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Effects of Atrial Fibrillation on Cognitive Functions in Patients Between 65-75 Years of Age

65-75 Yaş Arası Hastalarda Atriyal Fibrilasyonun Kongnitif Fonksiyonlar Üzerine Etkileri

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Effects of Atrial Fibrillation on Cognitive Functions in Patients Between 65-75 Years of Age

ABSTRACT

Objective: Atrial fibrillation (AF) is the most common arrhythmia in the elderly population and also the most common cause of ischemic stroke. Ischemic stroke is directly related to cognitive decline. The relationship between atrial fibrillation and cognitive decline has long been associated with stroke. This study aimed to reveal whether the mere presence of atrial fibrillation, independent of stroke, has negative effects on cognitive functions.

Material and Method: Male and female patients between the ages of 65 and 75 with no chronic diseases other than known hypertension were included in the study. They were divided into two groups according to electrocardiography findings: the group with newly diagnosed atrial fibrillation and the group with normal sinus rhythm (NSR). To evaluate cognitive functions, the Montreal Cognitive Assessment (MoCA) was applied to both groups and then the groups were compared in terms of scores.

Results: No statistically significant difference was observed between the groups in terms of age, patient characteristics, educational status, or laboratory findings. MoCA scores were significantly lower in the AF group than in the NSR group (p=0.001). Multivariable linear regression analysis demonstrated lower age and higher education status were independently associated with high MoCA scores (β: 3.392, 95% CI: 2.375 - 4.410, p<0.001 / β: -0.478, 95% CI: -0.664 - -0.292, p<0.001, respectively). In addition, AF was independently associated with low MoCA scores after adjustments by age and education status (β:-2.463, 95% CI: -3.448 - -1.478, p<0.001).

Conclusion: AF is a risk factor for cognitive decline regardless of the presence of ischemic stroke.

Keywords: Arrhythmia, atrial fibrillation, cognitive decline.

ÖZET

Amaç: Yaşlı popülasyonda en sık görülen aritmi olan atriyal fibrilasyon (AF), aynı zamanda iskemik inmenin de en sık nedenidir. İskemik inme bilişsel gerilemeyle doğrudan ilişkilidir. Atriyal fibrilasyon ile bilişsel gerileme arasındaki ilişki yıllardır inme ile ilişkilendirilmiştir. Bu çalışma, inmeden bağımsız olarak sadece atriyal fibrilasyon varlığının bilişsel işlevler üzerinde olumsuz etkilerinin olup olmadığını ortaya koymayı amaçlamıştır.

Gereç ve Yöntem: Çalışmaya bilinen hipertansiyon dışında kronik hastalığı olmayan, 65-75 yaş arası erkek ve kadın hastalar dahil edildi. Elektrokardiyografi bulgularına göre hastalar yeni tanı alan AF grubu ve normal sinüs ritmi (NSR) grubu olmak üzere ikiye ayrıldı. Bilişsel işlevleri değerlendirmek amacıyla her iki gruba da Montreal Bilişsel Değerlendirme (MoCA) uygulandı ve gruplar sonuçlar açısından karşılaştırıldı.

Bulgular: Gruplar arasında yaş, hasta özellikleri, eğitim durumu ve laboratuvar bulguları açısından istatistiksel olarak anlamlı fark yoktu. MoCA skoru AF grubunda NSR grubuna göre anlamlı derecede düşüktü (p=0,001). Çok değişkenli doğrusal regresyon analizi, düşük yaş ve yüksek eğitim durumunun bağımsız olarak yüksek MoCA puanıyla ilişkili olduğunu gösterdi (β: 3,392, %95 GA: 2,375- 4,410, p<0,001 / β: -0,478, %95 GA: -0,664 - -0,292, p<0,001, sırasıyla). Ayrıca AF, yaş ve eğitim durumundan bağımsız olarak düşük MoCA puanıyla ilişkili bulundu (β:-2,463, %95 GA: -3,448 - -1,478, p<0,001).

Sonuç: AF, iskemik inmenin varlığından bağımsız olarak bilişsel gerileme için bir risk faktörüdür.

Anahtar Sözcükler: Aritmi, atriyal fibrilasyon, bilişsel gerileme.

Introduction

Preserving cognitive functions in elderly patients is important in terms of both maintaining quality of life and preventing morbidity and mortality. Any undesirable event that may disrupt cranial vascularization poses a threat to brain functions. Ischemic stroke is the most important condition that threatens cerebral health and atrial fibrillation is the most common cause of ischemic stroke in patients over 65 years of age (1,2). Most studies in the literature have shown a linear relationship between AF and cognitive dysfunction (3). This relationship between AF and cognitive decline has been linked to the relationship between AF and ischemic stroke for years.

However, some studies have suggested that cognitive functions may decline in AF patients without a history of stroke (4). Silent cerebral infarctions, cerebral hypoperfusion resulting from fluctuations in ventricular rate, systemic inflammation, and changing hemodynamic conditions may have an impact on cognitive functions (5,6).

The Montreal Cognitive Assessment (MoCA) is one of many screening tests used in clinical practice to evaluate cognitive functions. This test, developed for the detection of moderate-mild cognitive impairment, is a rapid mini-mental test with high sensitivity and is easy to apply (7).

Clearly identifying risk factors is important to prevent cognitive decline. In the present study, cognitive functions in AF patients without a history of ischemic stroke were evaluated with the MoCa mini-mental test and compared with patients in normal sinus rhythm. The aim was to reveal whether the presence of AF without a history of ischemic stroke regresses cognitive functions.

Material and Method

This study was a double-center, case-control study which included male and female patients aged 65-75 who applied to the Istanbul Medipol University Hospital internal medicine and Altınbaş University cardiology outpatient clinic between September 2023 and February 2024 and were not diagnosed with chronic diseases other than hypertension.

Detailed anamnesis of the patients was taken, and physical examinations were performed. Blood pressure measurements were taken from both arms and the average was calculated (Omron M3 Upper Arm Blood Pressure Monitor). Electrocardiograms were examined (EDAN SE1200 12-channel ECG device). Patients who were diagnosed with AF (first diagnosis) according to electrocardiography findings and volunteers with normal sinus rhythm in the similar age group were included in the study. The initial diagnosis of AF was made by detecting a heart rhythm with no visible repeating P waves and irregular RR intervals on the standard 12-lead ECG recording. The first diagnosis of AF was defined as the first detection of AF, regardless of the presence/severity of symptoms and duration. To exclude patients with paroxysmal AF, patients whose ECG findings were compatible with AF were called for control after 10 days and electrocardiography was repeated. Echocardiography was performed on all patients (Philips Envisor HD Ultrasound Device). Patients with left ventricular ejection fraction ≥ 50% and echocardiography findings within normal limits were included in the study.

Demographic characteristics of the patients were recorded. Peripheral blood samples were taken after a 12-hour fast. Hemogram and simple biochemical analysis were performed.

The patients were subjected to a mini-mental test (MoCA) study under the supervision of a clinician. MoCA, which takes approximately 10 minutes to administer evaluates different cognitive functions including attention and concentration, executive functions, memory, language, visual structuring skills, abstract thought, calculation, and orientation. The highest total score that can be obtained from the test is 30. Accordingly, 21 points and the score obtained in the MoCA are considered normal (8). The atrial fibrillation group and the control group were compared in terms of MoCa test results. CHA2DS2-VASC score of patients with atrial fibrillation was calculated. It was examined whether there was a correlation between this score and MoCa.

Patients with any rheumatic valve diseases, moderate or severe valve insufficiency, mild or more severe valve stenosis and underwent valve repair or valve replacement treatment, patients with congenital heart disease, ischemic heart disease, structural heart disease, patients with a neurological disease such as

dementia/Alzheimer's, a history of ischemic stroke/transient ischemic attack, patients with psychiatric diseases, and patients with a metabolic abnormality that could cause cognitive dysfunction in blood tests were excluded from the study. Additionally, since the test may be affected by education level, only high school and university graduate patients were included. Only patients diagnosed with hypertension and who did not use any medication other than antihypertensive agents were included in the study. In addition to patient statements, all examination information and prescription details were reviewed from personal health record systems, and the information was confirmed.

All subjects received information about the content of this study and signed a written consent form before participating. All procedures complied with the Declaration of Helsinki and approval was granted by the Istanbul Medipol University Clinical Research Ethics Committee (Ethics Committee Date / Number: 28.09.2023 / 784).

According to descriptive statistics (effect size=0.739) in the study by Dautzenberg et al. (9) a sample size of 40 for each group (80 in total) was used to achieve 90% power at the two-sided 0.05 significance level. The sample size was calculated by using two-sample t test power analysis (Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

Statistical Analysis

IBM SPSS Statistics for Windows Version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Histograms and Q-Q plots were used to examine the conformity of the variables to normal distribution. Descriptive statistics were presented by using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables. Normally distributed continuous variables were analyzed with the independent samples t test. Non-normally distributed continuous variables were analyzed with the Mann-Whitney U test. Categorical variables were analyzed using the chi-square test. Relationship between MoCA score and CHA2DS2-VASC score was evaluated using Spearman correlation coefficient. Linear regression analyses were performed to determine significant factors independently associated with the Montreal Cognitive Assessment score. Variables were analyzed using univariable linear regression analysis and statistically significant variables were included in the multivariable linear regression analysis. Two-tailed p-values of less than 0.05 were considered statistically significant.

Results

Included in the study were 44 individuals with atrial fibrillation (AF) and 57 individuals with normal sinus rhythm (NSR). The median age of all individuals (49 females and 52 males) was 69 (interquartile range 66 - 71, range 65 - 75) years. There was no significant difference between the AF and NSR groups in terms of age, gender, educational status, systolic blood pressure, diastolic blood pressure, and blood results including fasting blood sugar, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), thyroid stimulating hormone (TSH), and hemogram parameters.

Table I. Summary of variables and analysis results with regard to groups

	AF (n=44)	NSR (n=57)	p value
Age (year)	69 (66 - 71.5)	69 (67 - 71)	*0.815*
Sex			*0.387*
Female	24 (54.55%)	25 (43.86%)	
Male	20 (45.45%)	32 (56.14%)	
Education status			*0.718*
High school	23 (52.27%)	33 (57.89%)	
University	21 (47.73%)	24 (42.11%)	
Systolic blood pressure (mmHg)	128.5 (121- 133)	128 (120- 134)	*0.658*
Diastolic blood pressure (mmHg)	76.55 ± 7.31	75.47 ± 7.89	*0.486*
Fasting blood glucose (mg/dl)	84.66 ± 7.65	83.19 ± 8.40	*0.368*
Urea (mg/dl)	27 (21.5- 30)	24 (19- 29)	*0.268*
Creatinine (mg/dl)	0.60 ± 0.15	0.61 ± 0.13	*0.788*
ALT (U/L)	28 (23- 29.5)	28 (19- 30)	*0.675*
AST (U/L)	23.98 ± 5.20	23.84 ± 6.37	*0.909*
TSH (µIU/Ml)	2.8 (1.65- 3.9)	2.8 (1.8- 4.2)	*0.891*
Hemoglobin (g/dL)	12.96 ± 0.64	13.17 ± 0.63	*0.103*
Montreal Cognitive Assessment score	22.80 ± 3.13	25.12 ± 3.37	*0.001*
Normal (≥21)	34 (77.27%)	51 (89.47%)	*0.164*
Low (<21)	10 (22.73%)	6 (10.53%)	

Descriptive statistics were presented by using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables.

MoCA scores of all individuals were 24.11 ± 3.45.

Table II. Association between variables and Montreal Cognitive Assessment score, linear regression analysis results.

	Univariable			Multivariable		
	Unstandardized coefficients (95% CI)	Standardized coefficients	*p value*	Unstandardized coefficients (95% CI)	Standardized coefficients	*p value*
Age (years)	-0.477 (-0.687 - -0.267)	-0.413	*<0.001*	-0.478 (-0.664 - -0.292)	-0.414	*<0.001*
Sex, Male	0.013 (-1.356 - 1.383)	0.002	*0.985*			
Education status, University	3.210 (1.991 - 4.430)	0.465	*<0.001*	3.392 (2.375 - 4.410)	0.491	*<0.001*
Systolic blood pressure (mmHg)	-0.033 (-0.102 - 0.037)	-0.093	*0.355*			
Diastolic blood pressure (mmHg)	-0.101 (-0.189 - -0.013)	-0.223	*0.025*	0.002 (-0.067 - 0.070)	0.004	*0.960*
Fasting blood glucose (mg/dl)	-0.010 (-0.095 - 0.076)	-0.022	*0.825*			
Urea (mg/dl)	0.034 (-0.054 - 0.122)	0.077	*0.446*			
Creatinine (mg/dl)	1.810 (-3.146 - 6.766)	0.073	*0.470*			
ALT (U/L)	-0.016 (-0.126 - 0.093)	-0.030	*0.767*			
AST (U/L)	0.026 (-0.091 - 0.143)	0.044	*0.662*			
TSH (µIU/Ml)	-0.535 (-1.010 - -0.059)	-0.219	*0.028*	0.005 (-0.389 - 0.400)	0.002	*0.978*
Hemoglobin (g/dL)	0.831 (-0.234 - 1.896)	0.154	*0.125*			
Atrial fibrillation	-2.327 (-3.627 - -1.027)	-0.336	*0.001*	-2.463 (-3.448 - -1.478)	-0.356	*<0.001*
Adjusted R^2	-			0.492		
Regression model	-			f=20.396, *p<0.001*		

CI: Confidence interval

MoCA scores were significantly lower in the AF group than in the NSR group (*p=0.001*) (Figure I). Overall, 16 (15.84%) individuals had low (<21) MoCA scores. Low (<21) MoCA scores were detected in 10 patients (22.73%) in the AF group and 6 patients (10.53%) in the NSR group (Table I).

Table III. Correlation between Montreal Cognitive Assessment score and CHA2DS2-VASC score

	Overall	AF group	NSR group
r	*0.026*	*0.130*	*0.031*
p	*0.797*	*0.399*	*0.817*

r: Spearman correlation coefficient

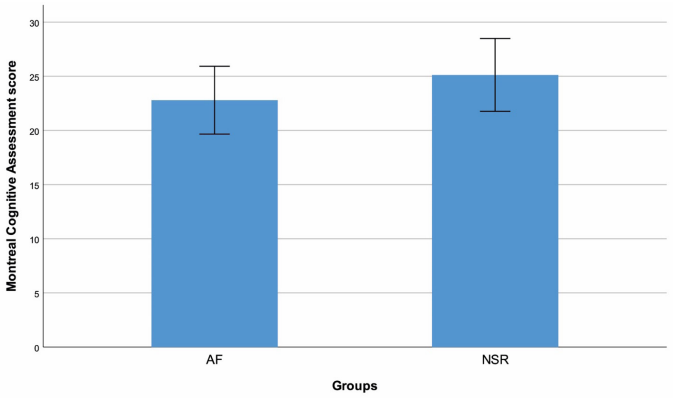

Figure I. Comparison of Montreal Cognitive Assessment (MoCA) score in AF and NSR groups (AF: Atrial Fibrillation, NSR: Normal Sinus Rhythm)

According to the multivariable linear regression analysis results, lower age (β: -0.478, 95% CI: -0.664 - -0.292, *p<0.001*) and higher education status (β: 3.392, 95% CI: 2.375 - 4.410, *p<0.001*) were independently associated with high MoCA scores. In addition, AF (β: -2.463, 95% CI: -3.448 - -1.478, *p<0.001*) was independently associated with low MoCA scores after adjustment for age and education status (Table II). We found no correlation between MoCA score and CHA2DS2-VASC score in all individuals (*r=0.026, p=0.797*), in the AF group (*r=0.130, p=0.399*) and in the NSR group (*r=0.031, p=0.817*) (Table III).

Discussion

The elderly population is increasing due to longer life spans. Age is a risk factor in itself that affects cognitive functions. Identifying and taking precautions for additional risk factors can help preserve cognitive function. In this study, it was determined that cognitive functions were significantly worse in patients with AF without a history of ischemic stroke than in patients with NSR. In other words, AF is a risk factor for cognitive decline, regardless of whether there is a history of ischemic stroke or not.

Silent cerebral infarctions, cerebral hypoperfusion resulting from fluctuations in ventricular rate, systemic

inflammation, and changing hemodynamic conditions are the main hypotheses explaining the relationship between atrial fibrillation and cognitive decline. Microemboli were detected at a rate as high as 30% by transcranial doppler ultrasonography in patients diagnosed with AF (10). To wit, microemboli, which have no obvious clinical consequences and cause silent infarctions, are found at a high rate in patients with AF. These silent infarcts may be the cause of cognitive decline (11).

The effect of hypoperfusion, another hypothesis, is explained as follows: the atrium systoles at the end of passive diastole and creates end-diastolic pressure in the ventricle. In AF, the atrium cannot perform systolic function, causing a negative effect on diastolic functions. In AF, cardiac output decreases with the withdrawal of atrium systolic support. It may cause hypoperfusion of the brain, leading to a progressive decrease in cognitive functions (12).

AF is a disease that originates from the atria but has widespread systemic effects. Fibroblast proliferation and differentiation increases in AF. Oxidative stress pathways are triggered. It may affect cognitive functions by creating localized but systemic proinflammatory effects (13).

Additionally, AF has been shown to be associated with endothelial damage. Platelet dysfunction may occur due to the pathophysiology of the disease, or the effect of the agents used (14,15).

It has been shown by different imaging methods that AF causes decline in cognitive functions. In a magnetic resonance study performed on individuals without a history of stroke, volume loss was observed in white and gray matter in the frontal cortex and cerebellum in patients with AF (16).

Various studies have been carried out around the world on this subject. In a cross-sectional study including 952 male individuals aged between 69 and 75 years, the adjusted mean cognitive score was lower in individuals with AF (+0.14+/-0.03; P=0.0003) when comorbidities and patient characteristics were adjusted (17). In a study conducted by Bunch et al, in which 37,025 cases were prospectively evaluated, a strong correlation was observed between all types of dementia, including Alzheimer's, senile and vascular dementia, and AF. Additionally, monitoring dementia in AF patients has predictive importance in terms of mortality (4). In recent studies, AF patients are divided into two: chronic and paroxysmal. The cognitive functions of both the chronic and paroxysmal AF group were found to be lower than those with normal sinus rhythm. When the chronic and paroxysmal AF groups were compared among themselves, the scores of the chronic AF group were found to be lower. This suggests that longer duration for AF is related to more decline in cognitive functions (6). A recently published systematic review reported that AF increases the impairment of cognitive functions by 1.7 to 3.3 times, independent of stroke (11).

Like these studies, in the present study, the MoCA scores, through which cognitive functions were evaluated, were significantly lower in the atrial fibrillation group. Additionally, patients with scores below normal (<21) were 22.73% in the AF group and 10.53% in the NSR group. Multivariate regression analyses also revealed that older age and the presence of AF were independently associated with lower MoCA score.

Some studies in the literature could not detect a significant relationship between AF and cognitive decline. A prospective study conducted by Park et al. on 74 newly diagnosed AF and 86 control patients, could not detect a relationship between AF and cognitive decline (18). However, in this study, the average age was 75.6 years and 59% of the patients died during the 36-month follow-up period. The reason for not finding a significant relationship may be that the remaining patients were healthy, which in turn affected the result. In another study conducted by O'Connell et al., although differences were detected between the AF group and the control group in terms of some verbal and non-verbal memory tests and some attention tests, no significant difference could be detected between the two groups in terms of cognitive functions when examined cumulatively. The reason for this may be that the number of patients diagnosed with AF included in the study consisted of a very low number of 27 (19). In a study including 533 patients, no relationship was found between AF and cognitive decline, but all patients included in this study were 85 years of age and older. Researchers interpreted this to mean that AF may not have made a significant difference because cognitive decline in very old people is affected by many other major

factors (20).

As can be seen, in cross-sectional, case-control, and cohort studies designed in different ways in the literature, patients with atrial fibrillation and normal sinus rhythm have been compared in terms of tests evaluating cognitive functions. Although there are conflicting results, results similar to those achieved in the present research have been reported more frequently.

The current study was a small-scale study conducted on 101 patients. Multicenter studies with a larger patient population are needed. Since all the patients included in this present study were newly diagnosed with atrial fibrillation, the duration of AF is unknown. Rhythm holter could be installed in patients to distinguish paroxysmal / permanent atrial fibrillation, but it could not be done due to cost. Additionally, heart failure with preserved ejection fraction was ruled out based on the fact that the patients did not have symptoms and signs of heart failure and their echocardiograms were normal, but NT-pro BNP could not be measured due to high cost.

Conclusion

The current study determined that patients with AF had more impairment in cognitive functions than individuals in sinus rhythm with similar demographic characteristics. Knowing the effects of AF on cognitive functions is especially valuable for close follow-up of elderly individuals. Early detection and treatment of AF is important to preserve cognitive functions in elderly individuals.

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