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Investigation of The Effect of Multiple Sclerosis on Peripheral Nerves

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ABSTRACT

Multiple sclerosis is an autoimmune central nervous system disease characterized by inflammation, demyelination and axon damage. The aim of this study was to determine peripheral nerve involvement and related factors in patients with multiple sclerosis.

In our study, 35 (70.0%) of the patients were suffering from Relapsing Remitting Multiple Sclerosis, and 15 (30.0%) of them had Secondary Progressive Multiple Sclerosis. The mean age of the symptom onset of the disease in patients was 30.44 ± 1.06 years, the mean score of the Multiple Sclerosis Disability Scale (EDDS) was 2.97 ± 2.58 points

Polyneuropatia was detected in 12 (24.0%) patients. Polyneuropathy was detected in 3 patients (6.0%) in the control group. In our study, peripheral nerve involvement was higher in male patients than female patients. There was a very strong positive correlation between the duration of disease development and the Extended Multiple Sclerosis Disability Scale scores.

In the study, it was determined that multiple sclerosis was more commonly seen in women in accordance with the literature, and EDDS scores increased as the disease duration increased.

Keywords: Multiple sclerosis, perpheral nerves, polyneuropathies

Introduction

Multiple sclerosis (MS) is a chronic neurodegenerative disease of the central nervous system (CNS). Characterized by demyelinating, inflammatory, astrogliosis and axonal degeneration (1). Although its etiology is not clearly known, it has been proven by recent studies that there are many autoimmune mechanisms in its etiopathogenesis and that they cause axonal damage and demyelination (2). The age of Multiple Sclerosis (MS) is usually observed between the ages of 15-50. It is two times more common in women than in men (3). Turkey is located in the transition zone between Northern Europe, where MS is common, and Asia, where it is rare. Its incidence is estimated to be 1/2000-2500 in our country (4).

Although Multiple Sclerosis disease, which has a very complex immunopathogenesis and is still not clearly clarified, primarily affects the gray matter and cortex, primarily the white matter of the Central Nervous System. Physical examination findings compatible with the involvement of peripheral nerves can also be seen. Cases suggesting peripheral nervous system involvement such as sensory loss, DTR loss and muscle atrophy have been reported in some studies (5,6).

In this study, we selected patients who had no clinical complaints of peripheral nerve involvement, possible peripheral nerve involvement and damage to the peripheral nerves in 35 Relapsing Remitting Multiple Sclerosis and 15 Secondary Progressive Multiple Sclerosis patients followed by our clinic. In addition, we planned this study in order to analyze it by comparing it with 50 volunteers who applied to our clinic without any signs of peripheral nerve involvement or complaints and to determine whether there was a significant effect.

Focal inflammation, demyelination, remyelination, loss of oligodendrocyte and reactive astrogliosis were detected in the histopathological examination of MS plaques (7).

The importance of B cells in the pathogenesis of the disease has been emphasized in studies (8). Studies of B cells; antigen retention and presentation of this antigen to T cells, cytokine synthesis, demyelination, tissue destruction and remyelination suggest that they are also to blame (9).

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McDonald criteria are used in Multiple Sclerosis. In 2017, these criteria were re-evaluated and some revisions were made. It was emphasized that the number of all plaques is important without the symptomatic/asymptomatic distinction. It was added in cortical plaques to the juxtacortical plaques, one of the four regions in the central nervous system. The number of plaques, which should be at least 1 in the periventricular region, was rearranged as three. OCD positivity examined in the cerebrospinal fluid was added to the time extension criteria.

It is a clinical condition that occurs with joint and widespread damage to peripheral nerves due to similar-same causes and pathophysiological processes. If the cell body is affected first, neuronopathy is mentioned, if there is axon damage first, axonopathy is mentioned, and if there is myelin cover damage on the nerve fibers first, myelinopathy is mentioned.

Diagnosis in polyneuropathies is made by detecting the presence of polyneuropathy in the patient and then scanning for the etiology. The main purpose here is to detect polyneuropathies that can be treated, and for this purpose, after detecting the polyneuropathy in the patient, it is necessary to determine the etiology using clinical and laboratory methods. Laboratory examinations electrophysiological tests nerve biopsy, skin biopsy, other laboratory examinations are performed in the diagnosis of polyneuropathies (10).

Materials and Methods

Our study included 50 patients with a diagnosis of Multiple Sclerosis, aged between 19 and 68 years, who applied to the Neurology Outpatient Clinic of Van Yüzüncü Yıl University Dursun Odabaş Medical Center between 20.08.2018 and 20.12.2018, and 50 healthy individuals for the control group. Participants of the study were informed and a voluntary consent form was filled. Permission for this study was obtained from Van Yüzüncü Yıl University Clinical Research Ethics Committee with the decision no. 02 dated 01.08.2018. Individuals who applied to our outpatient clinic but had chronic renal failure, vitamin B12 deficiency, diabetes mellitus, vitamin D deficiency, oncological disease and MS-like disease were not included in the study.

Within the scope of the study, individuals gender, age, expanded multiple sclerosis disability scale (EDDS). MS type, how many years they have had MS, radiological involvement localizations of MS lesions, number of attacks, last drugs used, sensory median amplitude (DMA), sensory median velocity (DMH), sensory ulnar amplitude (DUA), sensory ulnar velocity (DUH), sensory sural amplitude (DSA), sensory sural velocity (DSH), sensory supperoneal amplitude (DSPA), sensory supperoneal velocity (DSPH), median motor amplitude 1- 2 (MMA1-2), median motor speed (MMH), motor ulnar amplitude 1-2 (MUA1-2), motor ulnar velocity (MUH), motor common peroneal amplitude 1-2 (MCPA1-2), motor common peroneal velocity (MCPH), motor tibial amplitude 1-2 (MTA 1-2), and motor tibial velocity (MTH) variables were collected

Statistical Analysis: The analysis of the data obtained within the scope of the study was carried out using SPSS (Statistical Packages for the Social Sciences) version 22.0 package program. Descriptive statistics suitable for the data were obtained; number and percentage distributions are given with mean, standard deviation bar chart.

In the study, whether the numerical variables showed normal distribution or not was evaluated with the Kolmogorov - Smirnov Test. In the study, Mann Whtney U Test, a nonparametric test, was used to compare categorical variables with non-normally distributed numerical variables, and Student's T-Test, a parametric test, was used for comparison with normally distributed numerical variables. Fisher-Exact Chi-square Test was used to compare categorical variables with each other. The relationship between disease duration and EDSS skore was evaluated with the Spearman Correlation Test. Statistical significance level was accepted as $p < 0.05$ in the study.

Results

Our study included 50 patients with Multiple Sclerosis, aged between 19 and 68 years, who applied to Van Yüzüncü Yıl University Dursun Odabaş Medical Center Neurology Polyclinic between 20.08.2018 and 20.12.2018, and 50 healthy individuals for the control group, and the data obtained from these individuals were evaluated.

It was determined that the mean age of the individuals participating in the study was 39.02±9.61 years, the mean age of women was 38.15±9.23 years, and the mean age of men was 40.70±10.24 years. It was determined that 36 (72.0%) of the patient group included in the study were female, 14 (28.0%) were male, while 30 (60.0%) of the healthy group were female and 20 (40.0%) were male.

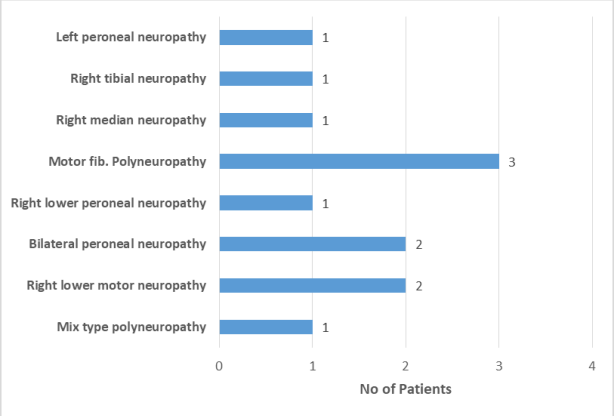

Fig. 1. Distribution of Polyneuropathy by EMG Results of the Patients

Of the cases included in the study, 35 (70.0%) had Relapsing Remitting Multiple Sclerosis and 15 (30.0%) had Secondary Progressive Multiple Sclerosis. The mean age of symptom onset of the patients participating in the study was 30.44±1.06 years, the mean duration of multiple sclerosis diagnosis was 8.70±7.40 years, the mean number of multiple sclerosis attacks was 3.52±2.99, and the mean Extended Multiple Sclerosis Disability Scale (EDDS) score was 2.97±2.58. According to the EMG results, 12 of them (24.0%) were found to have polyneuropathy. Polyneuropathy was detected in 3 people (6.0%) in the control group. The distribution of peripheral nerve involvement according to the EMG results of the patients is shown in Figure 1.

When the polyneuropathy status of the patients included in the study was evaluated according to the number of attacks; It was determined that the mean number of attacks in patients with polyneuropathy was 2.83±2.65 and the mean number of attacks in patients without polyneuropathy was 3.77±3.09 and the difference was not statistically significant (p=0.149) (Table 1).

When the relationship between polyneuropathy status and age of the patients included in the study was evaluated, it was determined that the mean age of the patients with polyneuropathy was 39.58±7.63 and the mean age of the patients without polyneuropathy was 38.97±9.99, and the difference was not statistically significant (p=0.847) (Table 1).

When the polyneuropathy status and disease development time of the patients included in the study were evaluated, it was determined that the MS disease duration of the patients with polyneuropathy was 11.0±1.79 years and the MS disease duration of the patients without polyneuropathy was 7.97±1.24 years, and the difference was not statistically significant (p=0.100) (Table 1). The distribution of polyneuropathy types according to the drug used by the patients included in the study is given in Table 2.

When the polyneuropathy status and age groups of the patients included in the study were evaluated in decades, 18.2% of the patients aged 20-30, 23.5% of the patients aged 31-40, 29.4% of the patients aged 41-50, and 24.0% of the patients aged 51-60 years had polyneuropathy, and the difference between the age groups was not found to be statistically significant (p=0.914) (Table 3).

When the relationship between polyneuropathy status and radiological involvement of the patients included in the study was evaluated, 18.2% of the patients aged 20-30, 23.5% of the patients aged 31-40, 29.4% of the patients aged 41-50, and 24.0% of the patients aged 51-60 years had polyneuropathy and the difference between the age groups was not found to be statistically significant (p=0.914) (Table 3).

When the polyneuropathy status and EDDS scores of the patients included in the study were evaluated. It was determined that the mean EDDS score of the patients with polyneuropathy was 3.20±2.50, the mean of the EDDS score of the patients without polyneuropathy was 2.89±2.64, and the difference was not statistically significant (p=0.661). It was determined that there was a very strong positive correlation between disease duration and EDDS score in the patients included in the study, and this correlation was statistically significant (p<0.001, r=0.784).

Discussion

In the study of Vukusic et al. it was reported that the ratio of females to males in terms of gender distribution in multiple sclerosis was 2.0, and in the study of Atilla et al. the ratio of females to males was 1.1 in SPMS (3,14). In the prevalence study conducted by Millefiorini et al. the female-to-male ratio was found to be 2.6 in patients with multiple sclerosis (15). In our study, the female-male ratio was found to be 2.6 in all patients and 1.1 in SPMS patients. While the findings of the study were consistent with the study findings of Atilla and Millefiorini et al. they were not found to be compatible with the study findings of Vukusic et al. (3,14,15).

In the study by Kister et al. the mean age of the patients was found to be 37.3, and in the study by Baklacıoğlu et al. it was found to be 42.1. In our

Table 1. Evaluation of Polyneuropathy Status and Number of Attacks

Variable	Polyneuropathy		z/t	p*
	Yes	No		
Attacks	2.83±2.65	3.77±3.09	-1.442	0.149*
Age	39.58±7.63	38.97±9.99	0.194	0.847**
Disease duration	11.0±1.79	7.97±1.24	-1.645	0.100*

*Mann Whtney U Testi, **Student T Test

Table 2. Distribution of Polyneuropathy Types by Drug Used

Polyneuropaty	Number of Patients Using the Drug										
	Glatiramer Asetat	Interferon beta 1 b	Fingolimod	Natalizumab	Teriflunamid	Interferon beta 1a	Dimetil Fumarat	Azatiopürin	Mitoksantron	Metotreksat	Okrelizumab
Left Peroneal Neuropathy		1									
Right Tibial Neuropathy		1									
Right Median Neuropathy		1									
Motor Fib. Polyneuropathy	1	1	1		1	2		1			
Right Peroneal Neuropathy	1	1	1	1		1					
Bil Peroneal Neuropathy			1	1		2					
Right Lower Motor Neuropathy	1		1					1			1
Mix Type Neuropathy	1					1		1		1	
Total	4	5	4	2	1	6	0	3	0	1	1

study, the mean age of the patients was found to be 39.1 (16,17). In the study of Vukusic et al. the age of symptom onset was 30, in the study of Kister et al. it was 31, and in the study of Atilla it was stated that it was 29.5 (3,14,16). et al. reported that patients with multiple sclerosis are most frequently between the ages of 35-44 in terms of age groups (15,18). Similar to the studies conducted in our study, it was determined that the most common age group of multiple sclerosis patients was the 35-44 age group (36.0%).

Baklacıoğlu et al. reported that 56.6% of the patients had Relapsing Remitting Multiple Sclerosis and 23.3% of them had Secondary Progressive Multiple Sclerosis (17). In the study conducted by Confavreux and Vukusic, it was determined that 58% of the patients had Relapsing Remitting Multiple Sclerosis and 27% of them had Secondary Progressive Multiple Sclerosis (7). In our study, 70.0% of the patients had Relapsing Remitting Multiple Sclerosis and 30.0% of them had Secondary Progressive Multiple Sclerosis.

Kaya Aygünoğlu et al. reported that the mean EDSS score was 2.86 in the study conducted on patients with multiple sclerosis, and the mean EDSS score was 3.91 in Baklacıoğlu's study (17,19). In the prevalence study conducted by Brola et al. the mean EDSS score was found to be 3.40 (18). In our study, it was observed that the mean EDSS score of the patients was 2.97 (19). In the study of Pittock et al. it was stated that the EDSS score increased as the duration of the disease increased (20). In the study conducted by Atila, it was determined that the EDSS score increased as the duration of the disease increased (14). In our study, a very strong positive correlation was found between the EDSS score and the duration of the disease, similar to the studies conducted.

Table 3. Comparison of Polyneuropathy Status with Age, Gender, Radiological Involvement and MS Types

Variable		Polyneuropathy		p*
		Yes (%)	No (%)	
Age	20-30	2 (%18.2)	9 (%81.8)	0.914
	31-40	4 (%23.5)	13 (%76.5)	
	41-50	5 (%29.4)	12 (%70.6)	
	51-60	1 (%20.0)	4 (%80.0)	
Gender	Female	6 (%16.7)	30 (%83.3)	0.05
	Male	6 (%42.9)	8 (%57.1)	
Radiological involvement	Cortical +	6 (%22.2)	21 (%77.8)	0.750
	Cortical -	6 (%26.1)	17 (%73.9)	
	Infratentorial +	4 (%33.3)	8 (%66.7)	0.385
	Infratentorial -	8 (%21.1)	30 (%78.9)	
	Spinal +	8 (%29.6)	19 (%70.4)	0.313
	Spinal -	4 (%17.4)	19 (%82.6)	
MS Types	RRMS	8 (%22.9)	27 (%77.1)	0.773
	SPMS	4 (%26.7)	11 (%73.3)	

*Fisher-exact testi

In the study of Sarova-Pinhas et al. it was determined that 14.7% of multiple sclerosis patients had polyneuropathy (21). In our study, it was found that 24.0% of the patients had polyneuropathy. The higher frequency of polyneuropathy in our study may be due to the different sample size. In the study of Hanewinckel et al. 29 studies were reviewed and it was stated that the frequency of polyneuropathy ranged from 0.1-3.3% in these studies (22). In the study conducted by Burns and Mauermann, it was reported that the frequency of polyneuropathy varies between 2-3% (23). In our study, the frequency of polyneuropathy was found to be 6.0% in the control group, and the current prevalence seems to be above the expected results.

In the study conducted by Emad et al. it was reported that there was a difference between the patient and control groups between median and tibial nerve involvement in patients with multiple sclerosis (24). In our study, eight different peripheral nerve involvements were defined in terms of polyneuropathy as a result of the evaluations, and no statistically significant difference was detected. It can be said that the finding of peripheral nerve involvement in many different regions according to the number of samples was effective in this result.

In our study, the mean age of patients with polyneuropathy (39.58±7.63) was found to be higher than the mean age of patients without polyneuropathy (38.97±9.99). In the study by Misawa et al. it was stated that epitope spread during the long prone of multiple sclerosis may play a role in the pathogenesis of polyneuropathy in multiple sclerosis (25). It is thought that the mean age of patients with polyneuropathy was higher due to the higher EDSS score of patients with longer disease duration in our study and the disease prognosis process reported in the study by Misawa et al.

The ratio of women to men in multiple sclerosis increases markedly because the disease is more commonly observed in women (24). In our study, it was determined that multiple sclerosis was more common in women, but the incidence of polyneuropathy was higher in men than in women, and the difference was statistically significant. This finding suggests that being male should be considered as a determining risk factor for polyneuropathy in patients with multiple sclerosis.

In our study, it was determined that the incidence of polyneuropathy in patients with multiple sclerosis and the incidence of polyneuropathy in the control group were higher than in previous studies (21,22,23). This may be related to modifiable risk factors such as environmental, genetic and epigenetic factors, vitamin D level, smoking and obesity, among the causes of multiple sclerosis (24). However, Misawa et al. in his study, reported that the incidence of polyneuropathy in multiple sclerosis was around 5%, and that it was not a common condition but it was a treatable condition.

As a result of the study, in accordance with the literature, multiple sclerosis patients were seen mostly in women, EDSS scores increased as the duration of the disease increased, and a very strong positive correlation was found between the EDSS score and the duration of the disease.

The small number of patients participating in the study creates a limitation in interpretation in terms of comparison with other studies. Further results can be obtained with larger studies by increasing the sample, which includes modifiable factors that cause multiple sclerosis, such as vitamin D level, smoking and obesity, in further studies.

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