Turkish Journal of Cerebrovascular Diseases 2021; 27(2): 133-138 Türk Beyin Damar Hastalıkları Dergisi 2021; 27(2): 133-138
Turk J Cereb Vasc Dis
doi: 10.5505/tbdhd.2021.59389

RESEARCH ARTICLE **ÖZGÜN ARAŞTIRMA**

THE EFFECT ON COGNITIVE FUNCTIONS OF VASCULAR LESION LOCALIZATIONS AND VASCULAR LOAD IN THE BRAIN

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ABSTRACT

INTRODUCTION: The presence of vascular lesions may be a risk factor for neurodegenerative diseases. The white matter lesions, small vessel disease, and lacunar infarcts are known to be associated with cognitive functions impairment. However, the location of these vascular lesions and the effect of vascular load on cognition have not been clarified yet. This study aimed to investigate the effects of the localization areas of vascular lesions and vascular load on the impairment of cognitive functions.

METHODS: Fifty-two patients who underwent Mini-Mental State Examination (MMSE) were included in the study. Exclusion criteria were ischemic stroke other than small vessel disease, alcohol abuse, and traumatic brain disease. The MMSE was divided into subitems (orientation, recording memory, attention and calculation, recall, and language). The magnetic resonance imaging (MRI) of the patients was analyzed. The locations areas of the vascular lesions (juxtacortical, periventricular, and deep brain structures) and the presence of subcortical atrophy were recorded. Fazekas scale was used for the severity of vascular lesion load.

RESULTS: The mean age of the patients was 75.01±10.23 (range 53-84) years; 61.5% of the patients were female. MMSE was normal in 14 (26.9%) of the patients. The factors affecting the orientation in the multiple regression analysis were as follows: subcortical atrophy (p=0.036, β=-0.323) and periventricular vascular lesions (p=0.024, β=-0.449). The recall was found to be affected by subcortical atrophy (p=0.048, β=-0.295). Additionally, it was analyzed that subcortical atrophy (p=0.024, β=-0.345), juxtacortical area (p=0.028, β=-0.423), and vascular lesions located in deep brain structures (p=0.031, β=-0.395) affected the recording memory. The only factor affecting the MMSE was the subcortical atrophy (p=0.034, β=-0.341). Subcortical atrophy was found to be the only effective factor in detecting dementia (p=0.034, β=0.291).

DISCUSSION AND CONCLUSION: It was found that subcortical atrophy detected in MRI was the most influential factor in the development and progression of dementia and that vascular load had no effect on dementia.

Keywords: White matter lesions, dementia, cognition, small vessel disease, lacunar infarct, Mini Mental State Examination, vascular lesions.

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Received: 24.12.2020 **Accepted:** 19.02.2021
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Please cite this article as following: Öztürk İ, Tantik Pak A, Şengül HS, Nacar Doğan N, Şengül Y. The effect on cognitive functions of vascular lesion localizations and vascular load in the brain. Turkish Journal of Cerebrovascular Diseases 2021; 27(2): 133-138. doi: 10.5505/tbdhd.2021.59389

BEYİNDE VASKÜLER LEZYON YERLEŞİM ALANLARININ VE VASKÜLER YÜKÜN KOGNİTİF FONKSİYONLARA ETKİSİ

ÖZ

GİRİŞ ve AMAÇ: Vasküler lezyonların varlığı nörodejeneratif hastalıklar için risk faktörü oluşturabilir. Kognitif işlevlerin bozulmasında beyaz cevher lezyonları, küçük damar hastalığı ve laküner enfarktların rolü bilinmektedir. Ancak bu vasküler lezyonların yerleşim yerleri ve vasküler yükün kognisyon üzerine etkisi tam olarak açıklık kazanmamıştır. Bu çalışmada amacımız vasküler lezyonların yerleşim alanlarının ve vasküler yükün kognitif fonksiyonların bozulması üzerine etkisini araştırmaktı.

YÖNTEM ve GEREÇLER: Çalışmaya mini mental test (MMT) uygulanan 52 hasta dahil edildi. Dışlama kriterleri, küçük damar hastalığı dışında iskemik inme geçirmek, alkol ve madde kullanımı olmak, travmatik beyin hastalığıydı. MMT alt gruplara (Yönelim, kayıt hafızası, dikkat ve hesaplama, hatırlama ve lisan) ayrıldı. Hastaların MRG'leri incelendi, vasküler leyonların yerleşim yerleri (juxtakortikal, periventriküler ve derin beyin yapıları) ve subkortikal atrofileri kaydedildi. Vasküler lezyon şiddetini belirlemek için Fazekas kullanıldı.

BULGULAR: Hastaların %61,5'i kadın olup, yaş ortalaması 75,01±10,23 (yaş aralığı: 53-84) idi. Hastaların %26,9'unda (n=14) MMT normaldi. Çoklu regresyon analizinde yönelime etkisi olan faktörler; subkortikal atrofi (p=0,036, β=-0,323) ve periventriküler yerleşimli vasküler lezyonlardı (p=0,024, β=-0,449). Hatırlamayı etkileyen faktörler; subkortikal atrofi (p=0.048, β=-0.295) olarak saptanmıştır. Kayıt hafızasını etkileyen faktörler ise subkortikal atrofi (p=0,024, β=-0,345), jukstakortikal alanda (p=0,028, β=-0,423) ve derin beyin yapılanlarında yerleşen vasküler lezyonlar (p=0,031, β=-0,395) olarak saptanmıştır. Toplam MMT etki eden tek faktör subkortikal atrofi olarak belirlenmiştir (p=0,034, β=-0,341). Demansın saptanmasında ise tek etkili faktörün subkortikal atrofi olduğu saptanmıştır (p=0,034, β=0,291).

TARTIŞMA ve SONUÇ: Demansın gelişiminde ve ilerlemesinde MRG'de saptanan subkortikal atrofinin en etkili faktör olduğu gözlenmiş olup Fazekas evrelerinin yani vasküler yükün etkisinin olmadığı saptanmıştır.

Anahtar Sözcükler: Beyaz cevher lezyonları, demans, kognisyon, küçük damar hastalığı, laküner enfarkt, Mini Mental Test, vasküler lezyonlar.

INTRODUCTION

Dementia is an irreversible clinical picture that causes the deterioration of more than one cognitive area, affects daily life activities, and impairs functionality in work, school, and social life. The incidence of dementia is 7% in individuals over the age of 65, and this rate is between 8-10% in developed countries since the average age of the population is higher (1). Although Alzheimer's disease (AD) is the most diagnosed cause of cognitive impairment in advanced ages, vascular dementia (VD) that occurs with vascular lesions is one of the crucial causes of cognitive impairment (2).

Vascular dementia can be defined as dementia characterized by vascular lesions in different localizations caused by various vascular mechanisms in the brain and with different clinical manifestations (3). While in the past, it was defined as dementia that developed only after a large infarction, the definition has changed over time with the detection of cortical multi-infarcts. However, it was later found that vascular lesions in subcortical areas also cause dementia, so it has been defined as a vascular cognitive disorder (4).

Many different vascular subtypes have been described. Multi-infarct dementia located in the cortical area, small vessel disease located in the subcortical area, and infarcts situated in the strategic location such as the thalamus are also included in this subgrouping together with many other groups (4,5). Small vessel disease is an important cause of cognitive impairment and dementia (2).

White matter hyperintensities are pretty common in the aging population and are seen in up to 80% of healthy individuals aged 60 years (6). Vascular lesions and white matter hyperintensities are also defined in AD pathology (7). It has been reported that the rate of conversion to AD is increased in patients with mild cognitive impairment with high white matter hyperintensities compared to those without white matter hyperintensities (8).

It is well known that the prevalence of white matter lesions increases with age. However, little is known about the differences between subcortical atrophy and lesions located in the periventricular region and the cognitive

impairment caused by lesions located in the lobar, and the frequency specific to the location of vascular lesions. It is essential to make this distinction, as subcortical, juxtacortical, periventricular white matter lesions, and vascular lesions in deep brain structures may lead to different cognitive or motor outcomes. Since dementia is an irreversible and progressive clinical condition, it is essential to detect cognitive impairment at an early stage and to develop preventive approaches and treatments that can be applied in this period. The importance of the relationship between vascular lesions and cognitive impairment comes from this situation. This study aimed to investigate the effects of vascular lesions and vascular load on the deterioration of cognitive functions.

METHODS

Our study was planned as a retrospective observational study. The study was approved by the Gaziosmanpaşa Training and Research Hospital Ethics Committee (Number: 124, Date: 01.07.2020) and was carried out in accordance with the ethical rules specified in the Declaration of Helsinki.

Patients: Fifty-two patients over 18 who underwent the Standardized Mini-Mental Test (MMT) and underwent brain magnetic resonance imaging (MRI) were included in the study. Our exclusion criteria; stroke, known dementia, alcohol or substance abuse, traumatic brain injury, mental retardation, psychotic disorder including schizophrenia or bipolar disorder, diagnosis of multiple sclerosis or motor neuron disease, developmental disability, progressive malignancy diagnosis, or existing evidence. The sociodemographic characteristics and the education level of the patients, the total score of MMT, and the evaluations of its subgroups (orientation, recording memory, attention, and calculation, recall, and language) were recorded to evaluate the cognition.

Mini-Mental Test (MMT): MMT was first published by Folstein et al. (9). The Turkish validity and reliability study was conducted by Güngen et al. in 2002 and by Babacan-Yıldız in 2015 (10). The test is a short, valuable and standardized method that can be used to determine the cognitive level globally. It consists of eleven items gathered under five main headings as orientation, recording memory, attention and calculation, recall, and language, and is evaluated out of a total score of 30. MMT was applied to our patients in outpatient clinic conditions by our MMT psychologist, adapted to the educated and uneducated, according to their education level.

Magnetic Resonance Imaging (MRI): Scans were performed in 1.5 T-MRI units (GE Signa Explorer; GE, Milwaukee, WI, USA) for all patients. Non-contrast T1-weighted, T2-weighted, and Flair sequences were applied. T1-weighted MRI (TR/TE:543/24 ms), axial and sagittal, T2-weighted MRI (TR/TE:5724/102 ms), axial and coronal sections were taken. Axial sections were taken for flair images (TR/TE:8000/86 ms). Imaging by the radiologist for the location of the lesions (juxtacortical, periventricular, and deep brain structures), subcortical atrophy, and lesion burden [Fazekas staging: Fazekas 0: No lesion or single point lesion (white matter hyperintensity), Fazekas 1: Many point lesions, Fazekas 2: Lesions tending to coalesce (bridging), Fazekas 3: Large, confluent lesions)] were evaluated and noted. Subcortical atrophy was calculated by the ventricle/brain ratio (no distinction between white and grey matter). While lesions located in the white matter adjacent to the cortex were considered to be located in the juxtacortical, the signals observed in the white matter extending from the ventricle neighborhood to the cortex at a distance of 5 mm were considered as periventricular localized. The radiologist (SND) performed the evaluation blinded to the demographic and clinical findings of the patients.

Statistics: IBM SPSS Statistics Version 20.0 package program was used. Categorical measurements were evaluated as numbers and percentages, numerical measurements were assessed as mean and standard deviation (median and minimum-maximum where necessary), and descriptive statistics were used. The distribution of data was evaluated with the Shapiro-Wilk test. In comparisons between groups, an Independent simple T-test was used for data with normal distribution, and the Mann-Whitney U test was used for data without normal distribution. Multiple regression analysis was used to evaluate the relationship between MMT and vascular lesion localization areas. Statistical significance level was taken as 0.05 in all tests.

RESULTS

The mean age of the patients was 75.01±10.23 years, and 61.5% (n=32) of the patients were female, and 38.5% (n=20) were male. The mean MMT of all patients was 18.56±6.49 points. The MMT score was normal (>24) in 26.9% (n=14) of the patients, was compatible with mild cognitive impairment (19-23) in 11.5% (n=6), was compatible with moderate cognitive impairment (10-18) in 25% (n=13), was compatible with severe cognitive impairment in 36.5% (n=19) (<10) (Table 1).

In multiple regression analysis, the factors affecting the orientation; subcortical atrophy (p=0.036, β=-0.323) and periventricular vascular lesions (p=0.024, β=-0.449); factors affecting recall; subcortical atrophy (p=0.048, β=-0.295); factors affecting recording memory; vascular lesions located in subcortical atrophy (p=0.024, β=-0.345), juxtacortical area (p=0.028, β=-0.423), and deep brain structures (p=0.031, β=-0.395) (Table 2). No significant correlation was found between the localization areas of vascular lesions and attention/calculation-recall-language impairment (p>0.5).

The only factor affecting the total MMT was determined as subcortical atrophy (p=0.034, β=-0.341). Subcortical atrophy was also found to be the only effective factor in the detection of dementia (p=0.034, β=0.291). No significant relationship was found between the phase of Fazekas and the occurrence and stage of dementia (the effect of age and education level was removed).

Table 1. Sociodemographic and clinical data of all patients.

N		**52**
Age		75,01±10,23 years
Gender		
	Female	61,5% (n=32)
	Male	38,5% (n=20)
Education Level		
	Uneducated	67,3% (n=35)
	Primary education	25% (n=13)
	High school	1,9% (n=1)
	University	5,8% (n=3)
MMT*		18,56±6,49
Cognitive Impairment		
	Normal (>24)	26,9% (n=14)
	Mild (19-23)	11,5% (n=6)
	Moderate (10-18)	25% (n=13)
	Severe (<10)	36,5% (n=19)

*MMT: Mini-Mental Test

Table 2. Comparison of vascular lesion areas and MMT subgroups.

	Subcortical atrophy		**Juxtacortical**		**Periventricular**		**Deep brain structures**	
	β	p**	β	p**	β	P**	β	p**
Orientation	-0.323	0.036	-0.030	0.874	-0.449	0.024	-0.068	0.704
Recording memory	-0.345	0.024	-0.423	0.028	-0.032	0.865	-0.395	0.031
Attention and calculation	-0.255	0.125	-0.228	0.276	-0.037	0.861	-0.027	0.891
Recall	-0.295	0.048	-0.124	0.554	-0.106	0.615	-0.075	0.705
Language	-0.226	0.173	-0.150	0.471	-0.228	0.280	-0.208	0.292
Total MMT*	-0.341	0.034	-0.179	0.369	-0.223	0.269	-0.089	0.636

*MMT: Mini-Mental Test, ** Multiple regression analysis

DISCUSSION AND CONCLUSION

White matter lesions, lacunar infarctions, and cerebral microhemorrhages can lead to cognitive impairment and dementia (11,12). It is essential to detect these clinically silent lesions, determine which group should be treated, and determine the necessary preventive treatment. It will seriously affect the quality of life of these patients and their relatives. In our study, in which we investigated the effects of vascular lesions in the brain and vascular load on cognitive functions, it was determined that subcortical atrophy was the most influential factor detected in MRI in the development and progression of dementia. It has been observed that the localization areas of the vascular lesions are associated with the deterioration of some cognitive functions. No correlation was found between Fazekas stages, i.e., vascular load, MMT score, MMT subgroups, and dementia development.

Subcortical structures such as the amygdala, accumbens, and hippocampus are particularly vulnerable to amyloid and tau deposition in the early stages of Alzheimer's disease. Amyloid and tau deposition then expands to include the thalamic nuclei and the caudate nucleus (13,14). With this pathology, it can be said that subcortical atrophy will occur even in the early stage of cognitive effects. In the study by Hilal et al., cognitive functions and subcortical structures were compared, and it was found that decreased

volumes of all subcortical structures except the pallidum and putamen were associated with the deterioration of cognitive functions (15).

Although the measurement of the subcortical area was calculated differently in our study, a significant relationship was found between subcortical area atrophy and deterioration of cognitive functions in accordance with this study.

In the study by Dadar et al., the volume and localization of white matter hyperintensities (periventricular, deep, and juxtacortical brain regions) were evaluated in patients with minimal cognitive impairment who developed dementia (N=178) and patients who remained stable (N=413). They found that the lesions were more intense in all regions in the group that turned into dementia ($p<0.001$), but the intensity of T1 hypointensity in the juxtacortical area was significantly higher than in other areas. They reported that the juxtacortical area was affected by different mechanisms compared to the deep and periventricular regions in the process of conversion to dementia (8). Our study determined that the most effective factor in the transformation process to dementia was subcortical atrophy, and no significant relationship was found between lesions in the juxtacortical area and the development of dementia.

In a population-based cohort study (Sydney Memory and Aging Study), 466 patients were included. The relationship between Voxel and tract-based DTI data and MMT was evaluated in the study. It has been reported that the location of vascular lesions is associated with cognitive functions (executive functions), but the vascular load does not affect cognitive functions. In this study, the 'Controlled Oral Word Association Test' and 'Trail Making Test B' were used to evaluate executive functions (16). Although a different MRI technique was used in our study, it has similar results with our research in that it states that the location of vascular lesions affects cognitive functions, and that vascular load does not affect cognition.

In a study which was planned longitudinally with the hypothesis that 'cortical cerebral microinfarcts may be a biomarker of the development of dementia, and included 313 patients, it was reported that there was a rapid decline in memory and language areas in people with cortical cerebral microinfarcts (17). The longitudinal planning of this study, the 3T MRI technique, and MoCA used for cognitive evaluation are the main differences in our research. However, it was similar to our study in that it reported that vascular lesions were associated with cognition. In a study using the data of the memory clinic, the relationship between cortical microinfarcts and cognition was evaluated, and a significant relationship was found between cortical microinfarcts and impairment in MMT, language, and visual function areas. In this study, the 'Boston naming test' was used for language evaluation, and the 'Wechsler memory scale-revised visual reproduction copy task' was used for visual functions. In addition, imaging techniques were planned with 3 Tesla MRIs. In this study, the rate of being diagnosed with vascular dementia was found to be higher in patients with cortical microinfarction (18). In our study, the factor affecting the total MMT score was determined as subcortical atrophy. Since we do not have a detailed neuropsychological evaluation, we do not have data on language and visual functions. However, in our study, cortex structure was found to be associated with vascular dementia.

In the study of Giorgio et al., which included 110 multicenter patients, the localization of white matter disease and the relationship between the volume of the lesions and cognition were evaluated. Regardless of lesion burden, poorer cognitive function with more intense white matter lesion in the inferior longitudinal fascicle, inferior frontal-occipital fascicle, and superior longitudinal fascicle has been reported. Voxel-based diffusion tensor imaging was used for imaging, and the 'Tuscany Neuropsychological Battery' was used for cognitive evaluation. Although different techniques were developed in our study, they reported that the localization areas of vascular lesions were effective on cognition as in our study (19). On the contrary, 1017 patients (Intervention project on cerebrovascular disease and dementia in the district of Ebersberg, INVADE II) were included in the study of Altermatt et al., and no correlation was found between lesion localization and test battery, but they found a significant relationship between lesion load and some cognitive scores (such as word learning, ranking). In this study, neuropsychological testing was performed using the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery Plus (CERAD - NAB Plus), and voxel -based diffusion

tensor imaging was used for imaging (20). Apart from the different imaging techniques and cognitive batteries used, the most important reason why the three studies obtained different results from each other is that the mean age was 68 years in the study of Altermatt et al., while the mean age was 75 years in the study of Giorgio et al., and it was 76 years in our research.

Limitations of our study: In our study, the vascular load was determined only by Fazekas staging. Advanced MRI techniques were not used; imaging was performed with 1.5 Tesla. A separate method was not used for the volume measurements of the lesions. Gray and white matter separation was not made in subcortical areas; more specifically, the volumes of regions such as the amygdala, hippocampus, caudate, putamen, and thalamus could not be calculated. A detailed neuropsychological and cognitive evaluation was not performed. There is no follow-up MRIs as it is a retrospective planned study.

As a result, it was observed that subcortical atrophy detected in MRI was the most effective factor in the development and progression of dementia, and it was determined that Phasekas stages, that is, vascular load, had no effect. However, it was observed that the localization areas of the vascular lesions were associated with the deterioration of some cortical functions.

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Ethics

Ethics Committee Approval: The study was approved by Gaziosmanpaşa Training and Research Hospital Ethical Committee (Number: 124, Date: 01.07.2020).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective observational study.

Copyright Transfer Form: Copyright Transfer Form was signed by all authors.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices: İÖ, ATP, HSŞ, SND, YŞ. Concept: İÖ, ATP, HSŞ, SND, YŞ. Design: İÖ, ATP, HSŞ, SND, YŞ. Data Collection or Processing: İÖ, ATP, HSŞ, SND, YŞ. Analysis or Interpretation: İÖ, ATP, HSŞ, SND, YŞ. Literature Search: İÖ, ATP, HSŞ, SND, YŞ. Writing: İÖ, ATP, HSŞ, SND, YŞ.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.