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DND Dementia and Neurocognitive Disorder

Original Article

Association of Type 2 Diabetes Mellitus With Perivascular Spaces and Cerebral Amyloid Angiopathy in Alzheimer's Disease: Insights From MRI Imaging

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Conflict of Interest
The author has no financial conflicts of interest.

ABSTRACT

Background and Purpose: According to the amyloid cascade hypothesis, fibrillary amyloid-beta load in the brain causes Alzheimer's disease (AD) with toxic effects. Recently, perivascular spaces (PVSs), fluid-filled cavities around small penetrating arterioles and venules in the brain, and the glymphatic system relationship with type 2 diabetes mellitus (DM2) and AD has been an important research topic from a physiopathological point of view. There are two types of PVSs that are associated with sporadic atherosclerosis and cerebral amyloid angiopathy. In this study, we evaluated the relationship between the number and localization of enlarged PVSs in AD.
Methods: A total of 254 patients with AD and 125 healthy controls were included in this study All the patients were evaluated with neurological and cognitive examinations and magnetic resonance imaging (MRI). PVSs on MRI were graded by recording their number and location. The study was a retrospective study.
Results: In our study, the number of white matter convexity-central semiovale localized PVSs was higher in patients than in the control group. In addition, the number of PVSs in this localization score was higher in patients with DM2. Cerebral PVS counts were higher in patients with AD than in the control group.
Conclusions: These results suggest the important role of cerebral amyloid angiopathy, one of the vascular risk factors, and the glymphatic system in the pathogenesis of AD. In addition, the results of our study suggest that the evaluation of PVSs levels, especially at the (centrum semiovale), using imaging studies in AD is a potential diagnostic option.

Keywords: Perivascular Fluid Space; Glymphatic Pathway; Small Vessel Disorders; Alzheimer Disease; Type 2 Diabetes Mellitus

INTRODUCTION

Perivascular spaces (PVSs) in the brain are interstitial fluid (ISF)-filled cavities surrounded by small penetrating arteries and arterioles and venules.[1] PVSs containing cerebrospinal fluid (CSF)-like fluid are bound internally by the vessel wall and externally by the astrocytic end feet and pia material. PVSs cannot be observed on conventional structural magnetic resonance

imaging (MRI) and can only be visualized when magnified. Enlarged PVSs are considered one of the earliest brain imaging findings in small vessel disease (SVD).[2] Previously, PVSs were considered benign neuroradiologic findings. In recent years, PVSs are believed to play an important role in the elimination of cerebral metabolic waste and CSF. Since the lymphatic system connects to the PVSs, a paravascular pathway spreads throughout the central nervous system (CNS), which allows the exchange of CSF with ISF in the parenchyma. The paravascular clearance system is known as the glimphatic system because it is associated with glial cells and is functionally similar to the peripheral lymphatic system.[3] Moreover, it has been suggested that enlarged and increased numbers of PVSs may be indicators of many degenerative brain diseases, especially vascular disorders and small-vessel disease.[2]

In addition to obstructions in CSF circulation or lymphatic drainage pathways, various pathophysiological mechanisms, such as increased permeability of arterial walls, perivascular demyelination, brain atrophy, and tissue fibrosis, may play a role in the expansion of PVSs.[4,5] PVSs are usually found in the basal ganglia, centrum semiovale, and midbrain.[6] Their anatomy depends on their location. PVSs in the cortex are smaller than those in the white matter. While there is only one layer of pia substance in the PVSs around the superficial perforating arteries, there are two layers in the PVS of the deep perforating arteries in the basal ganglia.[2]

Two important forms of PVSs are frequently encountered and differ in their physiopathological and anatomical locations. The first form, frequently observed in the basal ganglia, is associated with arteriosclerosis and hypertensive arteriopathy. The other form is associated with cerebral amyloid angiopathy (CAA) and is more frequently located in the centrum semiovale (CSO).[7] Charidimou et al.[8] have shown that severe PVS in the CSO white matter is more common in subjects with pathology-proven sporadic CAA than non-CAA subjects. These findings suggest that in this patient population, severe CSO PVS may be a promising new neuroimaging marker to improve the sensitivity of *in vivo* diagnosis of CAA.[8] In another multicenter study by Charidimou et al.,[9] results showed that PVSs in white matter are very common in CAA patients and that white matter PVSs may be used as a characteristic neuroimaging marker of CAA. In another study by Martinez-Ramirez et al.,[10] PVSs in white matter and basal ganglia were compared. Accordingly, it has been suggested that white matter PVSs may be an indicator of CAA and PVSs in the basal ganglia are associated with hypertension and other vascular risk factors. Current evidence indicates that PVSs play a role in SVD pathogenesis. For this reason, it is thought that glymphatic dysfunction is an important factor for SVD pathology.[2,6]

CAA is characterized by amyloid-beta deposition in the small/medium-sized cortical and leptomeningeal vessels.[4,11] CAA has been associated with cognitive impairment and Alzheimer disease (AD).[4,12] AD is a progressive degenerative disease, the most common cause of cognitive disorders, and the most common type of dementia.[13-15] The cognitive, psychological, and behavioral problems of individuals with AD and their dependency on daily living activities, negatively affect the quality of life of both the patients and the caregivers.[16,17]

Fibrillary amyloid-beta load in the brain causes AD with toxic effects.[7] In addition, there is a dysfunction of the large perivascular network in the CAA known as the glymphatic system, which facilitates the clearance of solutes containing amyloid β peptide (Aβ) from the brain parenchyma.[18] Decreased excretion of Aβ in the neurovascular unit of the blood-brain barrier also contributes to amyloid-beta accumulation.

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Toxic solutes such as Aβ are significantly reduced in neurodegenerative disease models of CNS clearance. The deterioration in vascular wall compliance and reactivity of SVD supports this reduction.[6] CAA, which is characterized by protein aggregation and accumulation, constitutes an important part of the SVDs. Diseases, such as aging, microinfarcts, AD, migraine, and diabetes, in which CAA is frequently observed, are thought to be associated with glymphatic system disorders.[2] Another important issue is the relationship between type 2 diabetes mellitus (DM2), which ranks first among the vascular risk factors, and dementia. Individuals with DM2 have a 65% increased risk of AD compared to individuals without DM2. In addition, individuals with DM2 have a 16% increased risk of dementia, and cognitive disorders are common among these patients.[19,20] In animal experiments, it has been determined that dysfunction of the glymphatic system and cognitive disorders occur in rats with DM2. Therefore, the relationship between AD and DM2, which is also called "type 3 diabetes (DM3)" because of its biochemical properties in the brain, has been given more importance by some researchers.[21]

Evaluation of enlarged PVSs and their locations may be useful in differentiating cognitive disorders caused by AD from subcortical SVDs. However, the role of small vessel pathologies in the pathogenesis of AD has been demonstrated, and the findings have become increasingly remarkable.[22] However, studies investigating the relationship between AD-PVSs have reported contradictory results.[22-24] In addition, different results have been reported in studies in which the results were evaluated according to the stages of AD and disease.[11,19] In this study, we investigated the relationship between the number and localization of enlarged PVSs in AD. We also examined the relationship between AD, DM2, and the glymphatic system and its clinical implications by evaluating PVSs that act as a channel for the glymphatic system.

METHODS

The patient group included patients registered in our hospital's dementia outpatient clinic diagnosed with probable AD according to the National Institute of Neurological and Communication Disorders and Stroke. They were also evaluated through the Alzheimer's Disease and Associated Disorders Association (NINCDS-ARDRA) criteria. The control group consisted of patients in the same age group who presented at the general neurology outpatient clinic with a headache and were diagnosed with tension-type headaches in the past. Data were collected between 1 June 2022 and 31 March 2023 by examining the files of patients with AD. Patients with severe systemic disease, a history of vasculitis and malignancy, neurologic diseases other than AD, pathologic findings other than non-specific physiochemical lesions on brain MRI, and contraindications for MRI were excluded from the study.

The patients' records from the Neurology Clinic Dementia Outpatient Department were evaluated, and their neurologic examinations, cognitive assessments, neuropsychological evaluations, and Mini-Mental State Examination (MMSE) test results were recorded. Additionally, memory, executive function, and processing speed were also taken into account during cognitive assessments. Patients with AD were categorized as mild, moderate, or advanced based on the Clinical Dementia Rating Scale (CDR). Vascular risk factors such as hypertension, dyslipidemia, diabetes mellitus, history of coronary artery disease and smoking were recorded in both the patient and control groups. Ethical approval for the study was obtained from the Ethics Committee of Ankara Etlik City Hospital: number AESH-EK1-2023-252.

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Patients who had at least two measurements of systolic >140 mmHg and diastolic >90 mmHg, or had a history of hypertension and received treatment were included in the study. Patients with a fasting blood glucose level >126 mg/dL and a postprandial blood glucose level >200 mg/dL, or a history of DM2 were considered to befv diabetes patients. Patients with LDL levels >100 mg/dL were considered to have dyslipidemia. Patients who were current smokers or had smoked cigarettes up to one year ago were considered cigarette smokers.

All patients were examined using axial T1-weighted, T2-weighted and axial and coronal fluid-attenuated inversion (FLAIR) recovery images on a 1.5 Tesla scanner (Philips Achiva, Philips Medical Systems, Eindhoven, Netherlands). The following criteria were used for PVSs in brain MRIs of the patient and control groups.[25] PVSs with a short axis >2 mm, often seen as punctate or tubular areas anatomically along the course of perforating arteries, were considered enlarged. In T1, T2 and FLAIR sequences, CSF and isointense signal characteristics (hypointense in T1 and FLAIR, hyperintense in T2) and no changes in the surrounding brain parenchyma were sought. PVSs were differentiated from chronic cavitary lacunar lesions by the absence of a hyperintense border compatible with gliosis around it on FLAIR sequences (**Fig. 1**).

Dilated PVSs on brain MRIs were evaluated in three regions (type I substantia perforata-anterior commissure, type II Type 1 white matter convexity-central semiovale and type III pontomesencephalic junction) on both sides (right and left).[8] The number of dilated PVSs in each region was determined and graded (grade 0=0, grade 1=1–5, grade 2=6–10, and grade 3≥11). For each region, the highest number on the right or left side was accepted and evaluated.[26]

The PVS score was calculated as follows: The number of patients in each grade of PVS type was added together, and then calculated by dividing it by the total number of patients in that PVS type. For example, the score for Type I PVS is calculated as follows: (1 × number of grade 1 patients) + (2 × number of grade 2 patients) + (3 × number of grade 3 patients)/Total number of Type I PVS patients. Type I, II and III and total PVSs scores (type 1+2+ 3 scores) were determined for each region in the patient and control groups. Patients with mild, moderate-to-advanced AD and control groups were compared in terms of PVSs location and grade. In addition, the Ads of patients with and without DM were examined in terms of the PVSs location and grade.

Statistical analysis

In this study, the analysis was conducted after transferring and organizing the data in IBM SPSS 26.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics such as number, percentage, mean, median, standard deviation, minimum and maximum values were examined. The normality of continuous data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests, revealing that the variables were not normally distributed. The Kruskal-Wallis test was used to compare three independent groups in the analysis of continuous variables, while the Mann-Whitney *U* test was used to compare two independent groups. In cases where a significant difference was found in the Kruskal-Wallis test, post hoc tests were conducted to determine specific group differences, considering Bonferroni corrected significance values. The analysis of categorical variables was performed using the χ^2 test, and the χ^2 test findings were evaluated based on the characteristics of the contingency table using the Pearson's χ^2 test, Yates' χ^2 test (with continuity correction), or Fisher's exact test. The Spearman correlation test was used to evaluate the correlational relationship between variables. Logistic regression analysis was employed to identify factors influencing the

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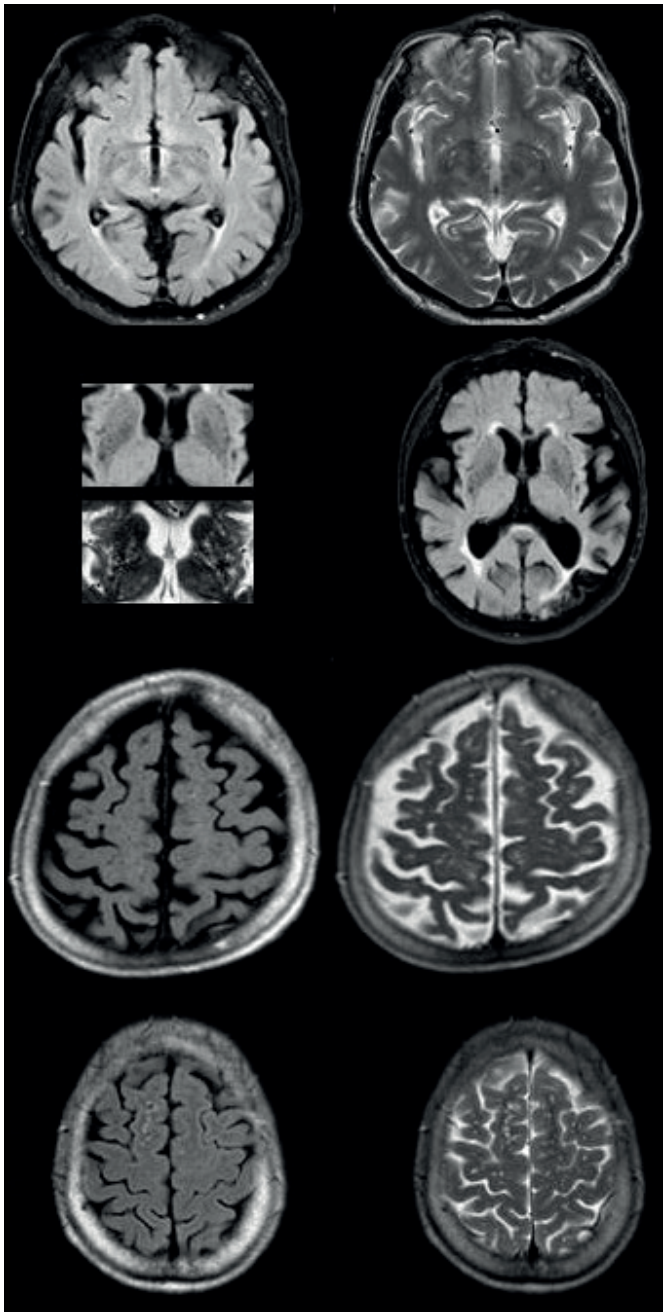

Fig. 1. Example of the perivasculer space in basal ganglia and white matter (axial, T2 weighted and FLAIR images).

presence of dementia. To include categorical variables in the analysis, dummy variables were created by selecting the first group as the reference group. The groups listed below were used as reference groups. In the analysis, a *p*-value <0.05 was considered statistically significant.

Reference groups: Sex: Female HT: No CAD: No Cigarette: No smoking Education: Less than 5 years DM: No Type1PVS: No Type2PVS: No Type3PVS: No.

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Compliance with ethical standards

All procedures were performed in accordance with the ethical standards of the institutional board and the 1964 Helsinki Declaration and ethical standards. Written informed consent was obtained from all patients included in the study.

RESULTS

A total of 254 patients (125 females, 129 males) with AD and 125 patients (65 females, 60 males) with tension headaches, the control group, were included in the study. Of the patients with AD, 141 had mild disease (68 females, 73 males; mean age 73.4±7.6) and 113 had moderate-to-advanced disease (57 females, 56 males; mean age 74.0±8.0) (**Table 1**). Smoking was higher in patients with moderate-to-severe dementia and mild dementia than in the control group (p=0.001). There were no statistically significant differences between the groups in terms of the other vascular risk factors (**Table 1**). There was no difference between the groups in terms of the frequency of type I PVSs on brain MRI, but the stage of type I PVSs differed between the groups. While the number grade 1 type I PVSs was higher in the control group than in the patient group, the number of grade 3 type I PVSs was higher in the moderate-advanced and mild dementia groups (p=0.002 and p=0.003, respectively) (**Table 1**).

The number of type II PVSs was higher in the moderate-to-advanced and mild dementia groups than in the control group (p<0.001). There was a difference between the groups in

Table 1. Demographic and imaging features of the subjects

Variables	Moderate to advanced dementia	Mild dementia	Normal control	p-value
Total	113	141	125	
Age	74.0354±8.01107	73.4823±7.64162	73.0960±5.73251	0.275
Sex. male	56	72	60	0.883
Hypertension	64	70	73	0.314
Diabetes mellitus	37	39	39	0.660
Hyperlipidemia	42	60	55	0.533
Coronary disease	32	53	40	0.284
Cigarette				
No smoking	71	81	102	
Quit smoking	26	37	15	0.001
Smoking	16	23	8	
Education				
Less than 5 yr	28	22	22	
5 yr and above	85	119	103	
Type I PVS	73	96	83	0.843
Type I Grade 1	25	39	54	0.001
Type I Grade 2	23	34	20 (18.0)	0.260
Type I Grade 3	25	23	9	0.005
Type I PVS point	1.2920±1.17018	1.2482±1.07674	0.9680±0.88842	0.081
Type II PVS	49	46	11	0
Type II Grade 1	15	14	7	0.128
Type II Grade 2	18	15	2	0.001
Type II Grade 3	16	17	2	0.001
Type II PVS point	0.8761±1.13494	0.6738±1.07900	0.1360±0.49748	0
Type III PVS	9	6	1	0.023
Type III Grade 1	2	4	1	0.508
Type III Grade 2	2	1	0	0.299
Type III Grade 3	5	1	0	0.014
Type III PVS point	0.1748±0.64818	0.0638±0.34253	0.0080±0.08944	0.021
Total PVS point	2.3540±1.98170	1.9858±1.53988	1.1120±1.07175	0

PVS: perivascular space.

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Table 2. Comparison of PVSs in Alzheimer's disease patients with and without DM2 with the control group

DM	(+)	(−)	*p*-value
Type I PVS	179	73	0.412
Type I Grade 1	85	33	0.499
Type I Grade 2	55	22	0.810
Type I Grade 3	39	18	0.949
Type I PVS point	1.1818±1.04513	1.1391±1.08326	0.639
Type II PVS	68	38	0.146
Type II Grade 1	26	10	0.872
Type II Grade 2	23	12	0.734
Type II Grade 3	20	15	**0.006**
Type II PVS point	0.4886±0.92692	0.7130±1.12207	0.086
Type III PVS	14	2	0.164
Type III Grade 1	7	0	0.107
Type III Grade 2	3	0	0.556
Type III Grade 3	4	2	1.000
Type III PVS point	0.0947±0.44735	0.0522±0.39389	0.120
Total PVS point	1.7652±1.63544	1.9043±1.64356	0.419

The bold-faced *p*-value indicates that it is statistically significant.
PVS: perivascular space, DM: diabetes mellitus.

terms of type II PVSs stages. Grade 2 (p=0.016) and grade 3 (p=0.006) type II PVSs were more common in the moderate-advanced and mild dementia groups than in the control group. Type II PVSs scores were higher in the moderate-to-advanced and mild dementia groups than in the control group (p<0.001) (**Table 1**).

Type III PVSs were more frequent in the moderate-to-severe dementia group than in the control group (p=0.047). The frequency of grade 3 type III PVSs was also higher (p=0.041). Type III PVSs scores were higher in the moderate-to-severe dementia group than in the control group (p=0.045) (**Table 1**).

A comparison between AD patients with and without and control group patients with and without AD DM2 showed that type II PVSs score was higher in patients with DM2 (p=0.000). No significant differences were found in the other PVSs types (**Table 2**).

Multivariant regression analysis was performed for AD. The findings obtained were as follows: The variables included in the regression model explained 23.9% of the variance in the state of AD, being Type II PVS increases the risk of AD by 6.52 times compared to non-Type II PVS, and smoking and quitting smoking compared to non-smokers increases the risk of AD 3.77 times. It was found that smoking increases AD by 5.30 times compared to non-smokers (**Table 3**).

The total PVSs score was higher in the moderate-to-advanced and mild dementia groups than in the control group (p<0.001) (**Table 1**). When moderate-to-severe and mild dementia patients were considered together, and the correlation between type I, type II, type III and total PVSs scores and MMSE scores were examined, a negative correlation was found between type II PVSs scores and MMSE scores (p=0.044) (**Table 4**).

DISCUSSION

In our study, the incidence of type II PVSs was higher in the AD patients group than in the control group. No difference was found between the groups in terms of the incidence of type

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Table 3. Logistic regression analysis findings for Alzheimer's disease

Variables	B	*p*-value	Exp(B)	95% CI
Age	0.012	0.505	1.012	0.976–1.050
Sex	−0.537	0.061	0.585	0.334–1.024
HT	−0.293	0.257	0.746	0.450–1.238
CAD	0.190	0.495	1.210	0.700–2.090
HL	−0.445	0.084	0.641	0.387–1.062
Cigarette		**<0.001**		
Quit smoking	1.328	**<0.001**	3.772	1.858–7.658
Current Smoking	1.669	**<0.001**	5.305	2.122–13.260
Education	−0.073	0.835	0.929	0.466–1.852
DM	−0.267	0.321	0.766	0.453–1.296
Tip1PVS	0.169	0.516	1.184	0.711–1.970
Tip2PVS	1.875	**<0.001**	6.522	3.241–13.124
Tip3PVS	1.943	0.074	6.977	0.830–58.634
Constant	1.810	0.224	6.111	
Nagelkerke R^2=0.239				
Dependent variable Alzheimer's disease (0=No; 1=Yes)				

The findings of the logistic regression analysis performed to determine the variables that have an effect on dementia are given in **Table 3**. In the model, dementia was coded as 0=no, 1=yes. In the analysis, dummy variables were created for categorical variables. While creating the dummy variables, the following groups were used as the reference group. The bold-faced *p*-value indicates that it is statistically significant.
Sex: Female; HT: No; CAD: No; Cigarette: No smoking; Education: Less than 5 years; DM: No; Type1PVS: No; Type2PVS: No; Type3PVS: No.
HT: hypertension, CAD: coronary artery disease, HL: hyperlipidemia, DM: diabetes mellitus.

Table 4. Relationship between MMSE and PVS scores

PVSs types	MMSE point	*p*-value*
Type 1 PVS point	−0.003	0.964
Type 2 PVS point	−0.133	**0.044**
Type 3 PVS point	−0.048	0.472
Total PVS point	−0.056	0.395

The bold-faced *p*-value indicates that it is statistically significant.
MMSE: Mini-Mental State Examination, PVS: perivascular space.
*Spearman correlation test.

I PVSs. According to PVSs grades (numbers), both the number of type II and type III PVSs were higher in the AD patients group than in the control group. However, the number of type II PVSs was higher in patients with AD. These results indicate the primary role of CAA in the pathogenesis of AD but also support the view that vascular processes associated with hypertension, atherosclerosis and SVD may also contribute to the development of AD.

Recent studies have shown that vascular changes play an important role in early AD.[12,27] Specifically, vascular changes are an early preclinical feature of AD pathology, and changes in cortical blood flow begin years or decades before the onset of the clinical symptoms.[24,25,28]

SVD, an important factor in the vascular hypothesis, affects approximately 80%–90% of AD patients with CAA pathology. This proves the relationship between SVD and AD.[2,29] CAA, defined as the deposition of Aβ on the walls of the leptomeningeal and cortical arteries, arterioles, capillaries, and (rarely) vessels, is strongly associated with AD.[3,19]

CAA causes large, low-resistance PVSs associated with the glymphatic flow of Aβ leading to their accumulation in vessels. In addition, CAA increases arterial stiffness and reduces arterial pulsatility, which affects the functioning of the lymphatic system. Consequently, the disorder that occurs in the glymphatic system causes a decrease in the clearance of Aβ from CSF [2]. Studies on the physiopathology of AD have shown that both the lymphatic system and

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vascular pathology are associated in AD. This supports the role of PVSs in AD as they are common markers for these two pathologies.[2,3]

PVSs play an important role in neurovascular and blood–brain barrier disorders.[12] However, studies have shown that the localization of PVSs differs in AD. Ramirez et al.[2] evaluated PVSs in terms of localization and volume in AD and NC groups. They concluded that PVSs localized in the white matter were significantly larger than the volumes of the basal ganglia PVSs in AD. In addition, PVSs localized in the white matter were larger in males than in females compared to those located in the basal ganglia in both groups.[26]

Banerjee et al.[6] showed that 40.9% of patients with AD had white matter PVSs, while PVSs were located in the white matter of 14.7% of patients with subcortical cognitive impairment (SCCI). PVSs localized in the basal ganglia were observed at a rate of 9.5% in patients with SCCI, while the corresponding rate in patients with AD was 0.91%.[22] Patankar et al.[23] concluded that the PVSs were significantly higher in the vascular dementia group, but there was no difference between the AD and normal controls (NC) groups.[30] Hansen et al.[20] examined PVSs and showed that those located in the basal ganglia were more common in patients with AD than in the control group.[28]

Chen et al.[24] conducted a study with 3T MRI and examined 50 NCs, 37 patients with AD, and 71 patients with MCI in terms of PVS localization and severity. They concluded that the number of PVSs in the AD and MCI groups were higher than those in the NC group. However, there was no difference in the location of the PVSs, as they were found in both the white matter and other parts of the brain. Although the mechanism is uncertain, they suggested that vascular risk factors might affect the neuropathogenesis of AD.

In our study, PVSs in AD patients with and without DM2 were compared, and a significant difference was observed in type II PVSs between AD patients with DM2. Accordingly, it was assumed that type II PVSs in the CSO might have a significant role in SVD in patients with DM2.

As it is widely known, DM2 is a major risk factor for SVD. Owing to the physiopathology of diabetes, its effects on SVD, PVSs and cerebral functions are quite complex. DM2 likely changes pulsatility, but not perfusion, due to endothelial cell and BBB damage, and causes the expansion of PVSs. Furthermore, chronic inflammation in DM2 causes reactive astrogliosis and alters AQP4 expression.[30] Although the effects of these changes on overall brain function are small, the combination of these effects, which will persist for years or decades, may have a significant clinical impact.[2]

Recent studies evaluated the glymphatic function in DM2, a known vascular risk factor for arteriosclerosis.[4] In an animal study conducted by Jiang et al.,[31] impairment of the glymphatic system by DM2, which is highly associated with cognitive deficits, was demonstrated using quantitative MRI measurements. The results of this study showed that the slowdown in the clearance of solutes in the glymphatic system in DM varies depending on the region of the brain parenchyma. In addition, clearance in the hippocampus was further reduced in animals with DM compared to animals without DM2.[30] This glymphatic system dysfunction, evident in the hippocampus, is an important indicator of cognitive impairment in DM2. Furthermore, it has been reported that hyperglycemia in DM2 may lead to cognitive impairment, as it results in cerebral neurovascular dysfunction, neurotoxicity, and deterioration in neural insulin metabolism [31]. Given the relationship between diabetes and vascular pathology, it

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has been suggested that diabetes contributes to the development of SVD and triggers the deterioration of glymphatic activity, leading to cognitive dysfunction.[19] These results support the increased risk of dementia in DM2.

Recent studies have suggested a relationship between DM3 and AD based on both the processing of amyloid-β (Aβ) precursor protein toxicity and impaired Aβ clearance as a result of impaired insulin resistance.[20] Nguyen et al.[21] point out the hypothesis that the correlation between diabetes and AD is due to the APOEε4 allele involved in lipid homeostasis in diabetes. The increase in APOEε4 in patients with diabetes increases the risk of AD compared to patients without diabetes.[19] In vitro and animal studies have shown that insulin resistance in DM2 may contribute to the pathogenesis of AD through various pathways.[20] Peripheral insulin resistance leads to decreased insulin signaling in the CNS and accordingly to changes in brain metabolism. Increased Aβ toxicity is attributed to central insulin resistance, which leads to tau hyperphosphorylation, oxidative stress and neuroinflammatory neurodegeneration. In this study, the processing of Aβ precursor protein toxicity and the association of Aβ clearance with impaired insulin resistance in the brain supported the relationship between DM3 and AD.[20] This study's results support the relationship between DM3 and AD, considering the processing of Aβ precursor protein toxicity and the association of Aβ clearance to impaired insulin resistance in the brain.[20]

Previous studies have shown that PVSs, which are intense in CSO, are associated with CAA.[23] Different pathogenic mechanisms have been suggested. The first is impaired clearance of amyloids throughout the arterial PVSs. Another mechanism is the neurovascular deposition of amyloid β.[32] In particular, type 1 CAA with amyloid deposition in cerebral capillaries is associated with AD, where neuritic plaques are commonly found in the neocortex and hippocampus. PVSs are markers of cerebral SVD and CAA.[28]

In our study, the incidence and number of type III PVSs were higher in patients with AD than in the control group. However, the statistically significant values were lower than those for type II PVSs. Brainstem-located PVSs, classified as type III, are frequently observed in the pontomesencephalic and mesencephalo-diencephalic junctions. In other studies, no relationship was observed between type III PVSs and AD.[33]

In our study, there was no difference in PVSs between the mild and moderate-severe AD groups. These results may be associated with the onset of AD pathology in the asymptomatic preclinical period, which is much earlier than the clinical findings. Histopathological findings reflected on MRI, such as enlargement and increase in PVSs, may be observed from the early stages of the disease. In the literature, there is a limited number of studies on the association between the AD stages and PVSs. Ramirez et al. reported that there was a pronounced difference in PVSs between patients with advanced AD and NC.[26] In our study, there was a negative correlation between type II PVSs scores and MMSE scores in patients with AD. Accordingly, an increase in the number of type II PVSs might be associated with impaired cognitive function. Chen et al.[24] concluded that there was no relationship between PVSs and MMSE scores.[34]

It has been reported that PVSs increases with advancing age.[29] In addition, the number of type 1 basal ganglia PVSs was found to be higher in people with hypertension and PVSs, suggesting that vascular factors pose a risk for the development of PVSs.[29] In our study, we found no difference in vascular risk factors other than smoking between the AD and control groups.

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The results of our study suggest that the evaluation of PVSs, especially at the CSO, level using imaging studies in AD is a potential diagnostic option. Our results also suggest that an increased number of PVSs at this level may be an indicator of worse cognitive function. Owing to the complex physiopathology of AD, the significant presence of type II PVSs in ADs with DM2 compared to AD without DM supports SVD and, accordingly, vascular pathology. The prominence of type II PVSs localized in the CSO highlights the lymphatic system pathology manifested by CAA and PVSs, apart from atherosclerosis, which is predictable only in DM2 in vascular pathology. However, more biomolecular and clinical studies are needed to understand AD with multiple pathologies.

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