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ARAŞTIRMA / RESEARCH

Evaluation of neuropsychiatric symptoms in patients with multiple sclerosis

Multipl skleroz hastalarında nöropsikiyatrik bulguların incelenmesi

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Abstract

Purpose: The aim of this study was to comprehensively assess the neurophyschiatric symptoms of multiple sclerosis (MS) such as apathy and pseudobulbar affect and their correlation with other concomitant factors.

Materials and Methods: Montreal Cognitive Assessment (MoCA), Apathy Evaluation Scale (AES), Fatigue severity scale (FSS), Center for Neurologic Study-Lability Scale (CNS-LS), Beck Depression Inventory (BDI) are applied to 258 MS patients. Correlation and regression analysis are conducted between scales and other possible causers.

Results: 53.6% of the patients have psuedobulbar affect, 76.2% of patient population have fatigue. Pseudobulbar affect had positive correlation with fatigue and also depression while apathy negatively correlate with pseudobulbar affect or fatigue. Additionally, apathy and depression correlated negatively. There was no relation between cognition and depression and/or disease duration and/or other scales' scores.

Conclusion: Pseudobulbar affect and apathy are quite common symptoms in MS patients, that are cross-cutting issues. Also, apathy may be an independent neuropyschiatric symptom of MS that need to be approached separately.

Keywords:. MS, apathy, pseudobulbar affect

Öz

Amaç: Bu çalışmanın amacı; multipl skleroz (MS) hastalarında apati ve emosyonel labilite gibi nöropsikiyatrik semptomları ve bunların eşlik eden diğer faktörlerle ilişkisini kapsamlı bir şekilde değerlendirmektir.

Gereç ve Yöntem: 258 MS hastasına Montreal bilişsel değerlendirme (MoCA), Apati değerlendirme ölçeği (AES), Yorgunluk şiddeti ölçeği (FSS), Emosyonel Labilite (CNS-LS), Beck Depresyon Envanteri (BDI) uygulandı. Ölçekler ve diğer olası nedenler arasında korelasyon ve regresyon analizleri yapıldı.

Bulgular: Hastaların %53,6'sında emosyonel labilite, %76.2'sinde yorgunluk mevcuttu. Emosyonel labilite ile yorgunluk ve depresyon arasında pozitif korelasyon izlenirken, apati ile emosyonel labilite ve yorgunluk arasında negatif korelasyon saptandı. Ek olarak, apati ve depresyon arasında negatif korelasyon izlendi. Bilişsel bozukluk ile depresyon ve/veya hastalık süresi ve/veya diğer ölçek puanları arasında ilişki yoktu.

Sonuç: Emosyonel labilite ve apati, MS hastalarında oldukça sık görülen ve birbiriyle kesişen/karışan sorunlardır. Buna ek olarak; apati, MS hastalarında ortaya çıkan bağımsız bir nöropsikiyatrik semptom olabilir.

Anahtar kelimeler: MS, apati, psödobulbar etkiler

INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory, neurodegenerative central nervous system disease that is one of the leading causes of disability in young adults. The prevalence of this disease, which is seen approximately 3 times more frequently in women than in men and involves white and gray matter together, is around 50/100,000 in Turkey[1].

It can be said that MS has a very wide symptomatology. Muscle weakness, loss of sensation, sphincter incontinence, fatigue, depression, anxiety, emotional lability (pseudobulbar affect), apathy, cognitive impairment are common problems.

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Expanded Disability Status Scale (EDSS) is used in the evaluation and follow-up of neurological disability but this scale is insensitive for cognitive and neuropsychiatric dysfunctions. Therefore, many batteries are used for cognitive and psychiatric evaluation.

Affective disorders affect approximately 2/3 of the patients[2]. The possible effects of different factors such as disease type, fatigue, cognition, pseudobulbar affect, pain, disease modifying agent, and gender on depression in MS patients are still being discussed.

Fatigue can be defined as the subjective loss of physical or mental energy required for the continuation of routine activities and is closely related to unemployment and decreased quality of life with its negative effects on cognitive, psychiatric and physical function[3]. Although there is evidence that fatigue occurs as a result of the primary pathology of MS, it is possible that it may occur secondary to depression, disability or apathy independent of MS pathophysiology[4,5].

Apathy is a multidimensional, transdiagnostic syndrome characterized by a quantitative decrease in goal-directed behavior and low motivation that cannot be attributed to altered consciousness, cognitive impairment, or emotional stress. Traditionally, apathy has been associated with cortico-striatal connections, especially ventral and limbic loops[6]. In the literature, the number of studies examining apathy in MS patients is quite limited compared to neurodegenerative diseases such as Parkinson's, dementia or Huntington's disease, and apathy in MS has been intensively investigated recently.

Pseudobulbar affect is seen in 10% of MS patients[7]. It is more common in those with MS who are younger and from a low socioeconomic level. It is also associated with higher disability, spasticity, vision-related symptoms, depression and cognitive impairment.

As a comprehensive MS center that follows up a large number of MS patients, we think that the relationship between cognitive impairment and psychiatric diseases in MS is unclear, and that comprehensive studies are needed to evaluate neuropsychiatric symptoms such as apathy, fatigue, pseudobulbar affect and depression in patients. Also, the relationship between PBA and depression is complex, and this relation can affect the frequency of PBA. There are few studies that address this effect. Neuropsychatric symptoms in MS are overlooked and frequaently left untreated that impair the quality of life of those patients. This study is designed to highlight the situation mentioned above may be occurring more than thought. We also planned this study to bring comprehensive data to the literature that will contribute to determining the relationship between the aforementioned symptoms, as well as with each other, as well as with disease duration, disease modifying agent, cognitive status, physical disability and demographic characteristics.

MATERIALS AND METHODS

The study protocol was approved by the ethics committee of the Ministry of Health Dr. University Sancaktepe Sehit Prof İlhan Varank Training and Research Hospital on 16th Dec 2020 with the dossier number 2020-21, and the study was conducted as per the Declaration of Helsinki and with the consent of the patients. The study was conducted at the same hospital.

Sample

The study included 258 patients diagnosed in accordance with the Mc Donald 2017 criteria. The most up-to-date and common diagnostic criteria are McDonald 2017 criteria which based on dissemination in the space and the time of the multiple sclerosis related attacks/lesions or having progressive disease for at least 1 year[8].

Clinical evaluations of the patients were made by 2 neurologists specialized in MS, a psychologist experienced in cognitive testing, and evaluation and interpretation of other scales by a neurologist working in the field of behavioral neurology.

Inclusion criteria were:being 18-65 years old and diagnosed with ms, being followed by Sancaktepe ms out patient clinic, fully filling the scales. Exclusion criteria were being 18-65 years, being diagnosed with radiological isolated syndrome.

Data collection

Our MS clinic team includes 2 MS specialist-neurologist, 1 cognitive neuroscience- behavioral neuroscience specialist-neurologist, 1 neuropsychologist, 1 dietitian, 1 physiotherapist, 2 MS nurses. The Montreal cognitive assessment (MoCA), apathy evaluation scale (AES), fatigue severity scale (FSS), Center for Neurologic Study-

Lability Scale (CNS-LS) and Beck Depression Inventory (BDI) were used in the evaluation of the patients.

BDI, FSS AES, CNS-LS results were collected by patients' self-reports online (due to the COVID-19 quarantine). All those scales were transformed into an online form with the help of Jotform program. Online forms were filled by the patients and saved as PDF in Jotform program. Online form filling process lasts 2 weeks. 2 neurologists calculated the online scales' scores at different times to ensure the correct results. Interpretention and analyses of the scale scores last 3 weeks.

Demographic data were collected from our MS clinic up-to-dated files. MoCA tests were performed face-to-face by our neuropsychologist as a part of our routine patient evaluation and follow up. Face-to-face examinations of the patients are carried out regularly in our neurology clinic, and as a result of the MS specialist examination, their current EDSS were noted. Information of current disease-modifying drug (DMD) were obtained from our MS database which is up-to-dated and regularly filled.

Measures

Expanded Disability Status Scale (EDSS)

This scale is based on neurological examinations of MS patients and is used as an indicator of disability by evaluating many sub-functions. In this scale, there are 20 steps between 0 (no deficiency) and 10 (death due to MS)[9].

Beck Depression Inventory (BDI)

It is recommended for screening for depression in MS patients. It consists of 21 self reported item that measure the severity of depressive symptoms. It includes somatic and affective symptoms, and each item is rated on a 4-point scale. It has been validated with people with MS who have been recently diagnosed and those who have had MS for several years[10,11]. Turkish validity and reliability were established [12]. In our study, BDI scores of 0-13 were accepted as no depression, 14-19 as mild depressive symptoms, 20-28 as moderate depression, over 29 as severe depression[13].

The Fatigue Severity Scale (FSS)

It is a uni-dimensional questionnaire of 9 statements evaluating the severity but also the impact of fatigue in patients with MS. Items are scored from 1 to 7 (1 = completely disagree to 7 = completely agree)[14]. Its validity and reliability in Turkish have been demonstrated in the evaluation of fatigue [15]. In the scale, which consists of 9 items that the patients can apply on their own, each item is scored between 1 and 7 (1 = strongly disagree, 7 = completely agree). The cut-off value for pathological fatigue is considered as 4 and above.

Apathy Evaluation Scale (AES)

The scale is developed to focus on the hobbies and occupations of individuals in daily life, and measures their loss in these areas [16]. Turkish adaptation and validity study were carried out by Gulseren et al[17]. The scale has both a "self-evaluation" and a "clinician" form. Evaluation on the scale, which has 18 items, is made by considering the last 4 weeks. The lowest score that can be obtained from the scale is 18, and the highest score is 72. We used the self-evaluation form in our study. No cut-off score was determined in the Turkish version of the scale.

Center for Neurologic Study-Lability Scale (CNS-LS)

It was used to determine the prevalence of pseudobulbar affect. The CNS-LS is a self-administered seven-item questionnaire with questions about the control of laughing and crying and validated in ALS and MS patients [18]. Total score ranging from 7 (no emotional lability) to 35 (severe extreme emotional lability). Turkish adaptation and validity study were carried out by Togrul et al. Patients with a score of 15 and above were considered to have PBA[19].

Montreal Cognitive Assessment (MoCA)

It is a test developed for rapid screening of mild cognitive impairment. It assesses attention and concentration, executive functions, memory, language, visual construction skills, abstract thinking, calculation and orientation. The highest possible score that can be achieved in test is 30. Accordingly, scores higher than 21 are considered normal. It has been used in studies in the Turkish MS patient population[20,21]. The Turkish validity and reliability of the test were performed[22].

Statistical analysis

Based on the percentage measurement values of the methods to be studied in the literature review, the total sample size found using the G-POWER

program with an effect size of 0.2, a power of 90% and a margin of error of 0.05 is n=258.

Data analysis was done with SPSS 24.0. In the study, the scale scores were calculated and the kurtosis and skewness coefficients were examined to determine the conformity of the scores to the normal distribution. The kurtosis and skewness values obtained from the scales are found to be between +3 and -3 for normal distribution (Groeneveld and Meeden, 1984; Moors, 1986; Hopkins and Weeks, 1990; De Carlo, 1997).

Table 1. Kurtosis and Skewness Values

	n	Kurtosis	Skewness
PBA (PseudobulbarAffect)	252	0.753	-0.131
FSS (Fatigue Severity Scale)	252	-0.897	-0.195
AES (Apathy Evaluation Scale)	252	-0.766	0.921

When the values are examined, it is seen that the kurtosis and skewness coefficients of each score are between -3 and +3 (PBA: skewness 0,753, kurtosis -0,131, FSS: skewness -0,897, kurtosis -0,195, AES: skewness -0,766, kurtosis 0,921). According to this result, it was concluded that the scores showed a normal distribution. Parametric test techniques were used in the study due to the normal distribution of scores. The relationship between PBA, FSS and AES was analyzed with the pearson correlation test, the relationship between MS type and gender, DMD, age groups and disease duration was analyzed with the chi-square test, and the relationship between EDSS and gender, MOCA and depression level was analyzed with the chi-square test. In the study, differences in PBA, FSS and AES values according to gender, MOCA groups, EDSS groups, DMD groups, MS type groups, depression levels, age groups and disease duration groups were observed in independent groups by T- test, Mann Whitney U test, ANOVA and Kruskal Wallis. analyzed with appropriate tests. The T-test and ANOVA test were used to analyze the variation of the scale score according to demographic characteristics. However, in groups with less than 20 observations, non-parametric tests, Mann Whitney and Kruskal Wallis tests, were used as comparison tests.

In the study, linear regression analysis was performed to determine the factors affecting PBA, FSS and AES. The categorical variables included in the independent variables were converted into dummy variables and added to the model. In the analysis performed with the enter method, the independent variables that were effective on the dependent variable were determined.

RESULTS

68.9% of the population were female. 71.8% of the population were at the age between 25 and 45. .34.1% of the patients were on first line DMD while %56,3 were on second line DMD. 77.4% of the patients were relapsing remitting multiple sclerosis (RRMS), while 6.3% is primer progressive multiple sclerosis (PPMS), 11,9% is seconer progressive multiple sclerosis (SPMS), clinically isolated syndrome (CIS) is total 4,4%. 69.4% of the patients' BDI scores were above 10. 53.6% of the patients have PBA and % 76,2 of them have fatigue. People with high CNS-LS value also have a high FSS value ($p<0.05$). People with high CNS-LS value have low AES value ($p<0.05$). People with high FSS values had low AES values ($p<0.05$).

Table 2. Correlation Between CNS-LS, FSS and AES

		CNS-LS	FSS	AES
CNS-LS	r	1	,395**	-,168**
	p		0,000	0,007
	n	252	252	252
FSS	r		1	-,332**
	p			0,000
	n		252	252
AES	r			1
	p			
	n			252

MoCA: Montreal cognitive assessment, AES: Apathy evaluation scale, FSS: Fatigue severity scale, CNS-LS: Center for Neurologic Study-Lability Scale, BDI: Beck Depression Inventory

Table 3. Correlation between MoCA and BDI also MoCA and CNS-LS, FSS, AES

		Chi Square Test					
		MoCA>21		MoCA<21			
		n	%	n	%	X^2	p
BDI	No Depression	74	96,1	3	3,9	6, 213[a]	0,102
	Mild depressive manifestions	50	94,3	3	5,7		
	Moderate depression	85	90,4	9	9,6		
	Severe depression	23	82,1	5	17,9		

Pearson correlation

	MoCA	n	Mean	sd	Median	U	p
CNS-LS	21 and over	232	15,78	6,85	15,00	1892,000	0,170
	below 21	20	18,30	8,14	18,00		
FSS	21 and over	232	5,07	1,65	5,60	1974,000	0,268
	below 21	20	5,47	1,51	5,85		
AES	21 and over	232	58,66	8,71	60,00	1778,500	0,083
	below 21	20	53,65	12,09	57,50		

MoCA: Montreal cognitive assessment, AES: Apathy evaluation scale, FSS: Fatigue severity scale, CNS-LS: Center for Neurologic Study-Lability Scale, BDI: Beck Depression Inventory

There is no significant correlation between MOCA and BDI. Also, MoCA and FSS, CNS-LS and AES scales. The FSS values of the group with an EDSS value of 5 and above were higher ($p<0.05$). This does not apply to apathy and pseudobulbar affect.

The FSS values of the group taking 2nd-line drugs were the highest. Post hoc analysis revealed a significant difference between those who took second-line drugs and those who received Copaxone/interferon.

Table 4. Comparison of EDSS Groups in terms of CNS-LS, FSS and AES

		n	**Mean**	**sd**	**t**	**p**
CNS-LS	<5	215	15.86	7.10	-0.659	0.510
	>5	37	16.68	6.26		
FSS	<5	215	4.95	1.66	-4.359	0.000*
	>5	37	5.97	1.26		
AES	<5	215	58.44	8.98	0.739	0.460
	>5	37	57.24	9.82		

***p<0,05.** MoCA: Montreal cognitive assessment, AES: Apathy evaluation scale, FSS: Fatigue severity scale, CNS-LS: Center for Neurologic Study-Lability Scale, BDI: Beck Depression Inventory

Table 5. Comparison of DMD Groups in terms of CNS-LS, FSS and AES

		n	**Mean**	**sd**	**F**	**p**
CNS-LS	No med.	24	15.54	5.88	**0.862**	**0.461**
	Copaxone / interferons	38	14.66	6.47		
	Other 1st Line Orals	48	15.54	8.26		
	2nd Line	142	16.55	6.82		
FSS	No med.	24	4.98	1.47	**5.391**	**0.001***
	Copaxone / interferons	38	4.35	1.80		
	Other 1st Line Orals	48	4.78	1.84		
	2nd Line	142	5.42	1.47		
AES	No med.	24	60.46	9.01	**0.801**	**0.494**
	Copaxone / interferons	38	59.29	10.12		
	Other 1st Line Orals	48	57.83	10.07		
	2nd Line	142	57.77	8.49		

***p<0,05.** MoCA: Montreal cognitive assessment, AES: Apathy evaluation scale, FSS: Fatigue severity scale, CNS-LS: Center for Neurologic Study-Lability Scale, BDI: Beck Depression Inventory

Table 6. Comparison of MS Type Groups and BDI groups in terms of CNS-LS, FSS and AES

		n	Mean	sd	F	p
CNS-LS	RRMS	195	16.09	7.18	**2.966**	**0.397**
	PPMS	16	17.94	6.94		
	SPMS	30	15.03	6.11		
	CIS	11	13.64	5.30		
FSS	RRMS	195	4.96	1.68	**16.677**	**0.001***
	PPMS	16	6.06	1.09		
	SPMS	30	5.84	1.01		
	CIS	11	4.17	1.99		
AES	RRMS	195	58.64	8.91	**2.068**	**0.558**
	PPMS	16	56.94	7.57		
	SPMS	30	56.27	10.57		
	CIS	11	59.00	10.48		
CNS-LS	No Depression	77	11.35	4.63	**22.840**	**0.000***
	Mild Depression	53	16.66	5.94		
	Moderate Depression	94	18.02	6.88		
	Severe Depression	28	20.54	7.97		
FSS	No Depression	77	3.81	1.67	**41.916**	**0.000***
	Mild Depression	53	5.00	1.42		
	Moderate Depression	94	5.78	1.16		
	Severe Depression	28	6.51	0.49		
AES	No Depression	77	63.74	7.59	**27.453**	**0.000***
	Mild Depression	53	59.25	7.21		
	Moderate Depression	94	55.94	7.83		
	Severe Depression	28	49.18	10.22		

***p<0,05** MoCA: Montreal cognitive assessment, AES: Apathy evaluation scale, FSS: Fatigue severity scale, CNS-LS: Center for Neurologic Study-Lability Scale, BDI: Beck Depression Inventory, RRMS: relapsing remitting multiple sclerosis, SPMS: seconder progressive multiple sclerosis, PPMS: primer progressive multiple sclerosis, CIS: clinically isolated syndrome.

There is a statistically significant difference between MS type groups only in terms of FSS ($p<0.05$). The FSS values of the PPMS group are the highest. In post hoc analysis, the difference between MS type RRMS and SPMS, PPMS and SPMS was statistically significant. Those with severe depression have the highest CNS-LS values. Post hoc analysis showed statistically significant differences between those without depression and mild depressives, and those with moderate and severe depression. Those in the severe depression group have the highest FSS values. In post hoc analysis, the differences between all groups were statistically significant.

The AES values of the group without depression were the highest. According to post hoc analysis, the differences between those without depression and those with mild depressive symptoms, moderate depression and severe depression were found to be statistically significant. The absence of depression reduces the CNS-LS score. As the depression worsens, fatigue increases. As the depression worsens, apathy decreases.

DISCUSSION

Neuropsychiatric symptoms in MS patients and their relationship with cognition and disease-related factors remain to be investigated. In the Turkish MS patient population, we see that apathy, fatigue, pseudobulbar affect, and depression have not been extensively studied, either separately or together with cognition and other disease-related conditions, and there is a limited number of studies in the global literature and there is no consensus on these symptoms. In our study, we aimed to obtain data on this deficiency.

In the literature, pseudobulbar affect has been reported in 7% to 52% of MS patients[7]. In our study, a pseudobulbar affect was found in 53.6% of the patients, and in accordance with the literature [18], the pseudobulbar affect was unrelated to the level of disability and was observed more frequently in women[18]. Our findings differ from previous studies in that no relationship was found between cognitive

status and MS type and pseudobulbar affect [18,23]. Besides, the pseudobulbar affect is unrelated to the treatment the patient is using. Our study is the first to examine this relationship. In addition to these analyses, if we look at the relationship between pseudobulbar affect and fatigue, apathy and depression, a positive correlation was found between pseudobulbar affect and fatigue and a negative correlation between apathy in correlation analyzes. In other words, the pseudobulbar affect is affected by these two conditions. However, we found a strong correlation between depression level and pseudobulbar affect in our study (p-0.000). As the level of depression increases, the pseudobulbar affect also increases. This may be the reason for the high incidence of pseudobulbar affect above the highest value reported in the literature. Since our study was conducted during the COVID-19 quarantine, at a time when we thought that patients were constantly at home and more prone to depression, we think that the increased depressive state may have been a trigger for the pseudobulbar affect

Table 7. Regression analysis

Dependent	Non-Dependent	Beta	t	p	R^2	F
CNS-LS	MOCA-below 21	0.040	0.693	0.489	**0.240**	**7.622***
	EDSS-5.6.7.8.9.10	0.012	0.138	0.890		
	MS Type PPMS	0.032	0.429	0.668		
	MS Type SPMS	-0.095	-1.333	0.184		
	MS Type RIS / CIS	-0.037	-0.644	0.520		
	No Depression	-0.432	-6.712	0.000*		
	Mild depressive manifestions	-0.067	-1.068	0.287		
	Severe depression	0.113	1.851	0.065		
	Age	-0.121	-1.653	0.100		
	Disease year	0.061	0.857	0.393		
FSS	MOCA-below 21	-0.030	-0.570	0.569	**0.368**	**14.040***
	EDSS-5.6.7.8.9.10	0.017	0.212	0.832		
	MS Type PPMS	0.060	0.881	0.379		
	MS Type SPMS	0.064	0.981	0.328		
	MS Type RIS / CIS	-0.065	-1.248	0.213		
	No Depression	-0.541	-9.217	0.000*		
	Mild depressive manifestions	-0.186	-3.239	0.001*		
	Severe depression	0.132	2.362	0.019*		
	Age	0.107	1.603	0.110		
	Disease year	-0.020	-0.318	0.751		
AES	MOCA-below 21	-0.078	-1.382	0.168	**0.270**	**8.924***
	EDSS-5.6.7.8.9.10	0.094	1.118	0.265		
	MS Type PPMS	-0.021	-0.284	0.777		
	MS Type SPMS	-0.065	-0.930	0.353		
	MS Type RIS / CIS	-0.010	-0.176	0.860		
	No Depression	0.405	6.421	0.000*		
	Mild depressive manifestions	0.161	2.610	0.010*		
	Severe depression	-0.228	-3.800	0.000*		
	Age	-0.098	-1.370	0.172		
	Disease year	0.111	1.603	0.110		

***p<0,05** MS: Multiple Sclerosis, MoCA: Montreal cognitive assessment, AES: Apathy evaluation scale, FSS: Fatigue severity scale, CNS-LS: Center for Neurologic Study-Lability Scale, BDI: Beck Depression Inventory, RRMS: relapsing remitting multiple sclerosis, SPMS: seconder progressive multiple sclerosis, PPMS: primer progressive multiple sclerosis, CIS: clinically isolated syndrome.

Fatigue was found at a rate of 76.2% in our study. Fatigue has been reported in the literature in the range of 52% to 88% of MS patients. The results of studies examining the relationship between fatigue and other related clinical or demographic factors in MS are controversial[4,24,25,26,27,28]. In our study, no difference was found between gender groups in terms of fatigue. The relationship between cognition and

fatigue has been examined in limited studies and a clear consensus has not been reached[24,28,29]. Our study also shows that fatigue is not affected by cognitive status, similar to a study in the literature[30]. Again, in line with the literature, a high level of disability increases fatigue[31].

The relationship between depression and fatigue is also controversial. While many studies in the literature state that depression and fatigue are related, others show that fatigue occurs independently of depression [4,24,25,26,27,31,32]. Our findings support that depression is associated with fatigue. However, it should be noted that many BDI questions may overlap with fatigue symptoms; for example, common symptoms such as changes in sleep, appetite and sexual desire make it difficult in these patients to distinguish whether depression is an independent symptom caused by MS disease or an entity that occurs with fatigue. This situation causes the diagnosis and treatment to be more complicated.

In our study, the level of fatigue was found to be higher in the group receiving second-line drugs compared to all other drug treatments. This finding was reported for the first time in this area with limited studies. The reason for this may be that these patients have a high level of disability or a high disease activity. In a study in the literature, it was reported that treatments did not have a significant effect on fatigue, but cladribine and ocrelizumab, which we included in the second step in this study, are not among the treatments[31]. We think that there is a need for comprehensive studies on the effect of all treatment options on fatigue in MS.

Although fatigue is more common in progressive disease forms, few studies examining fatigue and other associated symptoms have specifically examined the progressive patient population[27]. Fatigue was reported more common in progressive forms of the disease however, there are no data on fatigue in the PPMS and SPMS groups. In a recent study, the severity of fatigue was associated with quality of life, depression, anxiety, and cognition in these patients, and it was found to be similar for the progressive and non-progressive forms of the disease[29].

Our findings on this controversial issue show that fatigue is significantly higher in the PPMS group. We also observed this divergence between PPMS and SSMS. Although there is no clear pathophysiological explanation for this, the progressive progression of the disease from the onset may contribute to the cumulative higher levels of fatigue.

On the other hand, apathy is an under-researched topic in MS and affects approximately 22% of MS patients according to limited study data[34]. Apathy is examined in 3 sub-fractions (cognitive, emotional and behavioral). We know that cognitive apathy, in which goal-directed executive functions and planning are impaired, is mostly associated with the region that includes the dorsolateral prefrontal cortex and caudate nucleus, that emotional apathy followed by blunted affect, which cannot be attributed to depression, is related to the orbitomedial prefrontal cortex, anterior cingulate cortex, and amygdala, that behavioral apathy, which manifests itself with a decrease in the emergence of internal thought and behavior, occurs in large frontal and basal ganglia involvement [35]. In a study conducted in the Japanese MS population, a correlation was found between apathy, depression, cognition and physical disability in the patient population[30]. In another study, a relationship was found between apathy, impaired memory and mental speed[36]. According to our results, apathy scores are higher in women. Contrary to the literature, we did not find a relationship between cognition and apathy. Also, our study differs from previous studies in that apathy did not show a correlation with physical disability. The type of treatment used has no effect on apathy and this relationship was examined for the first time in our study as far as we can see. Again, for the first time in our study, the relationship between MS type and apathy was investigated. According to our findings, MS type has no effect on apathy. Another important finding, which differs considerably from the literature, is the negative correlation of depression and apathy in MS patients, which was also confirmed in our regression analysis. As the depression scores of the patients increase, apathy decreases and this negative correlation persists in all depression groups. This can probably be explained by the fact that the etiological mechanism of the emergence of apathy mentioned above is different from the mechanism of the emergence of depression (prefrontal, anterior temporal and parietal cortical involvement). In addition, patients apathy scores were negatively correlated with pseudobulbar affect (emotional lability) and fatigue. Apathy levels decrease as patients' fatigue and pseudobulbar affect increase. Although we do not have sufficient studies and evidence to explain the pathophysiological reason for this finding, considering that apathy has emotional

bluntness, behavioral and cognitive inertness, it makes sense that patients' being more depressed, emotionally labile, or feeling and expressing fatigue more deeply is inversely proportional to being apathetic. Emotional and cognitive bluntness may mask all these other findings or prevent them from being expressed or felt.

Symptoms such as fatigue, impaired attention and cognition, apathy, and sleep disorders are common symptomatology of MS and depression and are thought to complicate the clinical picture, diagnosis and treatment of neuropsychiatric syndrome. However, our findings contradict the view that depression and cognitive impairment contribute to the emergence of apathy and suggest that MS treaters should consider apathy as a neuropsychiatric entity independent of other neuropsychiatric symptoms.

Lifetime prevalence of depression in MS patients exceeds 50%[30,37]. In our study, depression was found in 69.4% of the patients and 48.4% of the patient population clustered at the level of moderate and severe depression. In the same studies, depression is also associated with cognitive dysfunction.

However, there are also studies that do not confirm this correlation[38]. In our findings, cognitive impairment was detected only in 7.9% of our patients, and no correlation was observed between the two symptoms. There is no consensus on this relationship in the literature, and our findings also support that depression occurs independently of cognition. Besides, depression showed a positive correlation with physical disability in our study. It is an expected and known situation that as disability increases, depression increases.

Correlation and regression analyses in our study suggest that the presence of depression is an important factor in the occurrence of fatigue and pseudobulbar affect. As the level of depression increases, the pseudobulbar affect and fatigue increase. On the contrary, as we explained above, apathy is less common in depressive MS patients. Besides, according to our findings supported by regression analysis, cognitive impairment in MS patients; in addition to depression, is unrelated to apathy, fatigue, and pseudobulbar affect.

There are some limitations of our study due to not being performed face-to-face. Patients may not be experienced in technology usage and the quality of the environment during the performance may affect the data accuracy.

In conclusion, symptoms such as fatigue, pseudobulbar affect and apathy are quite common in multiple sclerosis and pseudobulbar affect and apathy are an often-overlooked MS related symptoms that impair the quality of life. These symptoms and related factors are still discussed in the literature and more research is needed. We believe that our findings will contribute to a better understanding and treatment of these symptoms.

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