependency were increased. They found this increase was more prominent in patients with moderate/severe MS (15). In our study patients with SP MS had longer disease duration and higher EDSS. Although patients with SP MS had tendency to higher neuropathic pain scores the difference was not significant. Since we included the consecutive patients who were admitted to our outpatient clinics, the percentage of patients having SP MS was low, with an increasing number of patients the difference can be more prominent. However, in our study, the percentage of patients with RR MS (82.5%) was compatible with literature (85%) (16–18).

Pain in MS was related to the older age, female gender, disease duration, concomitant mental disorders, and progressive type MS (11, 19, 20). Consistent with this data, we found that female patients had significantly higher VAS, LANSS, and DN4 but we could not detect a correlation between the disease duration and pain scores. Other than this, we did not evaluate the patients' psychiatric status such as depression which is one of the limitations of the study. The other limitation was its cross-sectional design and it had no follow-up data.

In conclusion, both types of MS had high rates of neuropathic pain and female patients had higher pain scores. Patients with SP MS had longer disease duration and they were more disabled. All patients with the diagnosis of MS should be evaluated and examined for neuropathic pain.

Ethics Committee Approval: All procedures performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the local ethics committee of AciBadem University (17.05.2018/ATADEK-2018 7/28). The manuscript has three authors and each author is responsible for the content and writing of the paper.

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