RESEARCH ARTICLE

Association Between Enlarged Perivascular Spaces and Cognition in a Memory Clinic Population

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Abstract

Background and Objectives

Although enlarged perivascular spaces (EPVS) have been suggested as an emerging measure of small vessel disease (SVD) in the brain, their association with cognitive impairment is not yet clearly understood. We aimed to examine the relationship between each EPVS in the basal ganglia (BG-EPVS) and centrum semiovale (CSO-EPVS) with cognition in a memory clinic population.

Methods

Participants with a diverse cognitive spectrum were recruited from a university hospital memory clinic. They underwent comprehensive clinical and neuropsychological assessments and brain MRI. BG-EPVS and CSO-EPVS were measured on T2-weighted MRI and then dichotomized into low and high degrees for further analyses. Other SVD markers were assessed using validated rating scales.

Results

A total of 910 participants were included in this study. A high degree of BG-EPVS was significantly associated with poorer scores on the executive function domain, but not with other cognitive domains, when age, sex, education, MRI scanner type, and cognitive diagnosis were controlled as covariates. However, the association between BG-EPVS and executive function was no longer significant after controlling for other markers of SVD, such as lacunar infarcts and periventricular white matter hyperintensities, as additional covariates. CSO-EPVS did not have a significant relationship with any cognitive scores, regardless of the covariates.

Discussion

Our findings from a large memory clinic population suggest that EPVS, regardless of the topographical location, may not be used as a specific SVD marker for cognitive impairment, although an apparent association was observed between a high degree of BG-EPVS and executive dysfunction before controlling other SVD markers that share a common pathophysiologic process with BG-EPVS.

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Glossary

AD = Alzheimer disease; **BG** = basal ganglia; **BNT** = Boston Naming Test; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **CP** = construction praxis; **CR** = construction recall; **CSO** = centrum semiovale; **D/I** = deep or infratentorial; **DWMH** = deep white matter hyperintensities; **EPVS** = enlarged perivascular spaces; **FLAIR** = fluid-attenuated inversion recovery; **FOV** = field of view; **MB** = microbleeds; **MCI** = mild cognitive impairment; **PVWMH** = periventricular white matter hyperintensities; **SCD** = subjective cognitive decline; **SVD** = small vessel disease; **TE** = echo time; **TMT-B** = Trail Making Test, Part B; **TR** = repetition time; **TS** = total score; **VF** = verbal fluency; **WLM** = word list memory; **WLR** = word list recall; **WLRc** = word list recognition; **WMH** = white matter hyperintensities.

Perivascular spaces are cavities surrounding the penetrating cerebral small vessels which accord with extensions of the subarachnoid space[1] and act as interstitial fluid drainage routes and transport solutes from the brain.[2] Perivascular spaces are visible on MRI because they dilate and then are called enlarged perivascular spaces (EPVS).[3] EPVS have been suggested as an emerging measure of cerebral small vessel disease (SVD) along with existing SVD markers on MRI such as white matter hyperintensities (WMH), cerebral microbleeds (MB), and lacunes.[4,5] EPVS are commonly observed on T2-weighted MRI in the basal ganglia (BG) and the centrum semiovale (CSO), and several studies indicated that the associated factors of EPVS differ according to their topography: EPVS in CSO (CSO-EPVS) are associated with increased lobar MB or cerebral amyloid angiopathy, while EPVS in BG (BG-EPVS) are related to more deep or infratentorial (D/I) MB, higher WMH volumes, hypertension, and age.[6-8]

As EPVS are commonly found with other various SVD markers[4,9,10] which closely related to cognitive decline in older adults, the relationship between EPVS and cognitive impairment has been repeatedly investigated. However, the reported findings on the issue are still inconclusive. Some population-based studies that included relatively healthy older adults reported that increased overall EPVS or BG-EPVS were associated with greater cognitive impairment,[11-14] whereas others could not find such a relationship.[3,15] A hospital-based study conducted in patients at high risk of SVD reported a correlation between BG-EPVS and cognitive impairment,[16] whereas other studies in patients with ischemic stroke or transient ischemic attack found no association between EPVS and cognitive decline.[9,17] However, few previous studies investigated the issue in patients who visited the memory clinic with a diverse spectrum of cognitive impairment from subjective cognitive decline (SCD) to mild cognitive impairment (MCI) and dementia with various etiologies. Although a recent community-based study that included nondemented and demented older adults showed that the burden of EPVS is associated with faster cognitive decline independent of other neuropathologies,[18] the study did not consider the topography of EPVS, that is, BG-EPVS and CSO-EPVS.

Therefore, this study aimed to examine the relationship of each BG-EPVS and CSO-EPVS with cognition in a memory clinic population. To achieve this goal, we first attempted to identify other measures of cerebral SVD, that is, WMH, cerebral MB, and lacunar infarcts, on MRI, which are related to BG-EPVS or CSO-EPVS. Second, we investigated whether BG-EPVS and CSO-EPVS are associated with performance in various cognitive domains and whether the association is independent of other SVD measures related to EPVS, given that other SVD measures have been known as pathologic substrates of cognitive impairment in older adults.[13]

Methods

Participants

Participants who visited the Memory Clinic of the Seoul National University Hospital, Seoul, South Korea, with a diverse spectrum of cognitive impairment, including SCD, MCI, and dementia, between December 2004 and September 2014 were included in this study. The diagnosis of dementia was made according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition.[19] Patients with Alzheimer disease (AD) dementia met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[20] Diagnosis of vascular dementia was based on the criteria of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences.[21] Mixed dementia was defined as the coexistence of AD and vascular dementia. Other types of dementia groups included various diagnoses such as dementia with Lewy bodies,[22] Parkinson disease dementia,[22] frontotemporal dementia,[23] semantic dementia,[23] and progressive nonfluent aphasia.[23] All individuals with MCI met the international consensus criteria[24]: (1) cognitive decline confirmed by the patient, informant, or physician; (2) objective cognitive impairment; (3) preserved basic activities of daily living; (4) relatively intact in complex instrumental functions; and (5) not demented. SCD participants met the criteria for SCD that were established by the SCD-Initiative group.[25] The following exclusion criteria were applied to all participants: the presence of any serious medical, psychiatric, or neurologic disorder that could affect mental functioning other than MCI or dementia; the presence of severe behavioral or communication problems that would make a clinical or neuroimaging examination difficult; and the absence of a reliable informant.

Clinical and Neuropsychological Assessment

All participants underwent a standardized clinical evaluation according to the protocol of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) clinical assessment.[26] Psychiatrists with expertise in dementia research conducted the clinical evaluation, and diagnostic decisions including clinical dementia rating were made in consensus meeting by 4 or more psychiatrists after reviewing all available data. The Korean version of the CERAD neuropsychological battery[27,28] was applied to all participants by experienced clinical psychologists. The battery consists of several subsets including verbal fluency (VF), Boston Naming Test (BNT), Mini-Mental State Examination, word list memory (WLM), construction praxis (CP), word list recall (WLR), word list recognition (WLRc), construction recall (CR), and Trail Making Test, Part B (TMT-B). The total score (TS) for the CERAD neuropsychological battery was calculated by summing the scores of 6 tests (VF, BNT, WLM, CP, WLR, and WLRc) in the battery.[29] Individual cognitive tests were grouped into 4 cognitive domains: memory (WLM, WLR, WLRc, and CR), language (BNT), visuospatial function (CP), and executive function (VF and TMT-B). Raw scores of each individual test were transformed to *z*-scores using normative data,[27] and a summary score for each cognitive domain was an average of the *z*-scores of component tests (for memory and executive function) or the *z*-score itself of a single-component test (for language and visuospatial function). The *z*-score of TS was used as a measure of global cognition. The presence of 6 vascular risk factors, including hypertension, diabetes, dyslipidemia, transient ischemic attack, stroke, and coronary artery disease, was systematically evaluated, and a vascular risk score was calculated as the total number of vascular risk factors.[30]

MRI Image Acquisition and Analysis

All participants underwent brain MRI scanning using a whole-body 3.0 T General Electric Signa VH/I or 3.0 T Siemens Verio machine. The following sequences were obtained from a General Electric Signa VH/i (Milwaukee, WI): T1-weighted image (echo time [TE] 4.0 milliseconds, repetition time [TR] 22.0 milliseconds, matrix = 256 × 192, field of view [FOV] 240 mm, and flip angle 40°), T2-weighted image (TE 99.7 milliseconds, TR 4,000 milliseconds, matrix = 448 × 256, FOV 220 mm, and flip angle 90°), fluid-attenuated inversion recovery (FLAIR) (TE 162.7 milliseconds, TR 9,902 milliseconds, matrix = 320 × 192, and FOV 220 mm), and axial gradient-recalled echo T2* (TE 25.0 milliseconds, TR 400 milliseconds, FOV 220 mm, and flip angle 20°). The sequences from Siemens Verio (Washington DC) were as follows: T1-weighted image (TE 1.89 milliseconds, TR 1,500 milliseconds, matrix = 256 × 232, FOV 250 mm, and flip angle 9°), T2-weighted image (TE 101 milliseconds, TR 3,380 milliseconds, matrix = 384 × 231, FOV 240 mm, and flip angle 130°), FLAIR (TE 202 milliseconds, TR 5,000 milliseconds, matrix = 256 × 232, and FOV 250 mm), and susceptibility weighted image (TE 72 milliseconds, TR 6,700 milliseconds, FOV 240 mm, and flip angle 15°).

All images were first routinely checked by a neuroradiologist and then evaluated by a physician who received training for this research. Both the neuroradiologist and the physician rater were blinded to the clinical information of participants. EPVS were defined as round, ovoid, or linear structures of high-signal intensity on T2-weighted images and were <3 mm wide.[4] EPVS were counted in the slice with the highest number on one side of the brain. We assessed BG-EPVS and CSO-EPVS separately. The degree of each EPVS was coded using the following scale: 0 = no EPVS, 1 = 1–10 EPVS, 2 = 11–20 EPVS, 3 = 21–40 EPVS, and 4 = >40 EPVS. The intrarater reliability for EPVS was examined from 30 randomly selected scans by scoring twice after 4 weeks. The Cohen kappa value was 1.000 for BG-EPVS and 0.889 for CSO-EPVS.

Other MRI makers, including WMH, lacunar infarcts, cerebral MB, and superficial siderosis, were also assessed. On FLAIR images, we assessed periventricular white matter hyperintensities (PVWMH) and deep white matter hyperintensities (DWMH) using the Fazekas scale[31] and grade ≥2 was regarded as severe degree. Lacunar infarcts were defined as focal lesions less than 15 mm in diameter showing the same signal intensities as CSF and a hyperintense rim on the FLAIR images.[32] A small, homogeneous, round foci of low-signal intensity lesion on T2* images, less than 10 mm in diameter, was defined as MB.[33] We categorized cerebral MB into strict lobar MB and D/I MB. When MB were restricted to the frontal, parietal, temporal, and occipital lobes, they were categorized as strict lobar MB. MB in the deep brain regions (BG, thalamus, internal capsule, and external capsule) or infratentorial regions (brainstem and cerebellum) with or without concomitant lobar MB were categorized as D/I MB. We defined superficial siderosis as a linear gyriform pattern of hypointense signals on T2* images.[34]

Statistical Analysis

Because BG-EPVS and CSO-EPVS were not normally distributed, the degree of each EPVS was dichotomized into low (degree 0–1) and high (degree 2–4), as also previously used.[10,35] This cutoff was chosen to evenly distribute the degree of EPVS into the 2 groups. The clinical characteristics and SVD markers between the diagnostic groups were compared by analysis of variance for continuous variables and the χ^2 test or Fisher exact test for categorical variables. Comparison of clinical and neuroimaging characteristics between high and low degrees of each EPVS was performed using the Student *t* test for continuous variables and the χ^2 test or Fisher exact test for categorical variables. To select the cerebral SVD measures associated with each EPVS, a stepwise logistic regression analysis was performed using a model that included lacunar infarcts, severe PVWMH, severe DWMH, strict lobar, and D/I MB as independent variables; BG-EPVS or CSO-EPVS as dependent variables; and age and sex as covariates. We subsequently conducted general linear model analyses to investigate the association of a high degree of EPVS with performance in each cognitive domain by using 2 models.

Model 1 included age, sex, education, MRI scanner type, and cognitive diagnosis (SCD, MCI, and dementia) covariates, and model 2 included other SVD markers with significant association with a high degree of EPVS in the above logistic regression analyses as additional covariates, as well as the covariates of model 1. To overcome the issues of multiple comparisons, the Bonferroni correction method was used for the association of EPVS with cognitive scores by using a p value of <0.05/the number of cognitive domains (=5) as a threshold for statistical significance. All analyses were performed using IBM SPSS Statistics (version 21.0; SPSS Inc., Chicago, IL). p Values <0.05 were considered statistically significant when not otherwise specified.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was conducted following the principles stated in the Declaration of Helsinki,[36] and Institutional Review Board of Seoul National University Hospital approved the study. Written informed consents were obtained from all patients or their legal representatives.

Data Availability

Data sets that were generated and analyzed during this study are not publicly available because of ethical considerations and privacy restrictions. Data may be obtained from the corresponding author on approval of the Institutional Review Board of Seoul National University Hospital, South Korea.

Results

Participants' Characteristics

The clinical and neuroimaging characteristics of the study participants are summarized in Table 1. A total of 910 participants were included, and the distribution was as follows: SCD (7.0%), MCI (43.8%), AD (37.3%), vascular dementia and mixed dementia (6.4%), and other types of dementia (5.5%). One hundred eighty-three (20.1%) participants showed a high degree of BG-EPVS, and 189 (20.8%) participants had a high degree of CSO-EPVS. The rate of high degree of BG-EPVS significantly differed among diagnostic groups ($\chi^2 = 15.73$, $df = 4$, $p = 0.003$), and the highest rate was observed in patients with vascular dementia plus mixed dementia (39.7%). By contrast, the rate of high degree of CSO-EPVS was not different between the diagnostic groups.

Factors Associated With EPVS

The results of univariate analyses for differences in clinical and neuroimaging characteristics between high and low degrees of

Table 1 Clinical and Neuroimaging Characteristics by the Diagnostic Group

	Total (n = 910)	SCD (n = 64)	MCI (n = 399)	AD (n = 339)	VaD + MXD (n = 58)	Other types of dementia (n = 50)	p Value
Age, y	71.96 ± 8.44	68.48 ± 6.82	71.92 ± 7.33	72.51 ± 9.23	74.83 ± 7.82	69.72 ± 11.53	<0.001[a]
Male, n (%)	324 (35.6)	19 (29.7)	129 (32.3)	114 (33.6)	36 (62.1)	26 (52.0)	<0.001[a]
Education, y	9.09 ± 5.38	10.70 ± 4.74	9.28 ± 5.26	8.82 ± 5.37	7.66 ± 6.01	9.02 ± 5.99	0.024[a]
APOE ε4 carrier, n (%)	273 (36.1)	22 (34.4)	103 (25.8)	127 (37.5)	15 (25.9)	6 (12.0)	<0.001[a]
Vascular risk score	0.91 ± 0.89	0.73 ± 0.72	0.95 ± 0.91	0.80 ± 0.84	1.76 ± 0.82	0.68 ± 0.77	<0.001[a]
CDR SOB	3.13 ± 2.90	0.17 ± 0.41	1.37 ± 0.71	4.93 ± 2.92	6.14 ± 3.32	5.23 ± 2.50	<0.001[a]
MMSE	20.42 ± 5.89	27.30 ± 2.21	23.23 ± 3.93	16.76 ± 5.42	17.07 ± 5.67	17.88 ± 5.77	<0.001[a]
High degree of BG-EPVS, n (%)	183 (20.1)	9 (14.1)	77 (19.3)	64 (18.9)	23 (39.7)	10 (20.0)	0.003[a]
High degree of CSO-EPVS, n (%)	189 (20.8)	15 (23.4)	85 (21.3)	67 (19.8)	9 (15.5)	13 (26.0)	0.670
Severe PVWMH, n (%)	257 (28.2)	10 (15.6)	95 (23.8)	98 (28.9)	41 (70.7)	13 (26.0)	<0.001[a]
Severe DWMH, n (%)	163 (17.9)	10 (15.6)	60 (15.0)	63 (18.6)	22 (37.9)	8 (16.0)	0.001[a]
Lacunar infarcts, n (%)	222 (24.4)	8 (12.5)	91 (22.8)	72 (21.2)	43 (74.1)	8 (16.0)	<0.001[a]
Strict lobar MB, n (%)	121 (13.3)	3 (4.7)	44 (11.0)	58 (17.1)	9 (15.5)	7 (14.0)	0.034[a]
D/I MB, n (%)	77 (8.5)	2 (3.1)	32 (8.0)	27 (8.0)	14 (24.1)	2 (4.0)	<0.001[a]
Superficial siderosis, n (%)	24 (2.6)	1 (1.6)	9 (2.3)	12 (3.5)	2 (3.4)	0 (0.0)	0.636

Abbreviations: AD = Alzheimer disease; BG-EPVS = enlarged perivascular spaces in the basal ganglia; CDR SOB = clinical dementia rating sum of boxes; CSO-EPVS = enlarged perivascular spaces in the centrum semiovale; D/I MB = deep or infratentorial microbleeds; DWMH = deep white matter hyperintensities; lobar MB = lobar microbleeds; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; MXD = mixed dementia; PVWMH = periventricular white matter hyperintensities; SCD = subjective cognitive decline; VaD = vascular dementia.
Continuous variables are presented as mean ± SD, and categorical variables are presented as the number of participants (%).
Compared by analysis of variance for continuous variables, and the χ^2 test or Fisher exact test for categorical variables.
[a] $p < 0.05$.

BG-EPVS or CSO-EPVS are given in Table 2. A high degree of BG-EPVS was associated with old age, male sex, presence of hypertension and stroke, high vascular risk score, severe PVWMH and DWMH, presence of lacunar infarcts and strict lobar, and D/I MB. By contrast, a high degree of CSO-EPVS was associated with high education and the presence of strict lobar MB. Subsequent stepwise logistic regression analyses revealed that severe PVWMH, presence of lacunar infarcts, strict lobar, and D/I MB were significantly and independently associated with a high degree of BG-EPVS, while only the presence of strict lobar MB was related to a high degree of CSO-EPVS (Table 3).

Association Between EPVS and Cognition

As summarized in Table 4, general linear model analyses revealed that a high degree of BG-EPVS was significantly associated with poorer scores on the executive function domain, but not with those of other cognitive domains, when age, sex, education, MRI scanner type, and cognitive diagnosis were controlled as covariates (model 1). The association between BG-EPVS and executive function was no longer significant after controlling for SVD markers, which were significantly related to BG-EPVS in the logistic regression analysis (i.e., PVWMH, lacunar infarcts, strict lobar, and D/I MB), as additional covariates (model 2). CSO-EPVS did not have a significant relationship with any cognitive domains, regardless of the models. Additional general linear model analyses controlling for each individual SVD marker related to BG-EPVS revealed that the significant association between BG-EPVS and executive function was attenuated after controlling for the confounding effect of lacunar infarcts and PVWMH, but not after controlling for cerebral MB (Table 5).

Discussion

In our memory clinic population, PVWMH, lacunar infarcts, strict lobar, and D/I MB were independently associated with BG-EPVS, while only strict lobar MB was related to CSO-EPVS. These results are consistent with the findings of previous studies conducted in other populations. BG-EPVS were associated with lacunes, WMH, and deep MB in healthy adults[6] and with WMH in patients with memory impairment,[7] intracerebral hemorrhage,[37] strokes, and transient ischemic attack.[9,38,39] Regarding CSO-EPVS, a high degree of it was

Table 2 Comparison of Clinical and Neuroimaging Characteristics Between High and Low Degrees of EPVS

	BG-EPVS			CSO-EPVS		
	Low (n = 727)	High (n = 183)	*p* Value	Low (n = 721)	High (n = 189)	*p* Value
Age, y	70.89 ± 8.51	76.22 ± 6.59	<0.001[a]	72.02 ± 8.49	71.74 ± 8.25	0.685
Male, n (%)	238 (32.7)	86 (47.0)	<0.001[a]	253 (35.1)	71 (37.6)	0.527
Education, y	9.12 ± 5.35	8.98 ± 5.51	0.760	8.80 ± 5.43	10.20 ± 5.06	0.001[a]
APOE ε4 carrier, n (%)	223 (36.7)	50 (33.3)	0.437	222 (37.0)	51 (32.5)	0.294
Smoker, n (%)	125 (17.2)	41 (22.4)	0.103	129 (17.9)	37 (19.6)	0.593
Hypertension, n (%)	323 (44.4)	115 (62.8)	<0.001[a]	348 (48.3)	90 (47.6)	0.874
Diabetes mellitus, n (%)	158 (21.7)	38 (20.8)	0.776	160 (22.2)	36 (19.0)	0.349
Dyslipidemia, n (%)	61 (8.4)	13 (7.1)	0.569	54 (7.5)	20 (10.6)	0.166
Coronary artery disease, n (%)	12 (1.7)	5 (2.7)	0.358	11 (1.5)	6 (3.2)	0.136
Stroke, n (%)	64 (8.8)	43 (23.5)	<0.001[a]	91 (12.6)	16 (8.5)	0.114
Vascular risk score	0.85 ± 0.87	1.17 ± 0.91	<0.001[a]	0.92 ± 0.89	0.89 ± 0.88	0.659
Severe PVWMH, n (%)	155 (21.3)	102 (55.7)	<0.001[a]	206 (28.6)	51 (27.0)	0.666
Severe DWMH, n (%)	98 (13.5)	65 (35.5)	<0.001[a]	136 (18.9)	27 (14.3)	0.144
Lacunar infarcts, n (%)	127 (17.5)	95 (51.9)	<0.001[a]	170 (23.6)	52 (27.5)	0.262
Strict lobar MB, n (%)	82 (11.3)	39 (21.3)	<0.001[a]	83 (11.5)	38 (20.1)	0.002[a]
D/I MB, n (%)	43 (5.9)	34 (18.6)	<0.001[a]	63 (8.7)	14 (7.4)	0.559
Superficial siderosis, n (%)	20 (2.8)	4 (2.2)	0.801	18 (2.5)	6 (3.2)	0.611

Abbreviations: BG-EPVS = EPVS in the basal ganglia; CSO-EPVS = EPVS in the centrum semiovale; D/I MB = deep or infratentorial microbleeds; DWMH = deep white matter hyperintensities; EPVS = enlarged perivascular spaces; lobar MB = lobar microbleeds; PVWMH = periventricular white matter hyperintensities.
Continuous variables are presented as mean ± SD, and categorical variables are presented as the number of participants (%).
Compared by the Student *t* test for continuous variables and the χ^2 test or Fisher exact test for categorical variables.
[a] $p < 0.05$.

Table 3 Results of Stepwise Logistic Regression Analyses to Determine SVD Markers Associated With a High Degree of EPVS

	High degree of BG-EPVS		High degree of CSO-EPVS	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Lacunar infarcts	2.818 (1.896–4.189)	<0.001		
Severe PVWMH	2.213 (1.489–3.287)	<0.001		
Strict lobar MB	1.627 (1.012–2.614)	0.045	2.002 (1.299–3.085)	0.002
D/I MB	1.961 (1.125–3.417)	0.017		

Abbreviations: BG-EPVS = EPVS in the basal ganglia; CSO-EPVS = EPVS in the centrum semiovale; D/I = deep or infratentorial; EPVS = enlarged perivascular spaces; MB = microbleeds; OR = odds ratio; PVWMH = periventricular white matter hyperintensities; SVD = small vessel disease.
Age and sex were included as covariates.

related to lobar MB in healthy adults,[6] memory clinic cohort,[7] and patients with intracerebral hemorrhage.[37] Given the previous findings, our results support that BG-EPVS may share pathophysiologic mechanisms with lacunes, WMH, and deep MB. Such SVD markers commonly occur under the effects of hypertensive arteriopathy, which predominantly affects deep perforating arteries.[40,41] It is of interest that BG-EPVS also showed a significant association with strict lobar MB, as well as D/I MB. Consistent with this, a previous study using brain MRI and amyloid PET showed that subcortical SVD, as well as amyloid pathology, was related to lobar MB.[42] These findings may indicate that hypertensive arteriopathy affects superficial perforators related to lobar MB and deep perforating arteries. Meanwhile, beta-amyloid deposition in leptomeningeal and cortical arteries or cerebral amyloid angiopathy may be a pathophysiologic link that explains the relationship between CSO-EPVS and lobar MB, as previously suggested.[43]

We found that a high degree of BG-EPVS was significantly associated with a poorer performance in executive function, although the association was no longer statistically significant after adjustment for other related SVD markers. Several reports from various study populations are consistent with our findings. A hospital-based study reported that BG-EPVS were not associated with cognition after controlling for WMH and cerebral MB in patients with lacunar stroke syndrome.[17] Another recent study also showed no association between BG-EPVS and cognition in a population that included cognitively unimpaired and MCI older adults.[3] In a population-based prospective study, no significant associations were found between BG-EPVS and cognitive performance at baseline, while a higher BG-EPVS burden was related to a greater decline in information processing speed in the longitudinal follow-up evaluation.[12] In contrast to our findings, a recent observational study on community-dwelling older adults showed that BG-EPVS were related to information processing and executive function,[13] which differs from our results in that the relationship remained significant even after controlling for the effects of other SVD makers. It is difficult to directly compare the results because the definition of BG-EPVS was different from ours. A previous study used the distribution along with the number of BG-EPVS scoring, resulting in higher rates of severe BG-EPVS (92%)[13] compared with this study (20.1%) or another large population-based study (10.6%).[12]

Table 4 Results of General Linear Model Analyses on the Association of a High Degree of EPVS With Cognitive Function

	High degree of BG-EPVS								High degree of CSO-EPVS							
	Model 1				Model 2				Model 1				Model 2			
	df	MS	*F*	*p* Value	*df*	MS	*F*	*p* Value	*df*	MS	*F*	*p* Value	*df*	MS	*F*	*p* Value
Global cognition	1	0.334	0.246	0.620	1	0.017	0.013	0.909	1	0.943	0.696	0.404	1	1.230	0.909	0.341
Memory	1	1.833	2.209	0.138	1	1.786	2.155	0.142	1	0.831	1.000	0.318	1	0.923	1.111	0.292
Language	1	4.175	2.918	0.088	1	0.946	0.674	0.412	1	0.869	0.606	0.437	1	1.094	0.763	0.383
Visuospatial function	1	1.336	0.306	0.580	1	0.962	0.220	0.639	1	0.007	0.002	0.968	1	0.005	0.001	0.974
Executive function	1	8.932	10.417	0.001[a]	1	2.883	3.405	0.065	1	<0.001	<0.001	0.996	1	0.006	0.007	0.934

Abbreviations: BG-EPVS = EPVS in the basal ganglia; CSO-EPVS = EPVS in the centrum semiovale; *df* = degree of freedom; EPVS = enlarged perivascular spaces; MS = mean square; SVD = small vessel disease.
Model 1 included age, sex, education, MRI scanner type, and cognitive diagnosis (subjective cognitive decline, mild cognitive impairment, and dementia) as covariates, and model 2 included the covariates of model 1 plus SVD markers that showed significant association with EPVS in the stepwise logistic regression analysis.
[a] Significant after the Bonferroni correction (i.e., adjusted $p < 0.01$ [0.05/5]).

Table 5 General Linear Model Analyses on the Association of a High Degree of BG-EPVS With Executive Function After Adjustment for Each SVD Marker

	Adjusted SVD markers															
	Lacunar infarcts				Periventricular hyperintensities				Strict lobar microbleeds				Deep or infratentorial microbleeds			
	df	MS	*F*	*p* Value	*df*	MS	*F*	*p* Value	*df*	MS	*F*	*p* Value	*df*	MS	*F*	*p* Value
Executive function	1	5.384	6.304	0.012	1	4.338	5.125	0.024	1	8.592	10.017	0.002[a]	1	7.278	8.504	0.004[a]

Abbreviations: BG-EPVS = enlarged perivascular spaces in the basal ganglia; *df* = degree of freedom; MS = mean square; SVD = small vessel disease.
Adjusted for age, sex, education, MRI scanner type, cognitive diagnosis (subjective cognitive decline, mild cognitive impairment, and dementia), and each SVD marker.
[a] Significant after the Bonferroni correction (i.e., adjusted $p < 0.01$ [0.05/5]).

Furthermore, we investigated the association between BG-EPVS and executive function controlling for each individual SVD marker significantly related to BG-EPVS. The results revealed that the significant association between a high degree of BG-EPVS and poor performance in the executive function domain was attenuated after controlling for the confounding effect of lacunar infarcts and PVWMH, whereas cerebral MB did not affect the association. These findings indicate that a high degree of BG-EPVS seems not directly contribute to cognitive decline but is only indirectly associated with executive dysfunction due to its close linkage to lacunar infarcts and PVWMH, which can directly impair executive function by interrupting the prefrontal subcortical circuit.[44] BG-EPVS, lacunar infarcts, and PVWMH may represent different sequelae of the same underlying process of arteriosclerosis (e.g., fluid extravasation in BG-EPVS, hypoperfusion in WMH, and vessel occlusion in lacunes).[45]

No significant association was found between CSO-EPVS and cognition, and adjustment for SVD did not change this relationship. Consistent with our findings, previous studies have shown that CSO-EPVS have no significant correlation with cognitive performance.[3,9,17] Only 1 longitudinal study showed that CSO-EPVS had a greater decline in global cognition over 4 years independent of SVD.[14]

The main strength of our study was that it included a large memory clinic population, including individuals with a broad cognitive spectrum, such as SCD, MCI, and dementia due to various etiologies. Few previous studies on the relationship between EPVS and cognition targeted populations with diverse ranges of cognitive impairment. Nevertheless, our study has some limitations. First, the cross-sectional design made it difficult to explore longitudinal cognitive changes and to address the causal relationship between EPVS and cognition. Second, we did not assess EPVS in other regions, such as the hippocampus and midbrain. Third, visual rating scales for EPVS and other SVD markers were not truly quantitative and may be influenced by proficiency of rater and human error. Further studies adopting the quantitative technique such as volumetric measurement of WMH are warranted.

Our findings from a large memory clinic population, including individuals with a broad cognitive spectrum, suggest that EPVS, regardless of topographical location, may not be used as specific SVD markers for cognitive impairment, although an apparent association was observed between a high degree of BG-EPVS and executive dysfunction before controlling for other SVD markers, such as PVWMH and lacunar infarcts, which share the common pathophysiologic process of arteriosclerosis with BG-EPVS.

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Hyewon Baek, MD	Gyeonggi Provincial Hospital for the Elderly, Yongin, South Korea	Acquisition of data; analysis and interpretation of data; drafting and critical revision of manuscript for intellectual content

Appendix *(continued)*

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