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Araştırma

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Relationship Between Fatigue, Cognitive Functions, Depression, and Disability in Multiple Sclerosis Patients

Multipl Sklerozlu Hastalarda; Yorgunluk, Kognitif Fonksiyonlar, Depresyon ve Özürlülük İlişkisi

Gökçe Zeytin Demiral[1]

[1] *Afyonkarahisar University of Health Sciences, Faculty of Medicine, Department of Neurology, Afyonkarahisar, Turkey*

ABSTRACT

Aim: Multiple Sclerosis (MS) is a chronic, progressive, and neurodegenerative disorder of the central nervous system. It frequently leads to symptoms such as disability, cognitive impairment, fatigue, and depression. This study aims to examine the relationship between fatigue, cognitive functions, depression, and disability among individuals with MS.

Methods: Seventy-four MS patients were evaluated by using the Cognitive Failure Questionnaire (CFQ) battery. The Expanded Disability Status Scale (EDSS) was used in determining the level of disability, whereas the Fatigue Severity Scale (FSS) and the Beck Depression Inventory (BDI) were utilized in measuring the levels of fatigue and depression, respectively.

Results: Moderate positive correlations were found between EDSS and BDI (r1=0.342; p<0.001), between EDSS and FSS (r1=0.392; p<0.001), between CFQ and BDI (r1=0.451; p<0.001), between CFQ and FSS (r1=0.425; p<0.001), and between FSS and BDI (r1=0.424; p<0.001).

Conclusion: The results achieved in this study indicate that fatigue and depression increase as disability increases among Multiple Sclerosis patients and cognitive impairment is associated with both depression and fatigue.

Key Words: Multiple Sclerosis, Depression, Fatigue, Cognitive Failure

ÖZET

Amaç: Multipl skleroz (MS); kronik, ilerleyici ve nörodejeneratif bir merkezi sinir sistemi bozukluğudur. Multipl Skleroz; genellikle özürlülük, bilişsel yetersizlik, yorgunluk ve depresyon semptomlarına neden olur. Bu çalışmada amaç Multipl skleroz hastalarında bilişsel işlev, yorgunluk ve depresyonun özürlülük ile ilişkisini değerlendirmektir.

Yöntem: 74 MS hastası, Bilişsel Başarısızlık Anketi (CFQ) bataryası kullanılarak değerlendirildi. Engellilik düzeyini belirlemede Genişletilmiş Özürlülük Durumu Ölçeği (EDSS) kullanılırken, yorgunluk ve depresyon düzeylerini ölçmek için sırasıyla Yorgunluk Şiddeti Ölçeği (FSS) ve Beck Depresyon Envanteri (BDI) kullanıldı.

Bulgular: EDSS ile BDI arasında (r1=0.342; p<0.001), EDSS ile FSS arasında (r1=0.392; p<0.001), CFQ ile BDI arasında (r1=0.451; p<0.001), CFQ ile FSS arasında (r1=0.425; p<0.001) ve FSS ile BDI arasında (r1=0.424; p<0.001) orta düzeyde pozitif korelasyonlar bulundu.

Sonuç: Bu çalışmada elde edilen sonuçlar, Multipl Skleroz hastaları arasında engellilik arttıkça yorgunluk ve depresyonun arttığını, bilişsel bozulmanın ise hem depresyon hem de yorgunlukla ilişkili olduğunu göstermektedir.

Anahtar Kelimeler: Multipl Skleroz, Depresyon, Yorgunluk, Bilişsel Yetersizlik

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Corresponding author: Gökçe Zeytin DEMİRAL, Afyonkarahisar University of Health Sciences Faculty of Medicine, Department of Neurology, Afyonkarahisar, Türkiye

Phone: 05547250675 / **mail:** gokce_zeytin@hotmail.com

ORCID: 0000-0002-9635-5804

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Introduction

Multiple sclerosis (MS) is a chronic, progressive, autoimmune, neurodegenerative disorder affecting the central nervous system, characterized by axonal loss and demyelination in its pathogenesis [1]. The prevalence of MS in Turkey varies by region and was reported to have an average prevalence of 47.9/100,000 [2]. MS leads to brain atrophy and the development of widespread lesions or plaques in the brain and spinal cord [3]. It can cause disability in different domains, such as motor, sensory, visual, balance-coordination, and cognitive impairments in the central nervous system [4]. The prevalence of cognitive decline among individuals with MS ranges between 43% and 73%, the lifetime diagnosis rate of major depression was reported to be approx. 50%, and the prevalence of fatigue, which is closely associated with depression, was reported to be between 50% and 90% [5–7]. This study aims to assess the relationship between cognitive function, fatigue, depression, and disability among MS patients.

Materials and Methods

This study included 74 patients aged between 18 and 55 and diagnosed with MS by the 2017 McDonald criteria, who presented to the Neurology Clinic of Afyonkarahisar Health Sciences University Faculty of Medicine Hospital between 10 December 2022 and 01 February 2023. Patients, who had additional neurological diseases that could affect clinical evaluation and/or neurological and/or psychiatric conditions that could impact cognitive functions, those using antipsychotic medication, individuals with a history of severe head trauma, those with mental retardation or learning difficulties, pregnant or lactating women, alcohol or substance abusers, individuals with MS relapse, and/or those who had received corticosteroid treatment in the four weeks before assessment were excluded from the study. Patients' age, gender, education level, socioeconomic status, disease duration, medication usage, MS disease type, medical history, and neurological examination results were recorded, and their Expanded Disability Status Scale (EDSS) scores were determined by assessing the functional systems. The present study was carried out after obtaining written consent of the patients, supervised by medical students from the 3rd year of medical school. The cognitive impairment scale, fatigue severity scale, and Beck Depression Inventory were used for assessment.

Scales

Cognitive Failures Questionnaire (CFQ): CFQ is a self-report questionnaire that measures perception, memory, and motor function failures. It consists of 25 items, and participants rate the items on a five-point scale ranging between "never" and "always." The response options are: (0) Never, (1) Very rarely, (2) Occasionally, (3) Fairly often, and (4) Very often. CFQ scores can range between 0 and 100; higher scores indicate a greater tendency towards cognitive failures. CFQ's validity and reliability have been established [8–12].

Expanded Disability Status Scale (EDSS): EDSS is a scale utilized in assessing neurological examination findings among MS patients. Various subfunctions are evaluated to determine disability. The scale ranges between 0 (no disability) and 10 (death due to MS), with 20 levels in total [13].

Fatigue Severity Scale (FSS): FSS is a fatigue assessment scale, validity and reliability of which were tested in the Turkish language [14]. In this 9-item self-administered scale, each item is scored between 1 and 7 points. A cutoff value of 4 or higher indicates pathological fatigue [15].

Beck Depression Inventory (BDI): BDI is used for depression screening among MS patients. It includes 21 items rated on a scale of 0 to 3, assessing the degree of self-reported depression. A total score of 17 points or higher indicates depression (with a maximum score of 63) [16].

Patients were divided into two subgroups based on their EDSS scores: those with EDSS scores of 4 and above, and those with EDSS scores below 4. The patients were also divided into groups by disease duration: 5 years and above, and below 5 years. Statistical analyses were conducted within these subgroups.

Statistical Analysis

The data analysis was conducted with IBM Corporation's SPSS 24.0 statistical software package. Continuous variables are expressed using means, medians, and standard deviations, whereas categorical variables are expressed with numbers and percentages. The normal distribution of data was assessed using the Kolmogorov-Smirnov test. In cases of non-normal distribution of data, the Mann-Whitney U test was employed to examine differences between independent groups. The Kruskal-Wallis test was preferred for evaluating differences among three or more groups. Relationships between continuous variables were assessed using Spearman correlation analysis, considering the non-normal distribution of data [17]. A significance level of $p<0.05$ was considered for all statistical analyses.

Results

A total of 74 patients, comprising 54 (73%) females and 20 (27%) males, diagnosed with MS were included in this study. According to the subtypes of MS, 54 (73%) patients were classified as relapsing-remitting MS (RRMS), 17 (23%) as primary progressive MS (PPMS), and 3 (4.1%) as sec-

ondary progressive MS (SPMS). The mean age of the participants was 38.32±11.47 years. Examining the marital status, it was determined that 58 (78.4%) patients were married, and 16 (21.6%) were single. Regarding education, 4 (5.4%) patients were uneducated, 35 (47.3%) had completed primary education, 22 (29.7%) had completed high school, 10 (13.5%) had a university degree, and 3 (4.1%) had a master's degree.

The mean disease duration was 7.55±5.91 years, whereas the mean Expanded Disability Status Scale (EDSS) score was 2.83±1.54. The mean score on the Cognitive Failures Questionnaire (CFQ) was found to be 41.76±22.22, the mean Fatigue Severity Scale (FSS) score to be 4.45±1.93, and the mean Beck Depression Inventory (BDI) score to be 19.62±11.33. Symptoms of depression were present in 43 (58.1%) patients, and fatigue symptoms were present in 49 (66.2%) patients. Among the patients, 54 (73%) had an EDSS score of 4 or lower, whereas 20 (27%) had an EDSS score of 4 or higher. Considering disease duration, 31 (41.9%) patients had a disease duration of less than 5 years, and 43 (58.1%) had a disease duration of 5 years or more. Table 1 presents the statistical analysis of demographic and clinical data, along with mean, median, standard deviation, and minimum-maximum values. The statistical analysis and frequencies of demographic and clinical data are presented in Table 2.

There was no statistically significant difference between education level and CFQ, BDI, and FSS scores (p=0.644, p=0.937, p=0.727, respectively). Similarly, there was no statistically significant difference in marital status by CFQ, BDI, and FSS scores (p=0.259, p=0.524, p=0.507, respectively).

In Spearman correlation analysis, there was a strong positive correlation between age and disease duration (r1=0.597; p<0.001), in addition to the moderate positive correlations between EDSS and disease duration (r1=0.253; p<0.05), EDSS and BDI (r1=0.342; p<0.001), between EDSS and fatigue (r1=0.392; p<0.001), between CFQ and BDI (r1=0.451; p<0.001), between CFQ and fatigue (r1=0.425; p<0.001), and between fatigue and BDI (r1=0.424; p<0.001). Table 3 illustrates the Spearman correlation analysis of variables (Table 3).

Examining group analyses, significant differences were found in age, disease duration, BDI, and FSS scores by EDSS classification (p=0.02, p<0.001, p=0.027, p<0.001, respectively). Patients with EDSS scores of 4 and above exhibited significantly higher age, disease duration, BDI, and FSS scores. No statistically significant difference was found between CFQ and EDSS (p=0.105).

Using the disease duration for group analysis, it was determined that there were statistically significant differences in terms of age and EDSS (p<0.001, p=0.010, respectively). Patients with a disease duration of 5 years or more had significantly higher age and EDSS scores. However, there was no statistically significant difference between CFQ, BDI, FSS, and disease duration (p=0.200, p=0.645, p=0.089, respectively).

Discussion

In this study, a positive correlation was observed between disability and depression, fatigue, and disease duration in patients with MS. Similarly, a positive correlation was determined between cognitive functions and depression, as well as fatigue. In addition, a positive correlation was found between depression and fatigue. Among individuals with an Expanded Disability Status Scale (EDSS) score of 4 or higher, age, disease duration, depression, and fatigue were significantly elevated. Those with a disease duration of 5 years or more had significantly higher age and EDSS scores.

Multiple Sclerosis is the most prevalent neurological disease causing disability among young adults, and fatigue is one of its hallmark symptoms [18,19]. The pathophysiological mechanisms underlying fatigue include structural damage to white matter (WM) and gray matter (GM), inflammatory processes (both within and outside the central nervous system), incongruent connections due to distributed lesions or inflammation, and a heightened perception of internal states due to dishomeostatic condi-

Table 1. Statistical Analysis of Patients' Demographic and Clinical Data

(n=74)	Mean	Median	Std. Deviation	Minimum	Maximum	Test statistic*	p**
Age	38.32	37	11.47	18	70	0.976	0.172
Pain Duration	7.55	6	5.91	1	25	0.907	**<0.001**
EDSS	2.83	2.50	1.54	1	6.50	0.894	**<0.001**
CFQ	41.76	40.50	22.22	3	99	0.981	0.339
BDI	19.62	19	11.33	0	48	0.967	0.053
FSS	4.45	4.44	1.93	1	7	0.926	**<0.001**

*The Kolmogorov-Smirnov test was used for the analysis of normal distributions. ** p<0.05 was considered statistically significant.

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Table 2. Frequencies of Demographic and Clinical Data of Patients

		Frequency(n)	(%)	Test statistic *	p**
Gender	Female	54	(73)	0.555	**<0.001**
	Male	20	(27)		
Education level	Uneducated	4	(5.4)	0.855	0.855
	Primary education	35	(47.3)		
	High school	22	(29.7)		
	University degree	10	(13.5)		
	Master's degree	3	(4.1)		
Marital status	Married	58	(78.4)	0.507	**<0.001**
	Single	16	(21.6)		
MS clinical types	RRMS	54	(73)	0.593	**<0.001**
	PPMS	17	(23)		
	SPMS	3	(4.1)		
Disease duration classification	5 years or less	31	(41.9)	0.627	**<0.001**
	More than 5 years	43	(58.1)		
EDSS classification	Below 4	54	(73)	0.555	**<0.001**
	4 and above	20	(27)		
Fatigue	Absent	25	(33.8)	0.597	**<0.001**
	Present	49	(66.2)		
Depression	Absent	31	(41.9)	0.627	**<0.001**
	Present	43	(58.1)		

*The Kolmogorov-Smirnov test was used for the analysis of normal distributions. ** p<0.05 was considered statistically significant.

Table 3. Spearman correlation analysis between variables (n=74)

		Age	Year	EDSS	CFQ	BDI	FSS
Age	r	1					
Year	r	**0.597****	1				
EDSS	r	0.103	**0.253***	1			
CFQ	r	-0.145	0.039	0.186	1		
BDI	r	-0.052	-0.035	**0.342****	**0.451****	1	
FSS	r	0.150	0.213	**0.492****	**0.425****	**0.424****	1

** p < 0.001, *p < 0.05 values indicate the result of the Spearman correlation. CFQ: Cognitive Failures Questionnaire, EDSS: Expanded Disability Status Scale, BDI: Beck Depression Inventory, FSS: Fatigue Severity Scale

tions [18]. The prevalence of fatigue tends to increase with disease progression, eventually becoming a concern for approximately 80% of individuals with MS regardless of the MS phenotype. Fatigue is typically rated as one of the top two most inhibiting symptoms by individuals with MS; however, its severity fluctuates over days and between

days, posing challenges for clinical management [19]. The present study also demonstrated that the majority of patients exhibited fatigue symptoms as described in the literature. Furthermore, it was also revealed that fatigue tends to increase with increasing levels of disability.

When evaluating cognitive functions, despite clinical heterogeneity, cognitive decline has been consistently reported in patients with MS, regardless of the disease's processes. Deficits are most commonly observed in attention, processing speed, working memory, verbal fluency, and executive function. Moreover, individuals with MS tend to exhibit reduced performance in tasks related to social cognition, which includes interpersonal skills such as social perception, empathy, and theory of mind [20]. The underlying pathophysiology of cognitive impairment includes lesions in strategic cerebral white matter (WM) regions, microstructural WM damage, gray matter (GM) lesions, deep GM atrophy, and abnormal cerebral activation patterns [21]. Broadbent's Cognitive Failures Questionnaire (CFQ) is a tool widely used for evaluating cognitive function. Its validity and reliability were tested in Turkey, suggesting its utility in assessing non-demented cognitive functions [12]. In contrast to some previous studies, no significant relationship was found between increasing disability and cognitive function deterioration in the present study. However, most studies suggest that cognitive functions are associated with EDSS scores in MS patients. In general, a decline in cognitive function and an increase in disability levels are observed in parallel with the progression of the disease in MS patients [22]. Nevertheless, it's crucial to remember that there can be substantial variations among individuals; some might experience cognitive function decline, whereas others might experience minimal decline or none at all. The treatments used for MS can be useful in slowing down disease progression or alleviating symptoms. Different treatments might have diverse effects on cognitive functions and disability levels. Individuals with MS can develop various strategies to compensate for cognitive weaknesses, potentially resulting in fewer errors in daily life and a reduction in disability levels. The specific characteristics of the patients in the present study sample can influence the results. For instance, patients with milder symptoms or higher cognitive reserves might have been selected. Moreover, the limited number of patients might have contributed to an inconclusive correlation between cognitive functions and disability. Psychosocial factors such as stress, depression, and anxiety can influence both cognitive functions and disability levels. The worsening of depression and fatigue with increasing EDSS scores might indirectly relate to cognitive function impairment.

Regarding the relationship between MS and depression, it's evident that depression is a common finding among MS patients. Depressive disorders are experienced by up to 50% of patients, and major depression is a significant comorbidity of MS. Various dysfunctions, such as neuroinflammation, peripheral inflammation, gut dysbiosis, chronic oxidative and nitrosative stress, and neuroendocrine and mitochondrial abnormalities, are considered to contribute to the comorbidity between MS and major depression [23]. The present study, like others, also found a high prevalence of major depression among MS patients.

Fatigue, depression, and cognitive function impairment are closely interrelated clinical aspects among patients with MS. In a previous study, increased fatigue was found to not be associated with initial fatigue, cognitive impairment, disease variables, or disability levels. However, it was found to be related with higher anxiety, lower self-efficacy, and gender [19]. In this study, on the other hand, fatigue and depression were found to be associated with increasing disability scores, indicating a connection between fatigue and depression symptoms. Moreover, a similar relationship was identified between the increase in fatigue and depression and the increase in cognitive impairment. Similarly, another study demonstrated that psychological, demographic, and disease-related factors all contribute to inadequate performance in MS. For instance, depressive symptoms and anxiety were associated with inadequate performance in MS. More importantly, rates of inadequate performance were found to be higher in clinical populations characterized by fatigue and pain [24]. In another study, cognitive processing speed was not fully evaluated due to fatigue and depression, and it was determined that depression and fatigue contribute to cognitive processing speed and cognitive impairment [25].

Limitations of this study: The limitations of this study include not evaluating correlations and relationships between various cognitive tests used for cognitive function assessment, the limited number of patients due to the short study duration, and a lack of classification of patient treatments to assess their impact on cognitive functions.

Conclusion

As disability increases in MS, it likely contributes to higher levels of depression and fatigue. Additionally, depression and fatigue are correlated with each other, and these two factors probably negatively impact cognitive functions.

Conflict of Interest: The authors declare no conflict of interest related to this article.

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Ethical Committee Approval: Ethical approval was obtained from the Afyonkarahisar Health Sciences Univer-

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sity Clinical Research Ethics Committee on 4 November 2022, with decision number 2022/543, before initiating the study.

ORCID and Author contribution: ***G.Z.D (0000-0002-9635-5804);*** The responsible researcher carried out all stages of the manuscript.

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