RESEARCH ARTICLE

Association of Enlarged Perivascular Spaces With Amyloid Burden and Cognitive Decline in Alzheimer Disease Continuum

Seong Ho Jeong, MD,* Jungho Cha, PhD,* Mincheol Park, MD, Jin Ho Jung, MD, Byoung Seok Ye, MD, PhD, Young H. Sohn, MD, PhD, Seok Jong Chung, MD,** and Phil Hyu Lee, MD, PhD**

Correspondence
Dr. Lee
phlee@yuhs.ac

Neurology® 2022;99:e1791-e1802. doi:10.1212/WNL.0000000000200989

Abstract

Background and Objectives

To investigate the effects of enlarged perivascular space (EPVS) on amyloid burden and cognitive function in Alzheimer disease (AD) continuum.

Methods

We retrospectively reviewed 208 patients with AD across the cognitive continuum (preclinical, prodromal, and AD dementia) who showed amyloid deposition on ^{18}F-florbetaben PET scans and 82 healthy controls. EPVSs were counted for each patient in the basal ganglia (BG), centrum semiovale (CSO), and hippocampus (HP) on axial T2-weighted images. Patients were then classified according to the number of EPVSs into the EPVS+ (>10 EPVSs) and EPVS– (0–10 EPVSs) groups for the BG and CSO, respectively. In terms of HP-EPVS, equal or more than 7 EPVSs on bilateral hemisphere were regarded as the presence of HP-EPVS. After adjusting for markers of small vessel disease (SVD), multiple linear regression analyses were performed to determine the intergroup differences in global and regional amyloid deposition and cognitive function at the time of diagnosis of AD continuum. A linear mixed model was used to assess the effects of EPVSs on the longitudinal changes in the Mini-Mental State Examination (MMSE) scores.

Results

Amyloid burden at the time of diagnosis of AD continuum was not associated with the degree of BG-, CSO-, or HP-EPVS. BG-EPVS affected language and frontal/executive function via SVD markers, and HP-EPVS was associated with general cognition via SVD markers. However, CSO-EPVS was not associated with baseline cognition. A higher number of CSO-EPVS was significantly associated with a more rapid decline in MMSE scores ($\beta = -0.58$, standard error = 0.23, $p = 0.011$) independent of the amyloid burden. In terms of BG and HP, there was no difference between the EPVS+ and EPVS– groups in the rate of longitudinal decreases in MMSE scores.

Discussion

Our findings suggest that BG-, CSO-, and HP-EPVS are not associated with baseline β-amyloid burden or cognitive function independently of SVD at the diagnosis of AD continuum. However, CSO-EPVS appears to be associated with the progression of cognitive decline in an amyloid-independent manner. Further studies are needed to investigate whether CSO-EPVS is a potential therapeutic target in patients with AD continuum.

*These authors contributed equally to this work as co–first authors.

**These authors contributed equally to this work as co–senior authors.

From the Department of Neurology (S.H.J., M.P., B.S.Y., Y.H.S., S.J.C., P.H.L.), Yonsei University College of Medicine, Seoul, South Korea; Department of Neurology (S.H.J.), Inje University Sanggye Paik Hospital, Seoul, South Korea; Nash Family Center for Advanced Circuit Therapeutics (J.C.), Icahn School of Medicine at Mount Sinai, New York, NY; Department of Neurology (J.H.J.), Busan Paik Hospital, Inje University College of Medicine, Seoul, South Korea; Department of Neurology (S.J.C.), Yongin Severance Hospital, Yonsei University Health System, Yongin, South Korea; Yonsei Beyond Lab (S.J.C.), Yongin, South Korea; and Severance Biomedical Science Institute (P.H.L.), Yonsei University College of Medicine, Seoul, South Korea.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AD = Alzheimer disease; **ADL** = activities of daily living; **ANCOVA** = analysis of covariance; **BAPL** = brain amyloid plaque load; **BG** = basal ganglia; **CDR-SOB** = Clinical Dementia Rating–Sum of Boxes; **CMB** = cerebral microbleed; **CSO** = centrum semiovale; **EPVS** = enlarged perivascular space; **FBB** = florbetaben; **FDR** = false discovery rate; **FLAIR** = fluid-attenuated inversion recovery; **HP** = hippocampus; **ICC** = intraclass correlation coefficient; **MMSE** = Mini-Mental Status Examination; **MTA** = medial temporal lobe atrophy; **RCFT** = Rey-Osterrieth Complex Figure Test; **SE** = standard error; **SUVR** = standardized uptake value ratio; **SVD** = small vessel disease; **TR** = repetition time; **WMH** = white matter hyperintensity.

Enlarged perivascular spaces (EPVSs) are considered to result from the dilation of the potential space within the cerebral blood vessel wall, which may be secondary to impaired interstitial fluid drainage.[1,2] They are small, linear, or ovoid fluid-filled structures surrounding perforating vessels, which are frequently visible in the midbrain, hippocampus (HP), basal ganglia (BG), and centrum semiovale (CSO) in the brain MRI of the elderly.[3] Although the clinical relevance of EPVS needs to be elucidated, recent evidence has suggested that EPVS may imply dysfunction of the glymphatic system that affects the clearance of toxic waste such as misfolded protein.[4] This implies a potential relationship between EPVS and neurodegenerative disorders such as Alzheimer disease (AD) and Parkinson disease.[5,6]

Several previous studies have demonstrated the effect of EPVS on incident all-cause dementia and longitudinal cognitive impairment.[5,7-12] However, the role of EPVS in AD continuum has not been extensively investigated, and several studies have reported rather inconsistent results.[5,11,12] Based on recent conflicting results and increasing attention on the role of EPVS in neurodegenerative disorders, the present study aimed to evaluate the association between EPVS, amyloid burden, and cognitive function in patients with ^{18}F-florbetaben (^{18}F-FBB) PET-proven AD pathologic change. Thus, we performed comparative analyses of β-amyloid retention using standardized uptake value ratios (SUVRs) calculated from cerebral cortical areas and baseline and longitudinal cognitive performance in patients with AD continuum according to the degree of BG-, CSO-, or HP-EPVS.

Methods

Participants

We retrospectively reviewed 290 patients with AD continuum from Severance Hospital who visited our clinic for subjective symptoms of cognitive impairment, had brain MRI scans, and exhibited β-amyloid positivity on ^{18}F-FBB PET scans between June 2015 and May 2020. A detailed neuropsychological study was performed to assess the level of cognitive impairment in patients with cognitive complaints. All patients met the criteria of probable AD dementia with evidence of the AD pathophysiologic process, prodromal AD (mild cognitive impairment due to AD–high likelihood), or preclinical AD according to the National Institute on Aging–Alzheimer's Association guidelines.[13-15] In addition, we excluded (1) patients whose cognitive impairment was probably ascribed to other etiologies,[13] (2) patients whose interval between MRI and ^{18}F-FBB PET scans was more than 1 year, and (3) patients whose imaging data were not suitable for preprocessing (Figure 1). Cognitive status was categorized into nondementia (preclinical and prodromal AD) and dementia (probable AD). All participants in the control group were recruited via poster advertisements for healthy older adults visiting Severance Hospital and did not complain of cognitive impairment and had normal cognitive function according to the Korean version of the Mini-Mental State Examination (MMSE) and detailed neuropsychological tests (described later).

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Yonsei University Severance Hospital institutional review board. The need for informed consent was waived for patients with AD continuum (IRB No. 4-2021-0759) because of the retrospective nature of the study, whereas informed consent was obtained from all healthy controls (IRB No. 4-2015-0551).

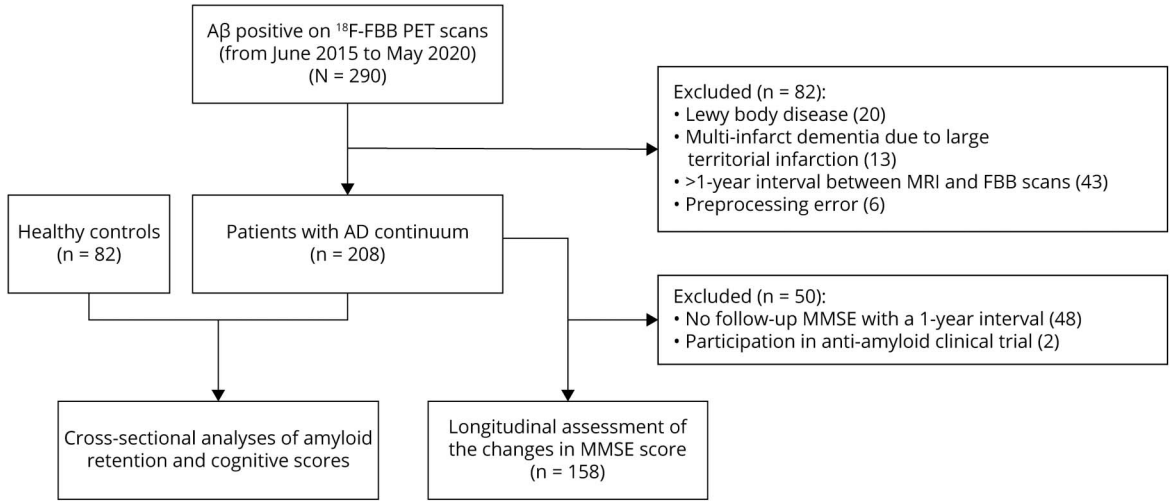
Acquisition and Visual Assessment of ^{18}F-FBB Scans

^{18}F-FBB PET scans were obtained using a Discovery 600 system (General Electric Healthcare, Milwaukee, MI). ^{18}F-FBB-PET images were acquired 90 minutes after administration of 300 MBq (8 mCi) FBB for 20 minutes. Images were acquired with a 256 × 256 matrix and reconstructed with an ordered-subsets expectation maximization algorithm in an iso-0.98-mm voxel size. Acquisition corrections included decay, attenuation, scatter, dead time, normalization, sensitivity calibrated using a dose calibrator, and random correction. Brain β-amyloid plaque load (BAPL) scores[16] were assessed based on visual ratings by an expert reader (Professor at the Department of Nuclear Medicine in Severance Hospital) who was blinded to the clinical diagnosis. All enrolled patients had BAPL scores of 2 or 3, which were classified as β-amyloid positivity.

Acquisition of MRIs

All patients underwent a brain MRI using a 3.0 T scanner (Achieva; Philips Medical Systems, Best, the Netherlands) with a 32-channel receiver array head coil. Head motion was minimized with restraining foam pads provided by the manufacturer. The imaging protocol included T2-weighted images (repetition time [TR]/echo time [TE], 2,800–3,000/80–100 ms; section thickness, 5 mm; matrix, 256 × 256), fluid-attenuated inversion recovery (FLAIR) images (TR/TE, 9,000–10,000/110–125 ms;

Figure 1 Flowchart of Participants



AD = Alzheimer disease; FBB = florbetaben; MMSE = Mini-Mental Status Examination.

section thickness, 5 mm; matrix, 256 × 256), and T2*-weighted gradient echo images (TR/TE, 500–1,000/15–25 ms; slice thickness, 5 mm; matrix, 256 × 256). A high-resolution, T1-weighted MRI volume data set was obtained from all subjects with a 3-dimensional T1-TFE sequence configured with the following acquisition parameters: axial acquisition with a 224 × 256 matrix; 256 × 256 reconstructed matrix with 182 slices; 220-mm field of view; 0.98 × 0.98 × 1.2 mm^3 voxels; 4.6 ms echo time; 9.6 ms repetition time; 8° flip angle; and 0 mm slice gap.

Quantitative Analyses of ^{18}F-FBB PET Scans

All image processing was performed using Statistical Parametric Mapping 12 (SPM12; Wellcome Trust Center for Neuroimaging, London, UK, fil.ion.ucl.ac.uk/spm/) and FreeSurfer 6.0 (surfer.nmr.mgh.harvard.edu/) software. The processing was performed in a manner similar to that previously described for the Alzheimer's Disease Neuroimaging Initiative PET pipeline in Berkeley.[17] PET images were co-registered onto the corresponding structural MRI. The structural MRI of each patient was segmented using FreeSurfer to create a reference region and target cortical regions. The SUVRs in the FreeSurfer-defined 4 cortical target regions, including the frontal, lateral parietal, lateral temporal, and anterior/posterior cingulate cortices, were calculated by dividing the whole cerebellum uptake. The global SUVR was also calculated as a volume-weighted mean across the 4 cortical regions of the SUVRs, which was used as a continuous variable in the present study.

Visual Rating of EPVS

EPVS was defined and rated on axial T2-weighted MRIs according to the Standards for Reporting Vascular Changes on Neuroimaging criteria[1] by 2 trained neurologists (S.H.J and M.P.) who were blinded to the clinical information. The neurologists used a 4-point visual rating scale (0 = absent EPVS, 1 = 1–10 EPVSs, 2 = 11–20 EPVSs, 3 = 21–40 EPVSs, and 4 = more than 40 PVSs) for the BG and CSO, respectively.[18,19] The rating was performed on a single predefined slice (first slice above the anterior commissure in the BG with the first slice above the level of the lateral ventricles for the CSO). EPVSs were counted in each hemisphere, and the hemisphere with the highest score was recorded. The interrater reliability was excellent for both BG-EPVS (intraclass correlation coefficient [ICC] = 0.866) and CSO-EPVS (ICC = 0.871). If the EPVS scores were discordant between the raters, the final score was determined by consensus. The severity was dichotomized as a high number of EPVS (score ≥2; EPVS+) or a low number of EPVS (score <2; EPVS−) as in previous publications.[6,12]

In terms of HP-EPVS, we used the method proposed by a previous study.[20] A slice visualizing the midbrain and parahippocampal gyrus was selected, and we manually counted HP-EPVS in both hemispheres (ICC = 0.876). We regarded HP-EPVS+ as the sum of the left and right HP-EPVSs was equal or more than 7.[20]

Visual Rating of Small Vessel Disease Burden: White Matter Hyperintensities, Lacunes, and Cerebral Microbleeds

The severity of white matter hyperintensities (WMHs) was rated on FLAIR images using the Scheltens scale and used as a continuous variable in this study.[21] Lacunes were defined as hyperintense lesions >3 mm and <15 mm in the subcortical area on T2-weighted images with a perilesional halo on FLAIR images.[1] Cerebral microbleeds (CMBs) are defined as small, rounded, homogeneous, hypointense lesions on T2*-weighted gradient-echo images.[22] Lacunes and CMBs were used as binary variables in the current study. The WMH severity in the periventricular and lobar (frontal, parietal, temporal, and occipital) regions and the presence of lacunes or CMBs in the whole brain area were determined by consensus between 2 neurologists (S.H.J. and J.H.J).

Visual Rating of Medial Temporal Lobe Atrophy

Visual assessment of medial temporal lobe atrophy (MTA) was performed by 2 neurologists (S.H.J. and J.H.J.) using the Scheltens scale.[23] The average of the right and left MTA scores was used as a continuous variable in the current study. The interrater reliability of the MTA scores was high (ICC = 0.876). If MTA scores were discordant between the raters, the final score was determined by consensus.

Neuropsychological Tests

At baseline, 202 (97.1%) patients with AD continuum and all healthy controls underwent a standardized neuropsychological battery test called the Seoul Neuropsychological Screening Battery,[24] which contains tests that assess attention/working memory, language, visuospatial function, memory, and frontal/executive function. Standardized z-scores were available for all scorable tests based on age- and education-matched norms. We included the following tests: the digit span forward and backward for the attention domain; the Korean version of the Boston Naming Test for the language domain; copying item of the Rey-Osterrieth Complex Figure Test (RCFT) for the visuospatial domain; immediate recall, 20-minute delayed recall, and recognition items of the Seoul Verbal Learning Test for the verbal memory domain; immediate recall, 20-minute delayed recall, and recognition items of the RCFT for the visual memory domain; and the Controlled Oral Word Association Test for semantic (animal and supermarket) and phonemic fluency and the Stroop color reading test for the frontal/executive domain. A composite score was calculated for each cognitive domain by dividing the sum of the z-scores by the number of tests. The operational definition of cognitive impairment that we used has been described in a previous study.[25] In addition, the MMSE and Clinical Dementia Rating–Sum of Boxes (CDR-SOB) were used to assess general cognition.[26] Cognitive status was established on the consensus of 2 neurologists and 1 neuropsychologist based on the evidence of abnormal activities of daily living (ADL), judged both clinically and based on instrumental ADL scales.[27,28]

Longitudinal Assessment of the Changes in MMSE Scores Over Time

Of the 208 patients with AD continuum, 50 were excluded from the longitudinal analysis for cognitive decline due to the following reasons: (1) unavailability of longitudinal MMSE data in 48 patients and (2) enrollment of 2 patients in a clinical trial of anti-amyloid therapy. Thus, 158 patients were included in the longitudinal analysis. The mean follow-up duration was 2.0 ± 1.0 years. A linear mixed model was used to compare the rate of longitudinal changes in the MMSE scores between groups according to the severity of EPVS.

Statistical Analyses

To compare the baseline demographic characteristics between groups according to the degree of BG-, CSO-, or HP-EPVS (EPVS− vs EPVS+), independent *t* tests were used for continuous variables, and Pearson's χ^2 tests or Fisher exact tests were used for categorical variables. An analysis of covariance (ANCOVA) was used to compare the SUVRs of each cortical region between the groups while adjusting for the effect of age at the ^{18}F-FBB PET scan, sex, cognitive status, and *APOE ε4* carrier status. When the analyses including healthy controls were performed, *APOE ε4* carrier status was omitted due to unavailable *APOE* genotype data in healthy controls. The false discovery rate (FDR) method was used for multiple comparison correction.

Multivariate linear regression analysis was used to determine the independent effects of EPVS in either BG, CSO, or HP on the composite scores of each cognitive domain and CDR-SOB. The equations of models 1 and 2 are available in Table 2 footnote. Model 2 was designed to investigate the effect modification by small vessel disease (SVD) markers using additional adjustment for WMHs, lacunes, and CMBs. When the regression analyses including healthy controls were performed, *APOE ε4* carrier status was omitted in the equation because there were no available *APOE* genotype data in healthy controls. The FDR method was used to correct for multiple testing.

A linear mixed model was used to compare the rate of longitudinal changes in the MMSE scores between groups according to the degree of BG-, CSO-, or HP-EPVS. The equations of models 1 and 2 are available in Table 3 footnote. Here, model 2 was designed to investigate the effect modification by amyloid burden using additional adjustment for a global SUVRs × time interaction term. The group effect on the longitudinal MMSE change over time was tested using an EPVS group × time interaction term. Subgroup analyses according to cognitive status (subgroups with and without dementia) were also performed by applying the same statistical model. Statistical analyses were performed using R (v4.0, r-project.org/). Results with a p value of <0.05 were considered statistically significant.

Data Availability

The deidentified data that support the findings of this study are available from the authors on reasonable request.

Results

Demographic and Clinical Characteristics

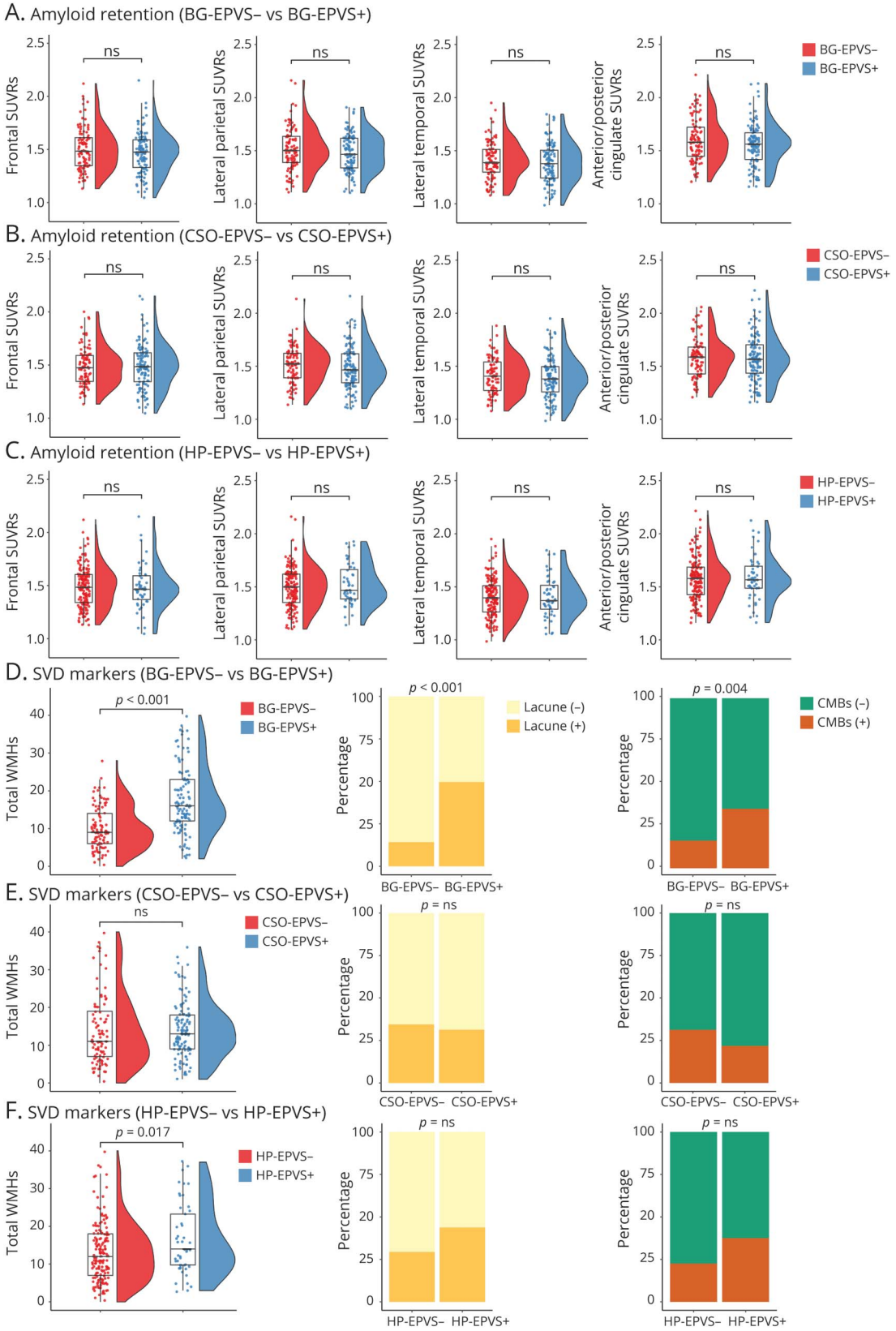
Consecutively, 208 patients with AD continuum and 82 healthy controls were enrolled in this study. The demographic and clinical characteristics of the patients with AD continuum or healthy controls according to the severity of EPVS are summarized in Table 1 and eTable 1 (links.lww.com/WNL/C241). Among patients with AD continuum, those in the BG-EPVS+ group were older than those in the BG-EPVS− group, whereas sex, years of education, the proportion of *APOE ε4* carriers, BAPL score 3, and dementia did not differ between the 2 groups. Vascular risk factors were comparable between the BG-EPVS groups, except for hypertension. The visual rating score of MTA was significantly higher in the BG-EPVS+ group than in the BG-EPVS− group. The BG-EPVS+ group had lower MMSE scores and higher CDR-SOB than the BG-EPVS− group, whereas there was no significant difference in each cognitive domain composite

Table 1 Demographic Characteristics of Patients With Alzheimer Disease Continuum According to EPVS

	BG-EPVS−	BG-EPVS+	CSO-EPVS−	CSO-EPVS+	HP-EPVS−	HP-EPVS+
No. of participants, n	**99**	**109**	**93**	**115**	**160**	**48**
Age at FBB, y	73.02 ± 7.75[a]	77.59 ± 5.62[a]	74.42 ± 7.51	76.22 ± 6.64	75.56 ± 7.39	74.93 ± 7.51
Age at MRI, y	72.84 ± 7.74[a]	77.51 ± 5.57[a]	74.30 ± 7.51	76.09 ± 6.62	75.41 ± 7.39	74.89 ± 5.95
Female, n (%)	67 (67.7%)	62 (56.9%)	58 (62.4%)	71 (61.7%)	100 (62.5%)	29 (60.4%)
Education, y	10.77 ± 5.24	10.67 ± 5.15	9.54 ± 5.16	11.67 ± 5.02	10.51 ± 5.49	11.41 ± 3.95
MMSE	23.64 ± 3.54	22.50 ± 4.15	22.85 ± 3.75	23.19 ± 4.03	22.94 ± 3.87	23.38 ± 4.05
***APOE ε4* carrier**	56 (58.3%)	52 (50.0%)	48 (53.3%)	60 (54.6%)	91 (56.9%)	25 (52.1%)
BAPL score						
2	5 (5.1%)	14 (12.8%)	9 (9.7%)	10 (8.7%)	14 (8.8%)	5 (10.4%)
3	94 (95.0%)	95 (87.2%)	84 (90.3%)	105 (91.3%)	146 (91.3%)	43 (89.6%)
Cognitive status						
Nondementia	66 (66.8%)	63 (57.8%)	57 (61.3%)	72 (62.6%)	93 (58.12%)	36 (75.00%)
Dementia	33 (33.3%)	46 (42.2%)	36 (38.7%)	43 (37.4%)	67 (41.88%)	12 (25.00%)
Other EPVSs						
BG-EPVS+	—	—	41 (44.1%)[b]	68 (59.1%)[b]	74 (46.3%)[c]	35 (72.9%)[c]
CSO-EPVS+	47 (47.5%)[b]	68 (62.4%)[b]	—	—	79 (49.4%)[c]	36 (75.0%)[c]
HP-EPVS+	13 (13.1%)[c]	35 (32.1%)[c]	12 (12.9%)[c]	36 (31.3%)[c]	—	—
Vascular risk factors						
Hypertension	44 (44.4%)[b]	66 (60.6%)[b]	47 (50.5%)	63 (54.8%)	88 (55.0%)	22 (45.8%)
Diabetes mellitus	19 (19.2%)	25 (22.4%)	18 (19.4%)	26 (22.6%)	34 (21.3%)	10 (20.8%)
Dyslipidemia	32 (32.3%)	27 (24.8%)	27 (29.0%)	32 (27.8%)	47 (29.4%)	12 (25.0%)
Cardiac disease	13 (13.1%)	20 (18.4%)	14 (15.1%)	19 (16.5%)	22 (13.8%)	11 (22.9%)
Ischemic stroke	3 (3.0%)	4 (3.7%)	3 (3.2%)	4 (3.5%)	5 (3.1%)	2 (4.2%)
SVD markers						
Total WMHs	10.14 ± 5.67[a]	17.38 ± 8.74[a]	13.84 ± 9.27	14.01 ± 7.38	13.19 ± 7.78[b]	16.42 ± 9.33[b]
Lacunes	14 (14.1%)[a]	54 (49.5%)[a]	32 (34.4%)	36 (31.3%)	47 (29.4%)	21 (43.8%)
CMB	16 (16.2%)[c]	38 (34.9%)[c]	29 (31.2%)	25 (21.7%)	36 (22.5%)	18 (37.5%)
MTA	1.60 ± 0.86[c]	1.93 ± 0.83[c]	1.78 ± 0.84	1.77 ± 0.88	1.84 ± 0.86[b]	1.55 ± 0.82[b]
CDR-SOB	2.21 ± 1.63[c]	2.94 ± 2.30[c]	2.53 ± 2.08	2.64 ± 2.01	2.56 ± 1.98	2.70 ± 2.22
Cognitive domain[d]						
Attention	−0.12 ± 0.95	−0.26 ± 0.77	−0.24 ± 0.82	−0.16 ± 0.90	−0.20 ± 0.89	−0.18 ± 0.79
Language	−0.69 ± 1.67	−1.14 ± 1.36	−0.73 ± 1.63	−1.08 ± 1.43	−0.84 ± 1.53	−1.20 ± 1.51
Visuospatial	−1.04 ± 2.74	−0.77 ± 1.69	−0.98 ± 2.49	−0.83 ± 2.04	−0.96 ± 2.38	−0.68 ± 1.76
Memory	−1.28 ± 0.93	−1.29 ± 0.78	−1.24 ± 0.87	−1.33 ± 0.85	−1.32 ± 0.84	−1.18 ± 0.92
Frontal/executive	−0.65 ± 0.79	−0.91 ± 0.78	−0.79 ± 0.77	−0.78 ± 0.82	−0.81 ± 0.81	−0.69 ± 0.73

Abbreviations: BAPL = brain amyloid plaque load; BG = basal ganglia; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CMB = cerebral microbleed; CSO = centrum semiovale; EPVS = enlarged perivascular space; FBB = florbetaben; FDR = false discovery rate; HP = hippocampus; MMSE = Mini-Mental Status Examination; MTA = medial temporal lobe atrophy; SUVR = standardized uptake value ratio; SVD = small vessel disease; WMHs = white matter hyperintensities. Values are expressed as mean ± SD or number (percentage). *p* Values are the results of the independent sample *t* test or χ^2 tests as appropriate.
[a] $p < 0.001$.
[b] $p < 0.05$.
[c] $p < 0.01$.
[d] FDR-corrected *p* value <0.05 for 5 cognitive domains was regarded as statistically significant.

Figure 2 Group Comparison of Amyloid Retention or SVD Markers



(A–C) Group comparison of regional amyloid retention using SUVRs between the EPVS– and EPVS+ groups. (D–F) Group comparison of SVD markers between the EPVS– and EPVS+ groups. BG = basal ganglia; CMB = cerebral microbleed; CSO = centrum semiovale; EPVS = enlarged perivascular space; HP = hippocampus; SUVR = standardized uptake value ratio; SVD = small vessel disease; WMHs = white matter hyperintensities.

score between the groups. In terms of CSO-EPVS, all the variables were comparable between the CSO-EPVS− and CSO-EPVS+ groups, except for years of education, which were greater in the CSO-EPVS+ group than in the CSO-EPVS− group. The burden of WMHs in the HP-EPVS+ group was greater than that in the HP-EPVS− group. The MTA score tended to be lower in the HP-EPVS+ group than in the HP-EPVS− group.

Among healthy controls, subjects in the BG-EPVS+ group were older and had more severe MTA than those in the BG-EPVS− group. There were no significant between-group demographic and clinical differences according to the presence of CSO-EPVS or HP-EPVS.

Comparison of the β-Amyloid Burden Between the Groups

Amyloid burden at the time of diagnosis of AD continuum was not associated with the degree of BG-, CSO-, or HP-EPVS (Figure 2, A–C): SUVRs in the frontal, lateral parietal, lateral temporal, and anterior/posterior cingulate cortices were not significantly different between the groups. ANCOVA results in patients with AD continuum, healthy controls, and all subjects (patients with AD continuum and healthy controls) showed that global and regional SUVRs did not differ between the groups according to the degree of EPVS in BG, CSO, and HP while adjusting for the effects of possible confounding factors (eTable 2, links.lww.com/WNL/C241).

Comparison of the SVD Markers Between the Groups

The burden or prevalence of all 3 SVD markers was significantly greater in the BG-EPVS+ group than in the BG-EPVS− group (Figure 2D). There were no differences in the SVD markers between the CSO-EPVS− and CSO-EPVS+ groups (Figure 2E). The burden of WMHs was significantly greater in the HP-EPVS+ group than in the HP-EPVS− group, whereas the prevalence of lacunes or CMBs was comparable between the groups (Figure 2F).

Effect of EPVS on Cognition

We further investigated the effect of EPVS on cognitive function at baseline using regression analysis (Table 2). Multivariate

Table 2 Multivariate Linear Regression Model of Each Cognitive Domain and CDR-SOB in Patients With Alzheimer Disease Continuum

			Attention	Language	Visuospatial	Memory	Frontal/executive	CDR-SOB
BG-EPVS	Model 1	β	−0.12	−0.60	−0.02	−0.17	−0.25	0.62
		SE	0.13	0.21	0.33	0.12	0.10	0.24
		p	0.405[a]	0.020[a]	0.943[a]	0.243[a]	0.043[a]	0.010
	Model 2	β	−0.15	−0.57	0.08	−0.10	−0.22	0.43
		SE	0.14	0.23	0.36	0.13	0.11	0.26
		p	0.467[a]	0.067[c]	0.819[a]	0.539[a]	0.146[a]	0.104
CSO-EPVS	Model 1	β	0.05	−0.22	0.10	−0.08	0.06	0.11
		SE	0.12	0.20	0.32	0.11	0.10	0.24
		p	0.744[a]	0.744[a]	0.744[a]	0.744[a]	0.744[a]	0.640
	Model 2	β	0.05	−0.25	0.13	−0.09	0.04	0.19
		SE	0.13	0.21	0.32	0.11	0.10	0.24
		p	0.679[a]	0.679[a]	0.679[a]	0.679[a]	0.679[a]	0.427
HP-EPVS	Model 1	β	−0.02	−0.40	0.31	0.10	0.06	0.56
		SE	0.15	0.24	0.37	0.13	0.12	0.27
		p	0.876	0.471	0.773	0.773	0.773	0.037
	Model 2	β	−0.01	−0.33	0.32	0.15	0.12	0.40
		SE	0.15	0.24	0.37	0.13	0.12	0.27
		p	0.956	0.489	0.489	0.489	0.489	0.150

Abbreviations: β = unstandardized coefficient; BG = basal ganglia; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSO = centrum semiovale; EPVS = enlarged perivascular space; HP = hippocampus; SE = standard error; SUVR = standardized uptake value ratio.
Model 1: CDR-SOB or each cognitive domain ~ β_0 + (β_1 × age) + (β_2 × sex [female vs male]) + (β_3 × years of education) + (β_4 × cognitive status [dementia vs nondementia]) + (β_5 × *APOE ε4* carrier status) + (β_6 × global SUVRs) + (β_7 × EPVS).
Model 2: CDR-SOB or each cognitive domain ~ β_0 + (β_1 × age) + (β_2 × sex) + (β_3 × years of education) + (β_4 × cognitive status) + (β_5 × *APOE ε4* carrier status) + (β_6 × global SUVRs) + (β_7 × WMHs) + (β_8 × lacunes) + (β_9 × CMBs) + (β_{10} × EPVS).
[a] Corrected *p* values for 5 cognitive domains using the false discovery rate method.

linear regression analyses revealed that language function (β = −0.60, standard error [SE] = 0.21, FDR-corrected p = 0.020), frontal/executive function (β = −0.25, SE = 0.10, FDR-corrected p = 0.043), and CDR-SOB (β = −0.60, SE = 0.21, p = 0.010) scores were significantly and independently associated with the presence of BG-EPVS in model 1, which did not reach statistical significance in model 2 after additional adjustment for SVD markers (language, β = −0.57, SE = 0.23, FDR-corrected p = 0.067; frontal/executive, β = −0.22, SE = 0.11, FDR-corrected p = 0.146; CDR-SOB, β = 0.62, SE = 0.24, p = 0.105, Table 2). Meanwhile, the degree of CSO-EPVS (i.e., CSO-EPVS− vs CSO-EPVS+) did not significantly affect the cognitive composite scores in all 5 cognitive domains and CDR-SOB scores at baseline, regardless of the adjustment for possible confounding factors. In terms of HP-EPVS, HP-EPVS was not relevant to each cognitive domain, whereas CDR-SOB (β = −0.60, SE = 0.21, p = 0.010) scores were significantly and independently associated with the presence of HP-EPVS in model 1, which were not significant anymore in model 2. When further analyses were performed in all study participants (i.e., 208 patients with AD continuum and 82 healthy controls), we obtained quite similar results (eTable 3, links.lww.com/WNL/C241). In healthy controls, the level of cognitive performance was not relevant to according to the presence of EPVS (eTable 3).

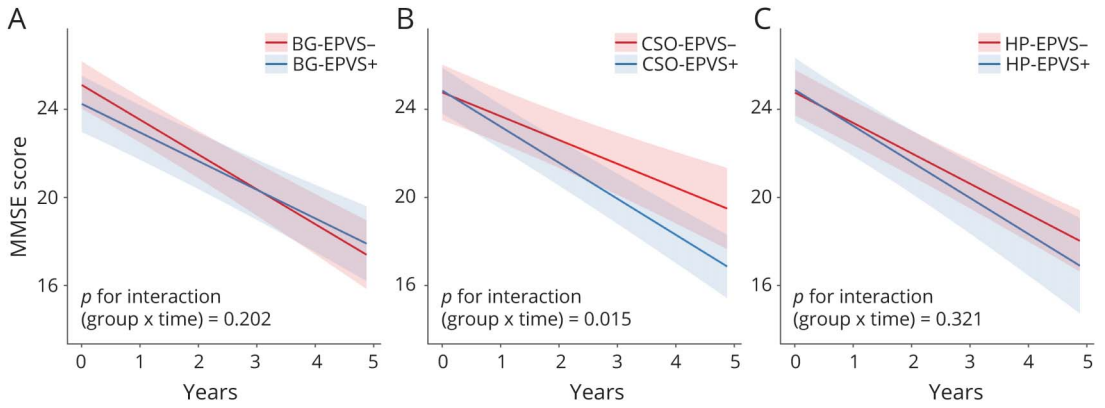
Longitudinal Assessment of the Changes in MMSE Scores Between Groups

The subsample of 158 patients with AD continuum who underwent MMSE at least twice with 1 year interval had similar demographic and clinical characteristics to the participants in this study (eTable 4, links.lww.com/WNL/C241). Before we conducted further analyses, we confirmed the effect of amyloid burden on longitudinal changes in MMSE scores (β = −1.51, SE = 0.75, p = 0.045) in AD continuum, which was also shown in a previous study.[29] In terms of BG-EPVS and HP-EPVS, group × time interaction terms were not significant in the linear mixed models, indicating that the longitudinal decreases in MMSE scores were not affected by BG-EPVS and HP-EPVS (Figure 3, A and C). In contrast, there was a significant CSO-EPVS group × time interaction term in the linear mixed model of the MMSE score (β = −0.56, SE = 0.23, p = 0.015, Table 3, model 1) after adjusting for potential confounding factors, indicating that the CSO-EPVS+ group exhibited a more rapid annual decline in MMSE scores (−0.56 per year) than the CSO-EPVS− group (Figure 3B). In the two-way interaction model, the regression coefficient and p value of the CSO-EPVS group × time interaction term barely changed (β = −0.58, SE = 0.23, p = 0.011, Table 3, model 2) after the addition of the global SUVRs × time interaction term in the linear mixed model, indicating that the effect of CSO-EPVS on longitudinal cognitive decline in AD continuum is independent of β-amyloid burden. In subgroup analyses according to cognitive status, a CSO-EPVS group × time interaction term in the linear mixed model for the longitudinal changes in MMSE scores was significant in the subgroup without dementia (β = −1.03, SE = 0.30, p < 0.001), whereas it was not significant in the subgroup with dementia (β = −0.06, SE = 0.34, p = 0.856, eTable 5, links.lww.com/WNL/C241).

Discussion

In this study, we investigated the association between BG-, CSO-, or HP-EPVS, baseline β-amyloid burden, and baseline and longitudinal cognition in AD continuum. The major findings were as follows: (1) BG-EPVS, CSO-EPVS, and HP-EPVS were not associated with β-amyloid burden at the diagnosis of AD continuum; (2) SVD markers were significantly associated with BG-EPVS and HP-EPVS, but not with CSO-EPVS; (3) BG-EPVS affected language and frontal/executive function via SVD markers; HP-EPVS was associated with general cognition via SVD markers; and CSO-EPVS was not associated with baseline cognition; (4) CSO-EPVS+ individuals experienced

Figure 3 Association Between EPVS and MMSE Score Over Time



(A) There was no significant difference in longitudinal MMSE score change between the BG-EPVS− and BG-EPVS+ groups. (B) The CSO-EPVS+ group had significantly faster decline of the MMSE score than the CSO-EPVS− group. (C) There was no significant difference in longitudinal MMSE score change between the HP-EPVS− and HP-EPVS+ groups. BG = basal ganglia; CSO = centrum semiovale; EPVS = enlarged perivascular space; HP = hippocampus; MMSE = Mini-Mental Status Examination.

Table 3 Longitudinal Models for Enlarged Perivascular Space and Amyloid Retention Predicting MMSE Score Change Over Time

		BG-EPVS		CSO-EPVS		HP-EPVS	
	Effect of Aβ	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Intercept	25.61 (3.94)[a]	24.43 (3.26)[a]	25.50 (3.94)[a]	24.32 (3.24)[a]	25.05 (3.94)[a]	24.92 (3.27)[a]	25.64 (3.95)[a]
Age	0.04 (0.04)	0.05 (0.04)	0.05 (0.04)	0.05 (0.04)	0.05 (0.04)	0.04 (0.04)	0.04 (0.04)
Female	−0.61 (0.59)	−0.69 (0.60)	−0.69 (0.59)	−0.57 (0.60)	−0.57 (0.59)	−0.61 (0.60)	−0.61 (0.60)
Education	0.31 (0.05)[a]	0.31 (0.05)[a]	0.31 (0.05)[a]	0.33 (0.05)[a]	0.32 (0.05)[a]	0.32 (0.05)[a]	0.31 (0.05)[a]
Cognitive status	−3.49 (0.52)[a]	−3.51 (0.52)[a]	−3.40 (0.53)[a]	−3.62 (0.52)[a]	−3.52 (0.52)[a]	−3.62 (0.53)[a]	−3.53 (0.53)[a]
***APOE ε4* carrier**	−0.16 (0.50)	−0.13 (0.50)	−0.18 (0.50)	−0.12 (0.50)	−0.16 (0.50)	−0.12 (0.50)	−0.15 (0.50)
WMHs	−0.07 (0.04)	−0.06 (0.04)	−0.06 (0.04)	−0.07 (0.04)	−0.08 (0.04)[b]	−0.07 (0.04)	−0.07 (0.04)
Lacunes	0.82 (0.61)	1.08 (0.63)	1.01 (0.63)	0.92 (0.61)	0.83 (0.61)	0.92 (0.62)	0.83 (0.62)
CMBs	−0.55 (0.57)	−0.53 (0.57)	−0.51 (0.57)	−0.61 (0.57)	−0.59 (0.57)	−0.53 (0.58)	−0.51 (0.57)
MTA	−0.56 (0.38)	−0.64 (0.38)	−0.59 (0.38)	−0.63 (0.38)	−0.58 (0.38)	−0.63 (0.39)	−0.58 (0.39)
Global SUVRs	−0.58 (1.63)	—	−0.84 (1.64)	—	−0.53 (1.62)	—	−0.51 (1.63)
EPVS+	—	−0.86 (0.62)	−0.89 (0.62)	0.08 (0.56)	0.11 (0.56)	0.12 (0.68)	0.16 (0.67)
Time, y	0.75 (1.09)	−1.58 (0.15)[a]	0.51 (1.15)	−1.08 (0.18)[a]	1.25 (1.10)	−1.38 (0.13)[a]	1.00 (1.11)
Aβ × time	−1.51 (0.75)[b]	—	−1.41 (0.77)	—	−1.60 (0.74)[b]	—	−1.63 (0.75)[b]
EPVS+ × time	—	0.28 (0.22)	0.19 (0.22)	−0.56 (0.23)[b]	−0.58 (0.23)[b]	−0.26 (0.26)	−0.33 (0.26)

Abbreviations: Aβ = global standardized uptake value ratios; BG = basal ganglia; CMB = cerebral microbleed; CSO = centrum semiovale; EPVS = enlarged perivascular space; HP = hippocampus; MMSE = Mini-Mental Status Examination; MTA = medial temporal lobe atrophy; SUVR = standardized uptake value ratio; WMHs = white matter hyperintensities.
Results of linear mixed model for MMSE score change over time. Values are expressed as unstandardized coefficient (standard error).
Model 1: MMSE score ~ β_0 + (β_1 × age) + (β_2 × sex) + (β_3 × years of education) + (β_4 × cognitive status) + (β_5 × *APOE ε4* carrier status) + (β_6 × WMHs) + (β_7 × lacunes) + (β_8 × CMBs) + (β_9 × EPVS) + (β_{10} × time) + (β_{11} × EPVS × time).
Model 2: MMSE score ~ β_0 + (β_1 × age) + (β_2 × sex) + (β_3 × years of education) + (β_4 × cognitive status) + (β_5 × *APOE ε4* carrier status) + (β_6 × global SUVRs) + (β_7 × WMHs) + (β_8 × lacunes) + (β_9 × CMBs) + (β_{10} × EPVS) + (β_{11} × time) + (β_{12} × global SUVRs × time) + (β_{13} × EPVS × time).
[a] $p < 0.001$.
[b] $p < 0.05$.

more rapid longitudinal declines in cognitive performance than CSO-EPVS− individuals, which appears to be independent of baseline β-amyloid burden. Meanwhile, BG-EPVS and HP-EPVS were not associated with longitudinal cognitive changes in AD continuum. These findings suggest that in AD continuum, EPVS seems to have a region-specific effect on cognition in an amyloid-independent manner.

Brain MRI is a widely used imaging modality to evaluate cognitive impairment. Incidental findings of EPVS on brain MRI are frequently observed in patients with dementia as well as in normal older adults.[2,30] Several studies revealed the relationship between EPVS and neurodegenerative disorders.[6,7,12] Of interest, the effect of EPVS on neurodegeneration appears to differ according to the anatomic location. One previous study showed that CSO-EPVS was significantly associated with clinically diagnosed AD while BG-EPVS negatively predicted the diagnosis of AD.[5] A recent study reported that CSO-EPVS was associated with tau deposition, not with amyloid burden, in the brain, whereas BG-EPVS was related to cerebral SVD in the cognitively normal older population.[12] In the present study, we were unable to find an association between baseline β-amyloid burden and BG-, CSO-, or HP-EPVS in patients with AD continuum and in healthy controls. This finding is in accordance with the results of previous studies[5,11,12] that failed to demonstrate the relationship between EPVS and amyloid deposition. However, these studies, including the present study, are limited by the cross-sectional study design, which may not be appropriate to demonstrate the association between the rate of β-amyloid accumulation and severity of EPVS in patients with AD continuum who may already be saturated with β-amyloid load.[31,32] Further longitudinal studies are warranted to demonstrate the association between β-amyloid accumulation and EPVS at the early stages of AD.

Until now, the region-specific role of EPVS has not been defined in AD continuum. In this study, we found that BG-EPVS was significantly associated with language and frontal/executive function after adjusting for confounders. Also, general cognition assessed using CDR-SOB was associated with BG-EPVS and HP-EPVS. However, this relationship was no longer

relevant after additional adjustment for SVD markers. This result suggests that SVD markers may mediate the relationship between BG- or HP-EPVS and cognition in AD continuum.[33] On the other hand, the present study did not show a correlation between CSO-EPVS and baseline cognition in AD continuum.

In healthy controls, we could not find any relationship between EPVS and cognition. Previous data on the association between EPVS and cognitive impairment in cognitively normal older adults are conflicting. Some evidence has shown that EPVS affects cognitive function, such as information processing and executive functioning performance, in older adults.[9,10] In contrast, a recent meta-analysis including 5 population-based cohorts found no association between visual scores of EPVS and cognitive dysfunction in older adults without dementia.[34] Regarding region-specific effects of EPVS on cognition, the relationship between CSO-EPVS and cognitive performance has been inconsistently reported, whereas BG-EPVS is associated with frontal lobe–based cognition.[8,35-37] In terms of HP-EPVS, 1 study showed that HP-EPVS was associated with verbal reasoning[20]; however, other studies were unable to find an association between cognition and HP-EPVS.[11,38]

In this study, a linear mixed model revealed that the CSO-EPVS+ group exhibited a more rapid longitudinal decline in the MMSE scores over time than the CSO-EPVS− group, independent of β-amyloid burden and SVD markers. It is interesting that this result suggests amyloid-independent and anatomic location–specific effects of EPVS on cognitive decline in AD continuum. Considering that baseline β-amyloid and SVD burden also did not differ between the groups according to the severity of CSO-EPVS, these results imply the possibility that CSO-EPVS is the manifestation of β-amyloid– or SVD-independent processes, such as the deposition of tau protein.[5] Tau pathology is most consistently related to a decline in cognition in AD continuum,[39] but elevated β-amyloid alone is not.[40] Recent studies also reported that CSO-EPVS was associated with baseline tau deposition but not β-amyloid deposition in the brain in cognitively normal older adults[12] and in patients with AD continuum.[41] Furthermore, our subgroup analyses according to cognitive status demonstrated that CSO-EPVS was a predictor of longitudinal decline in the MMSE scores only in patients without dementia with AD continuum. Although insignificant results in patients with dementia with AD continuum might be due to the floor effect,[42] this result suggests that CSO-EPVS is an important imaging marker of future cognitive decline in the early stage of AD. Further studies using biomarkers related to tau deposition (e.g., tau PET or CSF tau) are needed to clarify the association of CSO-EPVS with tau accumulation and the exact mechanisms of the detrimental effects of CSO-EPVS with respect to the progression of AD. Also, we hope that future study will elucidate whether CSO-EPVS is a potential therapeutic target in AD continuum.

We found that the rate of longitudinal changes in the MMSE score in the BG- or HP-EPVS+ group was not different from that in the BG- or HP-EPVS− group in AD continuum populations. Recently, one study reported that CSO-EPVS+ was closely related to a greater decline in global cognition over 4 years in community-dwelling older adults, whereas there was no association between BG- or HP-EPVS and longitudinal cognitive decline.[7] Another study also showed that large EPVSs, particularly in the BG, were associated with an increased risk of developing vascular dementia, but not with AD.[43] Although it is not fully understood how pathophysiologic mechanisms differ between BG-EPVS and CSO-EPVS, some evidence has suggested that BG-EPVS, but not CSO-EPVS, is associated with compromised blood-brain barrier integrity,[44] which may be a critical contributor to the pathogenesis of SVD.[45] In addition, BG-EPVS shares a common pathomechanism with WMHs and lacunes, which are driven by hypertensive arteriopathy that affects deep perforators.[11,33,43] In terms of HP-EPVS, previous studies have suggested that HP-EPVS is associated with SVD.[11,20] However, the role of HP-EPVS as an imaging marker in AD continuum may be limited because counting HP-EPVS is difficult in atrophic hippocampi.[11] In this study, we also observed that the severity of BG- or HP-EPVS was significantly associated with a burden of SVD markers, whereas the severity of CSO-EPVS was not. Taken together, the associations between EPVS and longitudinal changes in global cognition in AD continuum differ by their anatomic distribution, probably because of different pathophysiologic mechanisms (i.e., EPVS in the BG or HP may be more closely associated with SVD markers than neurodegenerative processes in AD continuum).

Our study has some limitations. First, due to the lack of three-dimensional isotropic T2-weight structural MRI data, we rated the grade of BG-, CSO-, or HP-EPVS visually in this study, which only provided qualitative estimates of the extent of perivascular space. Also, we used a single MRI slice for determining EPVS, which may underrate the effect of this finding on statistical assessments. Further studies using quantitative estimates of EPVS should be conducted to replicate our results. Second, we assessed the severity of EPVS only at baseline. In addition, due to the retrospective nature of this study, we could not conclude that the severity of EPVS has a predictive role in neurodegeneration in a region-specific manner. Causal relationships should be demonstrated in other longitudinal comparative studies using sequential MRI. Third, only 74 (35.6%) patients with AD continuum performed serial detailed neuropsychological tests during the follow-up period in this study, which makes it difficult to assess the longitudinal changes in cognitive function. Actually, serial cognitive assessment using a detailed neuropsychological test is very difficult in a real-world clinical setting because the cognitive function of patients with AD continuum deteriorates over time. We instead evaluated the longitudinal cognitive decline using the MMSE score, which is considered as an effective monitoring tool to assess global cognition.[46] The results should be replicated in future studies including patients with early-stage AD who are able to perform serial neuropsychological tests over years.

In conclusion, the present study demonstrated that all of BG-, CSO-, and HP-EPVS were not associated with baseline β-amyloid burden or cognitive function independently of SVD at the diagnosis of AD continuum. However, CSO-EPVS was associated with the progression of cognitive decline in patients with AD continuum in a β-amyloid–independent manner.

Study Funding

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and Future Planning (NRF-2019R1A2C2085462) and the Ministry of Education (grant number: NRF-2021R1I1A1A01059678).

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* October 4, 2021. Accepted in final form June 3, 2022. Submitted and externally peer reviewed. The handling editors were Brad Worrall, MD, MSc, FAAN, and Rawan Tarawneh, MD.

Appendix Authors

Name	Location	Contribution
Seong Ho Jeong, MD	Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea; Department of Neurology, Inje University Sanggye Paik Hospital, Seoul, South Korea	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Jungho Cha, PhD	Nash Family Center for Advanced Circuit Therapeutics, Icahn School of Medicine at Mount Sinai, New York, NY	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Mincheol Park, MD	Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea	Analysis or interpretation of data
Jin Ho Jung, MD	Department of Neurology, Busan Paik Hospital, Inje University College of Medicine, Seoul, South Korea	Analysis or interpretation of data
Byoung Seok Ye, MD, PhD	Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea	Analysis or interpretation of data
Young H. Sohn, MD, PhD	Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea	Analysis or interpretation of data
Seok Jong Chung, MD	Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea; Department of Neurology, Yongin Severance Hospital, Yonsei University Health System, Yongin; Yonsei Beyond Lab, Yongin, South Korea	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Phil Hyu Lee, MD, PhD	Department of Neurology, Yonsei University College of Medicine, Seoul; Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul, South Korea	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data

References

1. Wardlaw JM, Smith EE, Biessels GJ, et al; STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol.* 2013;12(8):822-838.
2. Weller RO, Hawkes CA, Kalaria RN, Werring DJ, Carare RO. White matter changes in dementia: role of impaired drainage of interstitial fluid. *Brain Pathol.* 2015;25(1):63-78.
3. Wardlaw JM, Benveniste H, Nedergaard M, et al; Fondation Leducq Transatlantic Network of Excellence on the Role of the Perivascular Space in Cerebral Small Vessel Disease. Perivascular spaces in the brain: anatomy, physiology and pathology. *Nat Rev Neurol.* 2020;16(3):137-153.
4. Rasmussen MK, Mestre H, Nedergaard M. The glymphatic pathway in neurological disorders. *Lancet Neurol.* 2018;17(11):1016-1024.
5. Banerjee G, Kim HJ, Fox Z, et al. MRI-visible perivascular space location is associated with Alzheimer's disease independently of amyloid burden. *Brain.* 2017;140(4):1107-1116.
6. Chung SJ, Yoo HS, Shin NY, et al. Perivascular spaces in the basal ganglia and long-term motor prognosis in newly diagnosed Parkinson disease. *Neurology.* 2021;96(16):e2121-e2131.
7. Paradise M, Crawford JD, Lam BCP, et al. Association of dilated perivascular spaces with cognitive decline and incident dementia. *Neurology.* 2021;96(11):e1501-e1511.
8. Zhu YC, Dufouil C, Soumaré A, Mazoyer B, Chabriat H, Tzourio C. High degree of dilated Virchow-Robin spaces on MRI is associated with increased risk of dementia. *J Alzheimers Dis.* 2010;22(2):663-672.
9. Maclullich AMJ, Wardlaw JM, Ferguson KJ, Starr JM, Seckl JR, Deary IJ. Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. *J Neurol Neurosurg Psychiatry.* 2004;75(11):1519-1523.
10. Passiak BS, Liu D, Kresge HA, et al. Perivascular spaces contribute to cognition beyond other small vessel disease markers. *Neurology.* 2019;92(12):e1309-e1321.
11. Gertje EC, van Westen D, Panizo C, Mattsson-Carlgren N, Hansson O. Association of enlarged perivascular spaces and measures of small vessel and Alzheimer disease. *Neurology.* 2021;96(2):e193-e202.
12. Wang ML, Yu MM, Wei XE, Li WB, Li YH; Alzheimer's Disease Neuroimaging Initiative. Association of enlarged perivascular spaces with Aβ and tau deposition in cognitively normal older population. *Neurobiol Aging.* 2021;100:32-38.
13. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease. *Alzheimers Dement.* 2011;7(3):263-269.
14. Dubois B, Hampel H, Feldman HH, et al; Proceedings of the Meeting of the International Working Group IWG and the American Alzheimer's Association on "The Preclinical State of AD"; July 23, 2015; Washington DC, USA. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement.* 2016;12(3):292-323.
15. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):270-279.
16. Barthel H, Gertz HJ, Dresel S, et al; Florbetaben Study Group. Cerebral amyloid-β PET with florbetaben (^{18}F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study. *Lancet Neurol.* 2011;10(5):424-435.
17. Jagust WJ, Landau SM, Koeppe RA, et al. The Alzheimer's disease neuroimaging initiative 2 PET core: 2015. *Alzheimers Dement.* 2015;11(7):757-771.
18. Potter GM, Chappell FM, Morris Z, Wardlaw JM. Cerebral perivascular spaces visible on magnetic resonance imaging: development of a qualitative rating scale and its observer reliability. *Cerebrovasc Dis.* 2015;39(3-4):224-231.
19. Doubal FN, MacLullich AMJ, Ferguson KJ, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease. *Stroke.* 2010;41(3):450-454.
20. Jiménez-Balado J, Riba-Llena I, Garde E, et al. Prevalence of hippocampal enlarged perivascular spaces in a sample of patients with hypertension and their relation with vascular risk factors and cognitive function. *J Neurol Neurosurg Psychiatry.* 2018;89(6):651-656.
21. Scheltens P, Barkhof F, Leys D, et al. A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *J Neurol Sci.* 1993;114(1):7-12.
22. Greenberg SM, Vernooij MW, Cordonnier C, et al; Microbleed Study Group. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol.* 2009;8(2):165-174.

23. Scheltens P, Leys D, Barkhof F, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry.* 1992;55(10):967-972.
24. Kang Y, Jahng S, Na D. *Seoul Neuropsychological Screening Battery. (SNSB-II): Professional Manual*. Incheon: Human Brain Research and Consulting; 2012.
25. Jang H, Ye BS, Woo S, et al. Prediction model of conversion to dementia risk in subjects with amnestic mild cognitive impairment: a longitudinal, multi-center clinic-based study. *J Alzheimers Dis.* 2017;60(4):1579-1587.
26. Kang YW, Na DL, Hahn SH. A validity study on the Korean mini-mental state examination (K-MMSE) in dementia patients. *J Korean Neurol Assoc.* 1997;15(2):300-308.
27. Ku HM, Kim JH, Lee HS, et al. A study on the reliability and validity of Seoul-activities of daily living (S-ADL). *Ann Geriatr Med Res.* 2004;8(4):206-214.
28. Kang SJ, Choi S, Lee BH, et al. The reliability and validity of the Korean instrumental activities of daily living (K-IADL). *J Korean Neurol Assoc.* 2002;20(1):8-14.
29. Farrell ME, Kennedy KM, Rodrigue KM, et al. Association of longitudinal cognitive decline with amyloid burden in middle-aged and older adults: evidence for a dose-response relationship. *JAMA Neurol.* 2017;74(7):830-838.
30. Zhu YC, Dufouil C, Mazoyer B, et al. Frequency and location of dilated Virchow-Robin spaces in elderly people: a population-based 3D MR imaging study. *AJNR Am J Neuroradiol.* 2011;32(4):709-713.
31. Thal DR, Rüb U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology.* 2002;58(12):1791-1800.
32. Camara H, De-Souza EA. β-Amyloid accumulation slows earlier than expected in preclinical Alzheimer's disease patients. *J Neurosci.* 2018;38(43):9123-9125.
33. Huijts M, Duits A, Staals J, Kroon AA, de Leeuw PW, van Oostenbrugge RJ. Basal ganglia enlarged perivascular spaces are linked to cognitive function in patients with cerebral small vessel disease. *Curr Neurovascular Res.* 2014;11(2):136-141.
34. Hilal S, Tan CS, Adams HHH, et al. Enlarged perivascular spaces and cognition: a meta-analysis of 5 population-based studies. *Neurology.* 2018;91(9):e832-e842.
35. Hurford R, Charidimou A, Fox Z, Cipolotti L, Jager R, Werring DJ. MRI-visible perivascular spaces: relationship to cognition and small vessel disease MRI markers in ischaemic stroke and TIA. *J Neurol Neurosurg Psychiatry.* 2014;85(5):522-525.
36. Uiterwijk R, Huijts M, Staals J, et al. Subjective cognitive failures in patients with hypertension are related to cognitive performance and cerebral microbleeds. *Hypertension.* 2014;64(3):653-657.
37. Valdés Hernández MDC, Ballerini L, Glatz A, et al. Perivascular spaces in the centrum semiovale at the beginning of the 8th decade of life: effect on cognition and associations with mineral deposition. *Brain Imaging Behav.* 2020;14(5):1865-1875.
38. Sim JE, Park M-S, Shin H-Y, et al. Correlation between hippocampal enlarged perivascular spaces and cognition in non-dementic elderly population. *Front Neurol.* 2020;11:542511.
39. Jeong HJ, Lee H, Lee S-Y, et al. [^{18}F]THK5351 PET imaging in patients with mild cognitive impairment. *J Clin Neurol.* 2020;16(2):202-214.
40. Aschenbrenner AJ, Gordon BA, Benzinger TLS, Morris JC, Hassenstab JJ. Influence of tau PET, amyloid PET, and hippocampal volume on cognition in Alzheimer disease. *Neurology.* 2018;91(9):e859-e866.
41. Vilor-Tejedor N, Ciampa I, Operto G, et al; ALFA study. Perivascular spaces are associated with tau pathophysiology and synaptic dysfunction in early Alzheimer's continuum. *Alzheimer's Res Ther.* 2021;13(1):135.
42. Houx PJ, Shepherd J, Blauw GJ, et al. Testing cognitive function in elderly populations: the PROSPER study. PROspective Study of Pravastatin in the Elderly at Risk. *J Neurol Neurosurg Psychiatry.* 2002;73(4):385-389.
43. Ding J, Sigurðsson S, Jónsson PV, et al. Large perivascular spaces visible on magnetic resonance imaging, cerebral small vessel disease progression, and risk of dementia: the age, gene/environment susceptibility-reykjavik study. *JAMA Neurol.* 2017;74(9):1105-1112.
44. Li Y, Li M, Yang L, et al. The relationship between blood-brain barrier permeability and enlarged perivascular spaces: a cross-sectional study. *Clin Interv Aging.* 2019;14:871-878.
45. Li Y, Li M, Zhang X, et al. Higher blood-brain barrier permeability is associated with higher white matter hyperintensities burden. *J Neurol.* 2017;264(7):1474-1481.
46. Kim J, Na HK, Byun J, et al. Tracking cognitive decline in amnestic mild cognitive impairment and early-stage Alzheimer dementia: mini-mental state examination versus neuropsychological battery. *Demen Geriatr Cogn Disord.* 2017;44(1-2):105-117.

Association of Enlarged Perivascular Spaces With Amyloid Burden and Cognitive Decline in Alzheimer Disease Continuum

Seong Ho Jeong, Jungho Cha, Mincheol Park, et al.

Neurology 2022;99;e1791-e1802 Published Online before print August 19, 2022
DOI 10.1212/WNL.0000000000200989