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ORIGINAL ARTICLE

The effect of hypertension on cognitive dysfunction in female patients with fibromyalgia syndrome

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Abstract

Objective: To evaluate the effect of the presence of hypertension (HT) on cognitive dysfunction in female patients with fibromyalgia syndrome (FM).

Methods: A total of 36 female patients diagnosed with FM were included in the study and the patients were divided into 4 equal groups. Group 1 was HT with impaired cognition, Group 2 was HT with normal cognition, Group 3 was non-HT with impaired cognition and Group 4 was non-HT with normal cognition. Mini mental status examination test (MMSE) was used to assess cognitive function. Groups were compared in terms of age, FM disease duration, education, and MMSE scores. Also, the correlation of variables was investigated within the hypertensive and non-hypertensive patient groups.

Results: The median age was 51 (41-77) years and median FM disease duration was 60 (3-336) months. There was no significant difference between the groups in terms of age and disease duration (p=0.423 and p=0.308, respectively). Median MMSE value was 23.5. Between the groups with normal cognition (groups 2 and 4), MMSE median value was similar (p=0.203). Median value of MMSE was also similar (p=0.192) between the groups with impaired cognition (groups 1 and 3). Also, the median MMSE value in patients with HT was similar to in those without HT (p=0.414). When the correlation of variables was investigated within the hypertensive and non-hypertensive patient groups, no significant correlation was detected

Conclusion: In conclusion, in our cohort, which included a group of middle-aged patients, there was no evidence that HT increases cognitive dysfunction in female FM patients.

Key words: Fibromyalgia syndrome; hypertension; cognitive dysfunction

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Introduction

Fibromyalgia syndrome (FM) is a chronic disease of unknown cause, characterized by widespread pain and tender points in the musculoskeletal system, and may be accompanied by sleep and mood disorders, fatigue, and cognitive dysfunction [1]. Cognitive functions such as focus, attention and memory are affected in patients with FM [2, 3]. Cognitive dysfunction is one of the diagnostic criteria of FM and is used to determine the severity of the disease [4]. Problems related to memory and focus are called fibrofog [2, 3, 5]. Fibrofog refers to cognitive impairment such as forgetfulness, blurring of mental activity, sensory overload, difficulty in thinking, decreased ability to process information or follow conversations [6]. Approximately 80% of patients diagnosed with FM have cognitive complaints [5].

The general definition of Hypertension (HT) is systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg [7]. In more than 90% of cases with HT, no underlying cause can be identified and this is called primary HT, while 5-10% have an underlying cause and this is called secondary HT. HT is a serious medical condition that significantly increases the risk of cardiovascular, cerebral, renal and other organ dysfunction, but cognitive impairment is relatively less important [8, 9]. However, HT is a risk factor that negatively affects cognitive functions [10]. Cognitive functions are affected by blood pressure. Studies have proven that cognitive impairment is common in HT [11]. In particular, high blood pressure in middle age has been shown to increase the risk of cognitive decline and dementia in elderly [12]. Hypertensives exhibit decreased cerebral blood flow and metabolism in certain brain regions, particularly the frontal and temporal lobes and subcortical areas [13]. There are reports that hypertensives show smaller cerebral blood flow responses than normotensives during memory tasks [14]. Neurochemical transmission and basic cellular functions in the brain are also affected by hypertension. Therefore, various neurophysiological changes in hypertensives may explain their loss of cognitive function. High blood pressure is found to be related to smaller total and regional brain volumes which can be contributed to cognitive impairment [15]. This atrophy can be due to cortical neuronal apoptosis related to subcortical vascular pathologies. Endothelial damage due to high blood pressure can also disrupt the blood-brain barrier and allow toxic substances to enter the brain [13]. Also, HT is a serious risk factor for small vessel disease of the brain, and can lead to microbleeds of brain, lacunar infarcts and white matter hyperintensities [15]. This small vessel disease can result in vascular dementia or interact with Alzheimer's pathology. In addition, HT was found to be associated with the beta amyloid deposition which may lead to cognitive impairment [15].

Cognitive dysfunction develops in the presence of HT and the dysfunction has been shown to be more severe in the presence of HT. Since cognitive impairment is associated with FM disease severity, it can be concluded that HT affects cognitive function in FM patients [16]. Although cognitive dysfunctions in HT and FM have been investigated separately, we have not found a study in the literature investigating the relationship between HT and FM according to the cognitive function. The aim of this study was to evaluate the effect of the presence of HT on cognitive dysfunction in patients with FM.

Methods

To determine the sample size, G*Power 3.1.9.4 (Duesseldorf, Germany) was used [17]. According to F tests, the total sample size for 4 groups was calculated as 36, with an effect size of 0.54, α= 0.05 and 95% power [18]. A total of 36 female patients over 18 years of age who applied to Ondokuz Mayıs University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation and who were diagnosed with FM according to American College of Rheumatology-2016 FM diagnostic criteria and who gave written consent to participate in the study were included in the study. Exclusion criteria were as follows: cognitive impairment that prevents patients from answering the questionnaire, psychiatric diagnosis, systemic diseases other than HT, secondary HT and patients who were taking medication for FM. Patients were divided into 4 equal groups. Group 1 was HT with impaired cognition, group 2 was HT with normal cognition, group 3 was non-HT with impaired cognition and group 4 was non-HT with normal cognition. Patients diagnosed by a specialist were considered to have HT. Age, education and disease duration of the patients were recorded.

The Mini Mental State Examination Test (MMSE) was used to evaluate cognitive function. It was developed to quantitatively assess cognitive performance [19]. Its subsections include time and space orientation, recording memory, attention and concentration, recall and language. It is scored by summing the scores obtained from each item. The MMSE, which can be administered in 10 minutes under outpatient clinic conditions, is scored over a total of 30 points [19].

A score of ≤ 23 is considered cognitive impairment [20]. Turkish reliability and validity was conducted by Güngen et al [21].

For statistical analysis SPSS 22 (IBM, USA) was used. Kolmogorov-Smirnov, skewness-kurtosis and histogram-plots were used for evaluating normal distribution. Descriptive statistics were used. Median (min-max) values were given for non-normally distributed data. Kruskal Wallis and Mann Whitney U test were used to evaluate the difference between groups in terms of continuous variables. The chi square test was used to evaluate the difference in frequencies between groups. Also, MANOVA test was used to find the difference originated between which groups. Levene's test was used to analyse the equality of variances. For Post Hoc analysis, when the variance of the dependent variable is equal across groups Tukey's test was used for correction and when the variance of the dependent variable is not equal across groups Tamhane's test was used for correction. Spearman correlation coefficient analysis was done to evaluate the correlations between age, disease duration and MMSE scores. A value between 0 and 0.3 was considered negligible correlation, a value between 0.3 and 0.50 was accepted as low correlation, a value between 0.51 and 0.7 was considered moderate correlation, a value between 0.7 and 0.9 was considered high correlation, and a value between 0.9 and 1.00 was considered very high correlation [22]. Significance level was set $p<0.05$.

Results

The total number of patients was 36, 9 in each group. All were female and married. The median age was 51 (41-77) years and median FM disease duration was 60 (3-336) months. There was no significant difference between the groups in terms of age, disease duration and education (p=0.423, p=0.308 and P=0.322, respectively). Table 1 shows the comparison of the groups according to demographic variables. Median MMSE value was 23.5. Between the groups with normal cognition (groups 2 and 4), MMSE median value was similar (p=0.203). Median value of MMSE was also similar (p=0.192) between the groups with impaired cognition (groups 1 and 3). Table 2 shows the comparison of the groups according to MMSE score. Also, the median MMSE score in patients with HT was similar to in those without HT (p=0.414, Table 3). A significant, low, negative correlation was found between age and MMSE scores when all patients were considered (Table 4). On the other hand, when the correlation of variables was investigated within the hypertensive and non-hypertensive patient groups, no significant correlation was detected (Table 5 and 6). Variance analysis showed no difference between groups according to age and disease duration, but MMSE (Table 7).

Table 1. Comparison of the groups according to demographic variables.

		Total N=36	Group 1 N=9	Group 2 N=9	Group 3 N=9	Group 4 N=9	P value
Age, years, Median (min-max)		51 (41-77)	55 (49-77)	51 (43-65)	50 (41-72)	51 (42-58)	0.423[1]
Education, N	Literate	2	1	0	1	0	0.322[2]
	Primary school	24	7	6	6	5	
	Secondary school	2	1	0	1	0	
	High school	6	0	2	0	4	
	University	2	0	1	1	0	
Disease duration, months, Median (min-max)		60 (3-336)	84 (24-246)	60 (3-120)	72 (12-144)	120 (6-336)	0.308[1]

* Significance level $p<0.05$, [1] Kruskal-Wallis test, [2] Chi-Square test, Group 1: Hypertension with impaired cognition, Group 2: Hypertension with normal cognition, Group 3: Non- Hypertension with impaired cognition, Group 4: Non- Hypertension with normal cognition, min: minimum, max: maximum, N: subject number.

Table 2. Comparison of the groups according to Mini mental status examination test score.

	Total N=36	Group 1 N=9	Group 2 N=9	Group 3 N=9	Group 4 N=9	P value
MMSE, score, Median (min-max	23.5 (12-28)	21 (17-23)[2,a]	24 (24-28)[2,b]	20 (12-22)[2,a]	24 (24-25)[2,b]	<0.001[1,*]
	Group 1 vs. Group 2					<0.001[2,*]
	Group 1 vs. Group 3					0.192[2]
	Group 2 vs. Group 3					<0.001[2,*]
	Group 2 vs. Group4					0.203[2]
	Group 3 vs. Group4					<0.001[2,*]

* Significance level p<0.05, [1] Kruskal-Wallis test, [2] Mann-Whitney U test, while same letters show no significance, different letters show significant difference, Group 1: Hypertension with impaired cognition, Group 2: Hypertension with normal cognition, Group 3: Non-Hypertension with impaired cognition, Group 4: Non- Hypertension with normal cognition, MMSE: Mini mental status examination test, min: minimum, max: maximum, N: subject number.

Table 3. Comparison of the hypertensive and non- hypertensive patients according to age, disease duration and Mini mental status examination test score.

	Hypertensive patients N=18	Non- Hypertensive patients N=18	P value
Age, years, Median (min-max)	54 (43-77)	50.5 (41-72)	0.326[1]
Disease duration, months, Median (min-max)	60 (3-246)	78 (6-336)	0.372[1]
MMSE, score, Median (min-max)	23.5 (17-28)	23 (12-25)	0.414[1]

* Significance level p<0.05, [1] Mann-Whitney U test, MMSE: Mini mental status examination test, min: minimum, max: maximum, N: subject number.

Table 4. Correlation of variables among the patients (N=36).

Spearman's rho		Disease duration	MMSE score
Age	R	,238	-,337*
	P value	,162	,045
Disease duration	R	1,000	-,200
	P value	.	,243

* Significance level p<0.05, MMSE: Mini mental status examination test, N: subject number, R: Correlation Coefficient.

Table 5. Correlation of variables among the hypertensive patients (N=18).

Spearman's rho		Disease duration	MMSE score
Age	R	,392	-,431
	P value	,108	,074
Disease duration	R	1,000	-,399
	P value	.	,101

* Significance level p<0.05, MMSE: Mini mental status examination test, N: subject number, R: Correlation Coefficient.

Table 6. Correlation of variables among the non-hypertensive patients (N=18).

Spearman's rho		Disease duration	MMSE score
Age	R	,136	-,269
	P value	,590	,280
Disease duration	R	1,000	,035
	P value	.	,889

* Significance level p<0.05, MMSE: Mini mental status examination test, N: subject number, R: Correlation Coefficient.

Table 7. Variance analysis to explore the differences between groups.

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	p	Partial Eta Squared
Between groups	Age	224,750	3	74,917	1,072	,375	,091
	Disease duration	21972,750	3	7324,250	1,577	,214	,129
	MMSE	232,111	3	77,370	17,826	,000	,626

* Significance level p<0.05, MMSE: Mini mental status examination test

Discussion

In our study, MMSE score in FM patients with HT was similar to in those without HT. A significant, low, negative correlation was found between age and MMSE scores when all patients were considered. On the other hand, when the correlation of variables was investigated within the hypertensive and non-hypertensive patient groups, no significant correlation was detected. Variance analysis showed no difference between groups according to age and disease duration, but MMSE.

It is known that the cognitive functions are affected in patients with FM [2, 3]. Some studies have reported that cognitive dysfunction in FM is not much different from other chronic painful conditions. In a study conducted by Dick et al., although FM patients showed significantly higher levels of anxiety than the rheumatoid arthritis and musculoskeletal pain patient groups, FM patients did not appear to have more severe attentional problems than other chronic pain patients. Furthermore, FM patients did not perform more poorly than patients with rheumatoid arthritis or musculoskeletal pain patients on any of the investigated domains of attention and cognitive function [Dick]. However, cognitive dysfunction is still one of the diagnostic criteria of FM and is used to determine the severity of the disease [4].

Hypertension is one of the most common comorbid

conditions in FM patients [23]. Cognitive dysfunction develops in the presence of HT and, it can be concluded that HT may affects cognitive function in FM patients [16]. However, we did not find significant differences in FM patients with and without HT according to cognitive functioning.

Since simple and rapid tests that can be used to evaluate cognitive functions in FM patients are limited in clinical practice, it is suggested that self-report can be used instead of complex tests [24]. However, scales that evaluate global cognitive function, such as the MMSE, come to the fore in investigating the effects of systemic diseases, including HT, on cognitive functions [25]. In our study, we used MMSE to investigate cognitive function and created subgroups according to the MMSE cut-off value.

Pulse pressure is a well-established predictor of cognitive variability in aging [26-28]. Similar to our study, Kircher et al. [29] used MMSE and the same cutoff value in the assessment of cognitive function in their study. However, unlike our study, they excluded those with cognitive dysfunction according to the MMSE score. The main hypothesis of their study was that systolic blood pressure, diastolic blood pressure, and pulse pressure would have an impact on the ability to solve daily life problems in older adults, beyond the contribution of demographic and neuropsychological variables. However, it was hypothesized that a concomitant FM condition would be a significant predictor of the ability to solve daily life problems. This assessment was made by applying the Everyday Problems Test to patients whose cognitive function was considered normal according to the MMSE score [29]. Their results revealed that higher systolic blood pressure and higher pulse pressure were both related to better everyday problem solving- real-world functioning on cognitive tasks of daily living, but no significant relation was found between presence of FM and worse performance in everyday problem solving [29]. In the study of Reyes del Paso et al. [30] in the healthy subjects, but not in the FM patients, blood pressure was found to be inversely associated with mental performance. In a meta-analysis conducted by Gifford et al. [25] small to modest correlations found between increasing blood pressure and poorer episodic memory and global cognitive performances as well as the modest correlation between increasing blood pressure and enhanced attention performances. It should be noted that some studies were designed to evaluate the relationship between hypertension and cognitive function, while some studies were designed to evaluate the relationship between blood pressure and cognitive function [13]. Results of studies examining the relationship between hypertension and cognitive function indicate that hypertensives perform worse than normotensives in almost all areas of cognitive function, including learning and memory, attention, abstract reasoning, executive functions, and visuospatial, perceptual, and psychomotor skills. However, hypertension has generally not been associated with verbal intelligence or language skills [13]. Our hypothesis was similar to these findings however, we did not find an effect of HT on cognitive functioning in FM patients. Results of studies examining the relationship between blood pressure and cognitive function generally show that increases in blood pressure are associated with gradual decreases in cognitive function. Interestingly, however, a few studies have found that lower blood pressure levels are associated with poorer cognitive function [13]. Contrary to the literature [25], Kircher et al. [29] found that higher blood pressure was associated with better everyday problem solving in older adults. So, the both high and low blood pressure are seemed to be associated with lower cognitive function [31].

Hypertensive patients are usually not clinically affected on cognitive tests [13]. They do not have the severe cognitive impairment known as dementia, and their test performance is usually within the normal range. However, the effect of hypertension on cognition may be considered clinically significant [13]. We can attribute the fact that the median value of the MMSE score in our study was so close to the cut-off value and that we did not find a significant difference in cognitive function between FM patients with and without HT to this situation.

Furthermore, meta-analysis reported by Gifford et al. [25] suggests that high blood pressure is associated with worse aspects of cognitive aging before the onset of clinical dementia or stroke, independent of important demographic variables (e.g., age, education) and medical or vascular comorbidities (e.g., diabetes, cholesterol, other prevalent cardiovascular disease). In our study, patients with systemic diseases other than HT were excluded and so this argument has not been investigated. In our study, increasing age was found to be correlated with deterioration in cognitive functions. However, this association was not present in the

subgroups of patients with and without HT. Also, the FM patients with and without HT did not differ according to the cognitive function.

Although, some studies have shown that HT at an early age can also affect cognitive functions [32], it is known that, especially high blood pressure in middle age increases the risk of cognitive decline and dementia in elderly [12, 33]. And also, HT affects cognitive function more in the elderly [34, 35]. One study reported lower memory test scores in those diagnosed with HT at age <55. They found that HT was associated with a decrease in global cognitive function score and memory test score [32]. Most of the patients in our study were middle aged. Despite the FM patients are generally from the middle age group FM disease can also be seen in the elderly, and new studies can be conducted among elderly FM patients [35].

Typically, HT patients in studies investigating the effects of HT on cognitive function are either not taking medication or have stopped taking their antihypertensive medications before cognitive testing, because antihypertensive medications can have small but significant effects on cognitive function on their own [13]. In spite of strong evidence of biological mechanisms, studies do not strongly show that the antihypertensive therapy should be better for cognition [15]. Also, animal experiments have shown that angiotensin-I inhibitors can cause FM-like symptoms in mice [37]. Although antihypertensive medications and cognitive function and FM seem to be so intertwined, medication was ignored in our study because the evidence was not strong and the possible effects were relatively small. However, it should be kept in mind that this situation may have affected the results of our study.

Depression, anxiety, sleep disturbance, and pain may be related to cognitive function in FM patients. Dick et al. [18] investigated these factors in their study and reported that only chronic pain had a significant negative effect on cognitive function. Similar findings were found by Reyes del Paso et al. [30] When considering the results of our study, it should be taken into account that depression, anxiety and sleep disorders were not examined in our study and a separate scale was not used for the pain parameter.

Although cognitive dysfunctions in HT and FM have been investigated separately [13,18], there is no other study examining the effect of blood pressure on cognitive function in FM patients except Kircher et al. [29] and Reyes del Paso et al. [30]. Those with MMSE score <24 were excluded from the study by Kircher et al., and in our study those with cognitive dysfunction according to MMSE score were also examined. Also, Reyes del Paso et al. [30] applied arithmetic task to assess the mental performance of FM patients and healthy controls, but in our study, we preferred to apply MMSE to examine the global cognitive function. In this respect, our study is the first in the literature. This can be considered the strength of our study. The lack of male patients was a limitation, but this was expected due to female gender dominance in FM. FM is generally seen among females [38], and only female patients were included in this study. That's why the conclusions cannot be generalized to males. Although the patients with psychiatric diagnosis are excluded, the lack of investigating depression and anxiety which are generally associated with cognitive functioning is another limitation. Another important limitation of our study was that we did not use a separate scale for the pain parameter, which may negatively affect cognitive function. In addition, although we determined the sample size by power analysis, another limitation of our study was that the sample size was too small. This may lead to such findings. Most of the patients in our study were middle aged and these findings may not be generalized to elderly FM patients. One of the shortcomings of our study was that we did not investigate the HT medications used. Also, we did not consider the severity of HT by following the patients for daily blood pressure. Another limitation of our study was that the study was single-centered. It should be taken into consideration that there may be differences in terms of understanding, comprehension and interpretation of the questions due to regional differences.

Conclusion

In conclusion, in our cohort, which included a group of middle-aged patients, there was no evidence that HT increases cognitive dysfunction in female FM patients. Further studies can be conducted with a larger number of FM patients by including elderly.

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24-26 May 2024 (Available at https://www.karat.org.tr/wp-content/uploads/2024/06/KARAT-2024-Tam-Metin-Bildiri-Kitabi.pdf). The study was conducted in accordance with the Declaration of Helsinki and followed the ethical standards of the TÜRKİYE.

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Ethical Declaration: Ethics approval for the study was obtained from the Ondokuz Mayıs University Clinical Research Ethics Committee (date: 29.04.2021, no: 2021/227)

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