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Evaluation of the effect of cervical cord lesion on upper extremity function in newly diagnosed persons with multiple sclerosis running head: upper extremity function in multiple sclerosis

Yeni teşhis konulan multipl sklerozlu bireylerde servikal omurilik lezyonunun üst ekstremite fonksiyonu üzerindeki etkisinin değerlendirilmesi

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ABSTRACT

Aim: To evaluate the effect of cervical cord lesions on upper extremity functions in persons with very early-stage multiple sclerosis (MS) and describe the factors that affect the upper extremity functions in that population.

Materials and Methods: Two hundred forty-five persons with MS (pwMS) were diagnosed 24 months after the first symptoms and three hundred seventy-eight pwMS initiated disease-modified treatment (DMT) within six months after diagnosis were included to study. Nine-Hole Peg Test (N-HPT) were performed to evaluate upper extremity functions. Participants divided two groups according to presence of cervical cord lesion.

Results: There were no significant differences between groups in terms of age, gender, disease duration, and the number of relapses. However, the total Expanded Disability Status Score (EDSS) score, pyramidal and sensory functional system scores were higher in pwMS with cervical cord lesions than without cervical cord lesions. Average and dominant hand N-HPT performance times were found significantly longer in pwMS with cervical cord lesion than without cervical cord lesion in participants-initiated DMT within six months after diagnosis. However, there were no significant differences between groups in participants diagnosed 24 months after first symptoms Age, disease duration, and time from diagnosis to treatment were identified as significant factors influencing N-HPT performance. PwMS who were younger, had a shorter disease duration, and received treatment sooner after diagnosis showed better performance than others.

Conclusion: Our study highlights the influence of cervical cord lesions on upper extremity function, even in the early stages of MS, and underscores the importance of early diagnosis and prompt initiation of DMTs.

Keywords: Multiple sclerosis, Upper extremity functions, cervical cord lesion, early diagnosis

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ÖZ

Amaç: *Çok erken evre multipl skleroz (MS) hastalarında servikal kord lezyonlarının üst ekstremite fonksiyonları üzerindeki etkisini değerlendirmek ve bu popülasyonda üst ekstremite fonksiyonlarını etkileyen faktörleri tanımlamak.*

Gereç ve Yöntem: *Çalışmaya 245 ilk semptomlardan 24 ay geçmiş ve 378 tanıdan sonraki altı ay içinde hastalık modifiye edici tedaviye (DMT) başlamış MS'li bireyler dahil edilmiştir. Üst ekstremite fonksiyonlarını değerlendirmek için Dokuz Çivi Peg Testi (N-HPT) uygulanmıştır. Servikal kord lezyonunun varlığına göre katılımcılar iki gruba ayrıldı.*

Bulgular: *Gruplar arasında yaş, cinsiyet, hastalık süresi ve atak sayısı açısından anlamlı bir fark bulunmamıştır. Ancak, toplam Genişletilmiş Engellilik Durumu Ölçeği (EDSS) skoru, piramidal ve duyusal fonksiyonel sistem skorları, servikal kord lezyonları olan MS'li bireylerde olmayanlara göre daha yüksek bulunmuştur. Tanıdan sonraki altı ay içinde DMT başlatılan katılımcılarda, dominant ve ortalama N-HPT performans süreleri, servikal kord lezyonu olan MS'li bireylerde olmayanlara göre anlamlı derecede daha uzun bulunmuştur. Ancak, ilk semptomlardan 24 ay sonra tanı konulan katılımcılar arasında gruplar arasında anlamlı bir fark gözlenmemiştir. Yaş, hastalık süresi ve tanıdan tedaviye kadar geçen süre, N-HPT performansını etkileyen önemli faktörler olarak belirlenmiştir. Daha genç, daha kısa hastalık süresine sahip ve tanı sonrası daha erken tedavi alan MS'li bireyler, diğerlerine göre daha iyi performans göstermiştir.*

Sonuç: *Çalışmamız, MS'in erken evrelerinde bile servikal kord lezyonlarının üst ekstremite fonksiyonları üzerindeki etkisini vurgulamakta ve erken tanı ile DMT'lerin hızlı bir şekilde başlatılmasının önemini ortaya koymaktadır.*

Anahtar Sözcükler: *Multipl skleroz, üst ekstremite fonksiyonları, servikal kord lezyonu, erken tanı*

INTRODUCTION

Although no studies specifically evaluated the prevalence of upper extremity disability in multiple sclerosis (MS), Johansson et al., on the magnitude of the problem, reported that up to 79% of dexterity difficulties were present in both the dominant and non-dominant hand (1). However, upper extremity dysfunction is less well-known than gait impairment, probably because the Expanded Disability Status Scale (EDSS), the most used measure of disability in MS, predominantly focuses on lower extremity function (2). The poor understanding of the disability in upper extremity functions in patients with MS (pwMS) has several negative effects. In particular, studies in older adults and disease populations such as stroke have shown that reduced grip strength is predictive of worse health, loss of independence, and increased morbidity and mortality (3,4). In pwMS, dexterity assessed using the Nine-Hole Peg Test (N-HPT) is a risk indicator for activity and participation restrictions, such as the ability to perform activities of daily living. In addition, it has been shown that the increase in upper extremity disability negatively affects independence and quality of life (5). Even in early-stage MS, mild upper extremity dysfunction may be present that will affect the performance of manipulation tasks and the ability to perform activities of daily living. This study included pwMS with EDSS<4 and disease duration<4 years (6). However, there is no research on newly diagnosed pwMS that demonstrates upper extremity functions.

MS is a complex neurological disorder characterized by a wide range of deficits and clinical outcomes, with cervical cord lesions being associated with functional limitations in upper extremity performance. Although focal spinal cord abnormalities are seen in most pwMS, the cervical region is more frequently affected than the thoracic and lumbar regions. Structural abnormalities in the spinal cord can be expected to affect patients' functional outcomes dramatically. However, the correlation between the number of focal spinal cord lesions and the degree of disability is uncertain (7). Lukas et al. evaluated 440 pwMS (311 relapsing-remitting MS, 92 secondary progressive [SP] MS, and 37 primary progressive [PP] MS) in terms of the presence of cervical cord lesions and their relationship to disability. As a result, they showed that pwMS with cervical cord lesions had a longer N-HPT. The mean disease duration of participants included in the study was ten years (8). There is no information about the existence of this relationship in persons with newly diagnosed MS.

Therefore, the study mainly aims to evaluate the effect of cervical cord lesions on upper extremity

functions in persons with very early-stage MS and describe the factors that affect the upper extremity functions in that population.

MATERIALS and METHODS

Participants

In this retrospective cross-sectional study, we evaluated the data collected from the baseline assessments of an ongoing study entitled, "Follow-up of physical, psychosocial and cognitive influences in persons with multiple sclerosis: a prospective cohort study" (ClinicalTrials.gov Identifier: NCT03878836) in Outpatient MS Clinic of Dokuz Eylül University Hospital, Izmir, Turkey. The Noninvasive Research Ethics Board of Dokuz Eylül University approved the study protocol (Protocol number: 7163-GOA, Approval Number: 2022/24-12, and Approval Date: 27.07.2022). All procedures performed in the study followed the provisions of the Declaration of Helsinki (as revised in Brazil 2013), and informed consent was obtained from all participants involved in the study. The data were subtracted from a patient registry electronic system called iMed (Version 6.1; Merck Serono SA, Geneva, Switzerland).

Inclusion criteria included a senior MS neurologist-confirmed diagnosis of definite MS according to 2017 McDonald criteria 24 months after first symptoms and/or initiate disease-modified treatment (DMT) within six months after diagnosis. In this line, EDSS scores below 2.0 and disease duration below 2 years were included in the study and described as people with very early stage of MS. These pwMS were divided into two groups: diagnosed 24 months after the first symptom (FS24) and time since the diagnosis to treatment no longer than 6 months group (DT6). Exclusion criteria included having a relapse within 30 days, being diagnosed with a neurological disease other than MS, having any severe cognitive disorder hindering test instructions, and being unable to follow instructions in Turkish. Besides these, patients who had a relapse between their initial presentation and the tests were excluded from the FS24 group.

Outcome Measures

Demographic and clinical characteristics (gender, age, MS course, and disease duration [time to first symptom to evaluation day]) were used as baseline data. The EDSS scoring, as the universal measure of the disability level in pwMS, is performed according to the neurological examination of seven functional systems (cerebellar, pyramidal, sensory, brainstem, bladder and bowel, visual, and cerebral). The ambulatory state of the patients is also recorded (9). A neurologist examined all patients and also calculated the EDSS scores.

The N-HPT is a valid, reliable, and widely used tool to measure finger dexterity in pwMS (5). Moreover, it is recommended as a gold standard test for upper extremity function. Also, N-HPT is the most utilized measure in 63% of studies on the upper extremity function. Test materials consist of nine holes on a flat, a small test battery, and nine matching rods. The subjects are asked to take the sticks one by one from the chamber in the test battery and place them into the holes on the battery, then take the sticks out of the holes and put them back into the chamber. Two repetitions are performed for both extremities, and the score is recorded.

The participants in the FS24 group were evaluated in the first month of diagnosis, and participants in the TD6 group were evaluated in the first month after the DMT started (Figure-1).

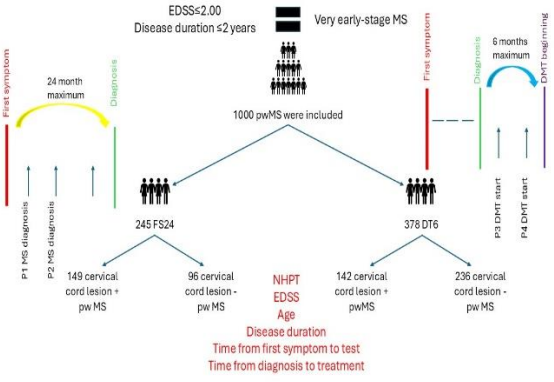


Figure-1. Flow diagram of the study.
EDSS= Expanded Disability Status Scale, MS=Multiple Sclerosis, P=Participant, pwMS=people with MS, DMT=Disease-modifying treatment, FS24= First symptom to MS diagnosis less than 24 months
DT6= Diagnosis to beginning of DMT less than 6 months, NHPT=Nine hole peg test

Procedure

Each patient who came to the MS Unit for routine control was evaluated regarding inclusion and exclusion criteria. Patients who met the criteria were included in the study after obtaining informed consent. Experienced neurologists then evaluated

the patients' 1.5 T MR images. Cervical cord demyelinating lesions were recorded. The neurologists evaluating etic resonance imaging (MRI) sections were unaware of the patient's clinical condition and test results. On the contrary, clinicians who examined the patients were unaware of the patient's MRI results.

Data Analysis

The data were analyzed using IBM SPSS Statistics (Version 25.0, Armonk, NY: IBM Corp.). The normality of data distribution was assessed with the Kolmogorov-Smirnov test and visualized using histograms. Continuous variables that do not show normal distribution were presented as medians and interquartile ranges, while normal distributed variables were presented as mean and standard deviation. Categorical variables were reported using frequencies and percentages. An independent sample t-test was performed to compare clinical and demographic factors between the groups (pwMS with and without cervical lesions). The Mann-Whitney U test was used to compare N-HPT performance. Effect sizes (ES) for between-group comparisons were calculated using Cohen's d and interpreted as small (0.2), medium (0.5), and large (0.8), following Kilic (10). Linear logistic regression was performed to determine which factors affect N-HPT performance in all participants (FS24 and TD6). A significance level of $p < 0.05$ was applied.

RESULTS

One thousand pwMS were included in the mentioned ongoing study. Two hundred forty-five were diagnosed 24 months after the first symptoms, while three hundred seventy-eight initiated disease-modified treatment within six months after diagnosis. All analyses were performed for both data sets. The participants were divided into two groups according to the presence of cervical cord lesions. Out of 245 pwMS diagnosed 24 months after the first symptoms, cervical cord lesions were detected in 149 (60.82%). There were no significant differences between groups regarding age, gender, disease duration, and the number of relapses. However, the total EDSS score and pyramidal and sensory functional system scores were higher in pwMS with cervical cord lesions than without cervical cord lesions. Detailed information regarding the characteristics of the participants is presented in (Table-1).

The presence of cervical cord lesions was identified in 142 pwMS among 378 who initiated disease-modified treatment within six months after diagnosis. The differences between groups were determined regarding age, time since diagnosis to treatment, number of relapses, EDSS score, and pyramidal and sensory functional system scores (Table-2).

Average and dominant hand N-HPT performance times were significantly longer in pwMS with cervical cord lesions than without cervical cord lesions in participants-initiated disease-modified treatment within six months after diagnosis. However, there were no significant differences between group participants diagnosed 24 months after the first symptoms (Table-3).

Both FS24 and TD6 groups are included for regression analysis. Age, disease duration, and time from diagnosis to treatment significantly influenced N-HPT performance. PwMS who were younger had a shorter disease duration and received treatment sooner after diagnosis and showed better performance than others (Table-4).

Table-1. Comparison of characteristics of the study sample (diagnosed in 24 months after first symptoms) (*n* = 245)

	pwMS with cervical cord lesion (n=149)	pwMS without cervical cord lesion (n=96)	p- Value
Age, years	32.51 (9.72)	30.41 (9.36)	0.095
Gender			
Female/Male, n (%)	98/51 (65.8/34.2)	74/22 (77.1/22.9)	0.059
Disease Duration, months	7.62 (6.07)	6.20 (5.63)	0.066
Number of relapses	1.39 (0.59)	1.28 (0.50)	0.138
EDSS score, range between 0-10	1.05 (0.93)	0.68 (0.79)	**0.002**
Pyramidal	0.52 (0.68)	0.25 (0.56)	**0.001**
Cerebellar	0.05 (0.34)	0.03 (0.23)	0.573
Brainstem	0.08 (0.32)	0.07 (0.30)	0.852
Sensory	0.66 (0.66)	0.30 (0.53)	**<0.001**
Visual	0.16 (0.42)	0.16 (0.39)	0.928

Table-2. Comparison of characteristics of study sample (time since diagnosis to treatment no longer than 6 months) (*n* = 378)

	pwMS with cervical cord lesion (n=142)	pwMS without cervical cord lesion (n=236)	p- Value
Age, years	34.43 (10.95)	31.62 (9.41)	**0.011**
Gender			
Female/Male, n (%)	98/51 (65.8/34.2)	74/22 (77.1/22.9)	0.059
Time from diagnosis to treatment, months	0.20 (0.61)	0.11 (0.53)	0.145
Disease Duration, months	3.02 (5.27)	1.95 (3.25)	**0.030**
Number of relapses	1.51 (1.04)	1.71 (0.83)	**0.035**
EDSS score, range between 0-10	1.17 (1.16)	0.71 (0.80)	**<0.001**
Pyramidal	0.61 (0.78)	0.31 (0.60)	**<0.001**
Cerebellar	0.06 (0.36)	0.02 (0.19)	0.191
Brainstem	0.11 (0.38)	0.08 (0.29)	0.446
Sensory	0.71 (0.73)	0.34 (0.56)	**<0.001**
Visual	0.13 (0.38)	0.13 (0.36)	0.867

Table-3. Differences between pwMS with and without cervical cord lesion in terms of N-HPT performance

	Participants initiated disease-modified treatment within six months after diagnosis			
	pwMS with cervical cord lesion (n=142)	**pwMS without cervical cord lesion (n=236)**	**Cohen's d**	**p**
N-HPT (dominant hand), s	19.73 (17.65 – 21.73)	18.77 (17.39 – 20.66)	-0.252 (-1.84; -0.174)	**0.015**
N-HPT (non-dominant hand), s	20.66 (18.91 – 22.95)	20.04 (18.65 – 22.25)	-0.0305 (-1.52; 1.13)	0.110
N-HPT (average), s	20.34 (18.48 – 21.97)	19.56 (18.14 – 21.23)	0.127 (-1.13; -0.030)	**0.038**
	Participants diagnosed in 24 months after first symptoms			
	pwMS with cervical cord lesion (n=149)	**pwMS without cervical cord lesion (n=96)**	**Cohen's d**	**p**
N-HPT (dominant hand), s	19.48 (17.61 – 21.44)	18.69 (17.41 – 20.43)	-0.223 (-1.51; 0.109)	0.052
N-HPT (non-dominant hand), s	20.18 (18.69 – 22.40)	19.90 (18.62 – 22.22)	-0.105 (-1.31; 0.553)	0.507
N-HPT (average), s	20.0 (18.32 – 21.59)	19.25 (18.10 – 20.95)	-0.171 (-1.35; 0.275)	0.142

Table-4. Risk factors on N-HPT test performance

Risk Factors	Beta Coefficient	95% CI	P value
Age, years	0.228	0.053; 0.143	**<0.001**
Presence of cervical cord lesions	-0.043	-1.270; 0.482	0.377
Number of relapses	-0.036	-0.661; 0.306	0.470
EDSS score	0.037	-0.699; 1.016	0.716
Pyramidal	0.155	-0.022; 1.930	0.055
Sensory	0.056	-0.620; 1.346	0.468
Disease duration	0.116	0.010; 0.215	**0.032**
Time from diagnosis to treatment, months	0.144	0.391; 1.811	**0.002**

DISCUSSION

The primary finding of this study is that upper extremity function in very early stages of MS may be influenced by age, disease duration, and the time between MS diagnosis and treatment initiation. Interestingly, cervical cord lesions did not appear to impair N-HPT performance as initially anticipated significantly. However, in individuals with very early-stage MS, those with cervical cord lesions displayed higher EDSS scores and increased pyramidal and sensory functional system scores, consistent with previous studies on MS disability progression.

Previous research highlights that upper extremity complaints tend to worsen over time in MS (11). Poor manual dexterity is frequently observed in patients with higher disability levels and progressive forms of MS (2,11,12). Notably, even among patients with low EDSS scores, mild impairments in upper extremity function are common (13). For instance, Bertoni et al. (2) demonstrated that 38% of MS patients with mild impairment levels (EDSS < 4) and a disease duration of around 10 years showed reduced upper limb performance. Our study aimed to assess whether upper extremity function is compromised at the very early stages of MS and to identify contributing factors.

Our findings indicate that N-HPT performance may be influenced by the time between diagnosis and assessment, as well as by patient age and the time from diagnosis to the initiation of DMT. These results reinforce the importance of early diagnosis and timely initiation of DMTs in managing MS. Initiating treatment promptly upon diagnosis could potentially play a crucial role in preserving upper extremity functions. This insight underscores the clinical importance of early MS diagnosis and treatment, especially in light of the newly revised 2024 McDonald diagnostic criteria, which aim to facilitate earlier diagnosis (14).

Interestingly, our findings did not reveal a direct correlation between N-HPT performance and EDSS scores, relapse number, or cervical cord lesions. This could be due to the characteristics of our study population, which consisted mostly of patients with very early-stage MS and, therefore, lower overall disease burden. Despite mild structural impairments, these patients may possess compensatory mechanisms that help maintain upper extremity function.

Additional insights into the potential impact of brain lesion load and brain volume on upper extremity function could complement our understanding of functional impairment in MS. Previous studies have suggested that cervical cord atrophy, rather than lesion volume or count, might be a stronger predictor of upper extremity performance and overall disability in MS patients (8,15,16). While we classified patients based on the presence of cervical cord lesions, we did not measure lesion volume or number, which could provide further insights. Future studies incorporating lesion quantification in cervical MRI could enhance our understanding of the mechanisms by which these lesions impact function.

Despite the valuable insights, this study has limitations that warrant consideration. First, the using a 1.5 T MRI scanner may have limited our ability to detect smaller cervical cord lesions, potentially underestimating the prevalence and impact of these lesions. Employing higher-resolution MRI, such as 3 T or 7 T, in future studies could provide a more detailed assessment of cervical cord pathology. Additionally, the N-HPT captures dexterity but may not fully represent

other upper extremity functions, such as muscle strength, sensation, or coordination, which are also important in MS. Including these additional measures in future research could offer a more comprehensive view of upper limb impairments.

CONCLUSION

In conclusion, our study highlights the influence of cervical cord lesions on upper extremity function, even in the early stages of MS, and underscores the importance of early diagnosis and prompt initiation of DMTs. Further studies are needed to explore the relationships between lesion characteristics, treatment timing, and upper extremity performance in greater detail. This approach could lead to more targeted interventions to preserve upper extremity function and improve quality of life in pwMS.

Ethical Approval: Ethical approval was obtained from the Ethics Committee of Non-Interventional Clinical Trials of Dokuz Eylül University with the Protocol number: 7163-GOA, Approval Number: 2022/24-12, and Approval Date: 27.07.2022.

Conflict of Interest: There are no financial, personal, or professional interests related to this article.

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