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The Effect of Cerebral White Matter Lesions on Walking Time & Vascular Risk Factors

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Abstract

Introduction: White matter lesions are common neurological diseases in the elderly. In this study, we aimed to investigate the impact of cerebral white matter lesions on walking time and daily living activities in the elderly population.

Methods: A total of 82 individuals, including 40 healthy volunteers and 42 age and sex-matched patients, were enrolled in this study. Magnetic resonance imaging findings were recorded based on the Fazekas Staging System. Risk factors potentially predisposing individuals to white matter lesions were documented through laboratory testing. Additionally, atherothrombotic plaque formations and stenosis were graded using Carotid and Vertebral Artery Doppler Ultrasonography in patients with white matter lesions. The Lawton Instrumental Activities of Daily Living Scale, Mini-Mental State Examination, and the Timed Up & Go Test were administered to both the patient and control groups to assess daily living activities and cognitive functions.

Results: The results of this research showed that as the percentage of stenosis increased in Carotid and Vertebral Artery Doppler Ultrasonography, there were corresponding decreases in Lawton Instrumental Activities of Daily Living Scale scores, haemoglobin and hematocrit values while fasting blood glucose and homocysteine levels increased as expected. Furthermore, significant differences were observed in the Timed Up & Go Test in advanced stages when evaluated according to the Fazekas Staging System.

Conclusion: Our study indicated that white matter lesions do not significantly affect daily living activities but prolong the walking time in elderly individuals.

Keywords: White Matter, Magnetic Resonance Imaging, Walking, Stroke, Brain, Gait

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Serebral Beyaz Cevher Lezyonlarının Yürüme Süresi ve Vasküler Risk Faktörleri Üzerine Etkisi

Öz

Giriş: Beyaz cevher lezyonları yaşlılarda sık görülen nörolojik radyolojik bulgulardandır. Bu çalışmada, yaşlı popülasyonda serebral beyaz cevher lezyonlarının yürüme süresi ve günlük yaşam aktiviteleri üzerine olan etkisini araştırmayı amaçladık.

Yöntemler: Bu çalışmaya 40 sağlıklı gönüllü ve 42 hasta yaş ve cinsiyet uyumlu toplam 82 birey dahil edildi. Manyetik rezonans görüntüleme bulguları Fazekas sınıflandırmasına göre kaydedildi. Bireyleri beyaz cevher lezyonlarına yatkın hale getirebilecek risk faktörleri ile ilgili laboratuvar testleri kayıt altına alındı. Ayrıca, beyaz cevher lezyonu olan hastalarda aterotrombotik plak oluşumları ve stenoz, Karotis ve Vertebral Arter Doppler Ultrasonografi kullanılarak derecelendirilmiştir. Günlük yaşam aktivitelerini ve bilişsel işlevleri değerlendirmek için hem hasta hem de kontrol gruplarına Lawton Enstrümantal Günlük Yaşam Aktiviteleri Ölçeği, Standardize Mini-Mental Test ve Zamanlı Kalk ve Yürü Testi uygulanmıştır.

Bulgular: Bu araştırmanın sonuçları, Karotis ve Vertebral Arter Doppler Ultrasonografisinde darlık yüzdesi arttıkça Lawton Enstrümantal Günlük Yaşam Aktiviteleri Ölçeği skorlarında, hemoglobin ve hematokrit değerlerinde azalma olduğunu, açlık kan şekeri ve homosistein düzeylerinde ise literatüre uyumlu olarak yüksek olduğunu göstermiştir. Ayrıca, Fazekas sınıflamasına göre değerlendirildiğinde, ileri evrelerde Zamanlı Kalk ve Yürü Testinde anlamlı bulgular saptanmıştır.

Sonuç: Çalışmamız, beyaz cevher lezyonlarının yaşlı bireylerde günlük yaşam aktivitelerini önemli ölçüde etkilemediğini ancak yürüme süresini uzattığını göstermiştir.

Anahtar kelimeler: Beyaz Cevher, Manyetik Rezonans Görüntüleme, Yürüme, İnme, Beyin, Denge.

INTRODUCTION

White matter diseases, also known as leukoencephalopathies, encompass a range of conditions that primarily or exclusively affect the brain's white matter[1].

White matter hyperintensities are prevalent in the ageing population, with up to 80% of healthy individuals aged 60 showing these abnormalities. These hyperintensities are also observed in Alzheimer's Disease (AD), dementia, cognitive impairment, and other conditions[2,3].

However, our understanding of the distinctions between subcortical atrophy and lesions in the periventricular region, the functional implications of lobar region lesions, and the frequency specific to the location of vascular lesions remain limited. Different disorders may exhibit variations in subcortical, juxtacortical, periventricular white matter lesions and vascular lesions in deep brain structures[4].

Consequently, making these distinctions becomes crucial as it can have significant implications. White matter lesions, an irreversible and progressive clinical condition, underscore the importance of early symptom detection and the development of preventive approaches and treatments[5].

Magnetic resonance imaging (MRI) is crucial in diagnosing patients with leukoencephalopathy. It is important to note that each leukoencephalopathy presents diverse patterns of MRI abnormalities, even among patients with the same disease[6].

Detecting clinically silent lesions is of utmost significance in identifying individuals who require treatment and determining appropriate preventive measures.

In this study, our primary objective was to investigate the impact of cerebral white matter lesions on walking time and daily living

activities in the elderly population. By understanding these effects, we aim to contribute to a better understanding of the condition and potentially develop interventions to improve the well-being of affected individuals and their families.

METHOD

A total of 82 individuals, comprising 40 controls (healthy volunteers) and 42 age- and sex-matched patients who were admitted to the outpatient clinic due to headache and myalgia, were included in this study. Patients aged between 40 and 80 years who presented to the outpatient clinic with white matter lesions on cerebral MRI and were diagnosed with headache, myalgia and neuralgia, but without a history of falls and balance disorders were included in the study after a detailed neurological examination by a neurologist. History of additional systemic diseases, systolic and diastolic blood pressure values, body mass index (BMI), The Lawton Instrumental Activities of Daily Living (IADL) Scale, Mini-Mental State Examination (MMSE) and the Timed Up & Go Test (TUG) were administered

by the same neurologist. Individuals with a history of symptomatic stroke or neurodegenerative diseases that may cause gait disturbance were excluded.

All procedures followed the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval was granted by our institution on 09/06/2022 with protocol number 1982, and informed consent was obtained from all participants.

MRI imaging of the patients was performed on a 1.5 Tesla scanner (General Electric Optima 360, Milwaukee - USA, 2014) using 16-channel phased array coils. MRI findings were recorded according to the Fazekas Staging System [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)]. The evaluation of MRI white matter lesions according to the Fazekas Staging System was performed by two interventional neurologists in a double blinded manner.

Risk factors that may predispose to white matter lesions (WML) were recorded in laboratory examinations, including the neutrophil-to-lymphocyte ratio, lipid panel, homocysteine levels.

Atherothrombotic plaque formations and stenosis were graded by performing carotid and vertebral Doppler ultrasonography (CVDUSG) in patients with WML.

Statistical Analysis

Statistical analysis was performed using the SPSS software package (Version 25.0, SPSS Inc., Chicago, IL, USA). Normal continuous variables were expressed as the mean ± standard deviation ($p > 0.05$ in the Kolmogorov-Smirnov test or Shapiro-Wilk, $n < 30$), and in case of non-normality, they were described as the median. Comparisons between groups were conducted using the Student's t-test or One-Way analysis of variance (ANOVA) for normally distributed data, and the Mann-Whitney U test or Kruskal-Wallis test was utilized for data that were not normally distributed. A p-value of < 0.05 was considered statistically significant.

The categorical variables between the groups were analyzed using the Chi-square test or Fisher's Exact test. Spearman's correlation coefficient was used to test correlations between parameters.

Correlation coefficients were interpreted as: Strong Correlation $r \geq 0.91 \geq r \geq 0.71$; Medium Correlation; $0.70 \geq r \geq 0.51$; Weak correlation $0.50 \geq r \geq 0.31$; and Very Weak or no correlation $r \leq 0.3$.

RESULTS

The mean age of the patients (n = 42) included in the study was 65.3 ± 10 years, while the mean age in the control group (n = 40) was 56.1 ± 12 years (p = 0.052). The gender distribution was as follows: 65.9% (n = 54) of the included individuals were female, and 34.1% (n = 28) were male. Among the 82 people in both groups, 37.8% (n = 31) had hypertension, 17.1% (n = 14) had diabetes mellitus, 14.6% (n = 12) had coronary artery disease, 24% (n = 12) had psychiatric illness, 2.4% (n = 2) had urinary incontinence, 13.4% (n = 11) had constipation, 25.6% (n = 21) had balance disorder, and 13.4% (n = 11) had a history of falling. Antiaggregant use was reported in 17.1% (n = 11) of the patients (Table 1).

Table I: Correlation Analysis for the Patient Group

		CVDUSG	Fazekas Staging	IADL	MMSE	TUG
IADL	r	**-0.32**	-0.23			
	p	**0.041**	0.147			
MMSE	r	-0.301	0.071	**0.60**		
	p	0.053	0.657	**0.0001**		
TUG	r	-0.05	**0.44**	**-0.50**	**-0.56**	
	p	0.737	**0.004**	**0.0001**	**0.000**	
B12(pg/ml)	r	0.22	0.11	0.03	0.06	-0.14
	p	0.157	0.479	0.799	0.603	0.223
Vitamin D(µg /l)	r	0.07	-0.08	0.10	0.14	-0.07
	p	0.654	0.621	0.365	0.215	0.505
WBC(10^3/µl)	r	-0.01	0.26	-0.07	-0.10	0.18
	p	0.960	0.098	0.544	0.367	0.104
HGB(g/dl)	r	**-0.38***	-0.15	0.05	-0.13	0.16
	p	**0.014**	0.339	0.634	0.259	0.143
HTC(%)	r	**-0.42**	-0.21	0.04	-0.16	0.15
	p	**0.006**	0.185	0.728	0.148	0.176
PLT(10^3/µl)	r	0.16	0.18	-0.01	0.02	-0.02
	p	0.311	0.248	0.963	0.839	0.849
FPG(mg/dl)	r	**0.35**	0.01	**-0.23**	**-0.30**	0.17
	p	**0.022**	0.981	**0.034**	**0.006**	0.124
LY(10^3/µl)	r	0.06	0.21	0.03	-0.05	0.03
	p	0.681	0.184	0.754	0.674	0.778
NE(10^3/µl)	r	0.01	0.19	-0.04	-0.07	0.15
	p	0.966	0.216	0.698	0.526	0.179
NLR	r	-0.01	0.02	-0.07	-0.01	0.09
	p	0.939	0.881	0.525	0.899	0.385
Total Cholesterol(mg/dl)	r	-0.03	-0.136	-0.024	-0.048	0.045
	p	0.824	0.390	0.833	0.669	0.687
LDL(mg/dl)	r	-0.172	-0.140	0.048	-0.042	0.060
	p	0.277	0.377	0.666	0.705	0.592
HDL(mg/dl)	r	-0.111	-0.134	0.025	0.142	-.241*
	p	0.486	0.399	0.826	0.204	0.029
Triglyceride(mg/dl)	r	0.031	0.174	-.235*	-.288**	.282*
	p	0.845	0.271	0.034	0.009	0.010
Homocysteine(mmol/l)	r	**0.33**	0.09	**-0.36**	**-0.59**	**0.35**
	p	**0.034**	0.570	**0.001**	**0.0001**	**0.001**
Age(years)	r	-0.04	0.16	**-0.35**	**-0.54**	**0.48**
	p	0.821	0.297	**0.001**	**0.0001**	**0.0001**
BMI(kg/m^2)	r	-0.07	-0.05	-0.13	**-0.43**	**0.31**
	p	0.664	0.747	0.243	**0.0001**	**0.004**

CVDUSG= Carotid and vertebral Doppler ultrasonography, IADL= The Lawton Instrumental Activities of Daily Living, MMSE= Mini-Mental State Examination, TUG= the Timed Up & Go Test, WBC= white blood cell, HGB=haemoglobin, HTC=hematocrit,FPG=fasting blood glucose,LY=lymphocyte, NE= neutrophil, NLR=neutrophil lymphocyte ratio,LDL=low-density lipoprotein, HDL=high-density lipoprotein, BMI= body mass index

In addition, at the beginning of the study, the patient group exhibited higher levels of BMI (p = 0.047), systolic blood pressure (p = 0.004), diastolic blood pressure (p = 0.027), fasting blood glucose (p = 0.006), total cholesterol (p = 0.048), triglycerides (p = 0.009), and homocysteine (p = 0.0001) parameters when compared to the control group. According to the Fazekas System Staging, 31% (n = 13) of the patients were classified as Stage 1, 38.1% (n = 16) as Stage 2, and 31% (n = 13) as Stage 3 (Table 2).

Table II: Comparison of variables according to Fazekas System Staging

	Control Group	Fazekas Stage 1 (n=13)	Fazekas Stage 2 (n=16)	Fazekas Stage 3 (n=13)	P Value	Fazekas Stage 1-2-3 P Value
Age(years)	56.1±12.0	64.5±7.2	65.3±10.7	66.2±12.0	0.051	0.908
BMI(kg/m^2)	26.9±3.9	29.6±4.8	27.4±2.9	30.9±8.7	0.052	0.250
Systolic Blood pressure(mm/hg)	121.5±11.6	129.6±9.9	130.3±15.5	131.5±20.3	**0.042**	0.952
Diastolic Blood pressure(mm/hg)	78.2±8.5	83.4±5.2	80.9±6.4	83.4±13.2	0.130	0.678
WBC((10^3/µl)	6.9±1.5	7(0.0-9.9)	7.2(5.4-11.7)	8.2(5.4-10.4)	0.121	0.190
HGB(g/dl)	12.8±1.7	13.8±1.1	13.2±1.4	13.2±1.1	0.204	0.385
HCT(%)	38.5±4.1	41.4±3.5	39.0±4.1	39.2±2.8	0.147	0.186
PLT(10^3/µl)	259(162-437)	248(177-421)	237(141-376)	293(216-389)	0.377	0.180
FPG(mg/dl)	95(63-112)	100(78-238)	99(73-219)	101(91-340)	**0.016**	0.475
LY(10^3/µl)	2.1±0.6	2.1±0.4	2.2±0.6	2.5±0.6	0.316	0.249
NE(10^3/µl)	3.8(2.1-7.4)	4.3(2.8-64.4)	4.3(2.8-64.4)	5.4(3.0-66)	0.154	0.403
NLR	2.07(0.6-8.2)	1,89(1.1-37.9)	1.96(0.9-4.2)	1.87(1.5-3.1)	0.190	0.363
Total cholesterol(mg/dl)	188(119-271)	222(138-328)	225(125-280)	195(117-302)	0.183	0.703
LDL(mg/dl)	125(67-177)	147(88-241)	148(86-179)	130.615	0.204	0.606
HDL(mg/dl)	45(33-80)	51(31-78)	50(25-76)	46(33.82)	0.841	0.710
Triglyceride(mg/dl)	125(38-271)	149(67-249)	162(75-319)	176(101-248)	**0.039**	0.463
Homocysteine(mmol/l)	8(5-44)	13(10-24)	14(8-17)	16(-24)	**0.0001**	0.284
B12(pg/ml)	258(100-1500)	197(50-1044)	231(123-523)	254(111-1500)	0.116	0.145
Vitamin D(µg /l)	16.0(7.3-25.4)	13.7(7.0-30.9)	16.6(3.1-30.6)	16.7(6.5-38.0)	0.944	0.904
CVDUSG	-	1(0-3)	1(0-3)	1(0-3)	-	0.536
IADL	8(6-8)	8(3-8)	7(5-8)	7(1-8)	**0.011**	0.432
MMSE	30(25-30)	25.1±3.6	25.6±3.4	25.2±3.9	**0.0001**	0.931
TUG	8.2(5.6-14.7)	10.1±1.7	11.1±2.1	15.6±3.1	**0.0001**	**0.008**
Gender *(Female)*	28(70.0)	6(46.2)	12(75.0)	8(61.5)	0.354	0.282
Presence of Urinary incontinence	0(0.0)	3(23.1)	1(6.3)	7(53.8)	**0.0001**	**0.014**

Mean±SD; Medyan (Min-Min); n (%) CVDUSG= Carotid and vertebral Doppler ultrasonography, IADL= The Lawton Instrumental Activities of Daily Living, MMSE= Mini-Mental State Examination, TUG= the Timed Up & Go Test, WBC= white blood cell, HGB=haemoglobin, HTC=hematocrit, FPG=fasting blood glucose, LY=lymphocyte, NE= neutrophil, NLR=neutrophil lymphocyte ratio, LDL=low-density lipoprotein, HDL=high-density lipoprotein, BMI= body mass index

According to laboratory clinical findings, only the TUG-Test showed statistical significance when assessed according to the Fazekas Staging System. No statistically significant correlations were found between gender, hypertension, diabetes mellitus, coronary artery disease, psychiatric diseases, falls, constipation, imbalance, anti-aggregant use, and Fazekas stage. Moreover, based on laboratory clinical findings, only the TUG-Test demonstrated statistical significance when considering Fazekas stages. No difference was observed between Stage 1 and Stage 2 Fazekas concerning the TUG-Test; however, Fazekas Stage 3 exhibited a statistically significant increase.

A positive correlation was identified between the Lawton IADL Scale and MMSE. The Lawton IADL Scale also revealed negative correlations between the TUG-Test, fasting plasma glucose (FPG), homocysteine, and age.

Upon evaluating the correlation table, we observed a statistically significant inverse correlation between CVDUSG and the Lawton IADL Scale, haemoglobin (Hgb), and hematocrit (Htc) variables. Atherosclerotic plaque formation was present in most patient groups (n = 29). Moreover, the correlation table indicated a statistically significant inverse correlation between CVDUSG and the Lawton Brody scale and haemoglobin and hematocrit variables. We expect that as the CVDUSG value increases, the Lawton Brody, Hgb, and Htc values will decrease. A positive correlation was also found between CVDUSG and FPG and homocysteine values (Table 3).

Table III: Distribution of patients according to CVDUSG and Fazekas Staging

	n	%
CVDUSG		
Atherosclerosis	3	7.1
ICA stenosis 0-50%	29	69.0
ICA stenosis 50-70%	7	16.7
ICA stenosis 70-99%	2	4.8
ICA occlusion	1	2.4
Fazekas Staging		
1	13	31.0
2	16	38.1
3	13	31.0

CVDUSG=carotid vertebral doppler ultrasonography, ICA= internal carotid artery

DISCUSSION

WML, also known as leukoaraiosis, are defined as diffuse or localized areas of abnormality in the white matter, often symmetrical, and frequently observed in the periventricular white matter, particularly adjacent to the lateral ventricular horns. Leukoaraiosis is a term used in radiological imaging methods, and its prevalence tends to increase with age, especially after the age of 60. While the average incidence is around 5–8% before the age of 60, this rate rises significantly to 30–40% in individuals exhibiting cerebral white matter changes, as reported in the literature.

Furthermore, leukoaraiosis is found in many patients with certain medical conditions. In Alzheimer's patients, its occurrence ranges from 26 to 70%, while in patients with vascular dementia, the prevalence is between 50 and 80%. Additionally, leukoaraiosis is reported in approximately 44% of patients who have experienced a stroke or a transient ischemic attack[7-9].

These areas of low density can be observed in regions such as the centrum semiovale. This condition, known as leukoaraiosis, is typically associated with small vessel disease, such as lacunar infarction. Leukoaraiosis has been linked to mental deterioration and dementia, and it is believed to result from hemodynamic ischemia of the white matter, which occurs secondary to atherosclerotic thickening of the penetrating arteries that supply the white matter[10].

Various risk factors contribute to the development of leukoaraiosis. While hypertension can be a significant factor in these cases, there is often the involvement of small vessels due to the combination of multiple risk factors[11].

Most patients presenting with headaches, myalgia, and dementia show involvement in the subcortical, periventricular, and basal ganglia regions. Lesions in the cortical and brainstem areas (except for the pons) are infrequent. Additionally, it has been reported that caudate atrophy may be observed, particularly in patients with Parkinson's disease, leading to potential impairments in executive function and the dopaminergic pathway. Tuladhar et al. conducted a study in 2015 that identified a connection between memory and corpus callosum lesions[12].

The presence of WML on MRI does not typically result in a significant change in the activities of daily living in asymptomatic patients with vascular risk factors[13]. However, it should be noted that WML can prolong walking time, and therefore, the underlying cause should be thoroughly investigated. Precautions should be taken due to the higher risk of stroke, dementia, and falls associated with these lesions. In our study, while there was no significant difference observed in phases 1 and 2, it was found that walking time was significantly prolonged in phase 3.

Extensive WML are strongly associated with an increased risk of dementia, cognitive decline, and memory impairment. Research has indicated that a higher burden of diffuse WML elevates the risk of developing dementia[14]. Additionally, considering the risk of dementia associated with microbleeds, it has been found to pose a potential threat. However, it is worth noting that extensive white matter involvement does not necessarily correlate with lacunae, microbleeding, and perivascular spaces.

The incidence of WML tends to rise with advancing age and is commonly observed in various cerebrovascular diseases, such as multi-infarct dementia, amyloid angiopathy, Binswanger's disease, as well as conditions like hydrocephalus and multiple sclerosis[15].

The vascularization of cerebral white matter is more delicate than cerebral cortical areas. This is particularly evident in the subcortical white matter, supplied by deep perforating arteries originating from the pial network on the brain surface, resulting in a relatively weaker capillary structure. Due to this vulnerable vascularization, chronic ischemic microangiopathic changes tend to occur in these areas, and hypoxic regions can form even before the onset of clinical symptoms[16].

The formation of lipo hyalinosis and fibrinoid necrosis in the intima-media layers leads to the degeneration of the muscular layer in the vessels. Consequently, over time, the blood-brain barrier deteriorates in these regions, resulting in increased extravascular fluid collection and gliosis in the glia and oligodendrocytes. This sets the stage for ischemic pathologies, including the formation of lacunas, which can eventually lead to infarction[17].

WML can also be seen as asymptomatic infarct appearances or as a predisposition for infarct formation. They can be distinguished from ischemic infarcts based on certain features, such as lacking well-circumscribed boundaries, being limited to the cerebral white matter without cortical extension, and not causing enlargement of the ventricles and cortical sulci[18].

The current study revealed a positive correlation between the Lawton IADL Scale and MMSE. A negative correlation was found between Lawton Brody, the get-up-walk test, FPG, homocysteine, and age. An increase in the Lawton IADL Scale score was associated with a statistically significant decrease in the results of the get-up-walk test, FPG, homocysteine, and age.

However, due to technical inadequacy, we could not measure the volume of WML in MRI; therefore, an evaluation was conducted based on the Fazekas Staging System. In future studies, obtaining more objective data by performing volumetric measurements of WML in MRI could provide comprehensive insights and a more detailed understanding.

CONCLUSION

In asymptomatic individuals with vascular risk factors, the presence of WML on MRI does not typically result in a significant change in daily living activities. However, it is important to note that these lesions can cause a prolongation of walking time. Due to the potential high risk of stroke, dementia, and falls associated with

WML, a comprehensive investigation of their aetiology is

Ethics Committee Approval: All procedures in this study followed the ethical standards of the responsible committee on human experimentation (both institutional and national) and complied with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been obtained from our institution, and informed consent has been duly obtained from all participants involved in the study.

Conflict of Interest: The authors declared noconflicts of interest.

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