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Amyloid Positivity in the Alzheimer/Subcortical-Vascular Spectrum

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Abstract

Objective

We investigated the frequency of β-amyloid (Aβ) positivity in 9 groups classified according to a combination of 3 different cognition states and 3 distinct levels of white matter hyperintensities (WMH) (minimal, moderate, and severe) and aimed to determine which factors were associated with Aβ after controlling for WMH and vice versa.

Methods

A total of 1,047 individuals with subjective cognitive decline (SCD, n = 294), mild cognitive impairment (MCI, n = 237), or dementia (n = 516) who underwent Aβ PET scans were recruited from the memory clinic at Samsung Medical Center in Seoul, Korea. We investigated the following: (1) Aβ positivity in the 9 groups, (2) the relationship between Aβ positivity and WMH severity, and (3) clinical and genetic factors independently associated with Aβ or WMH.

Results

Aβ positivity increased as the severity of cognitive impairment increased (SCD [15.7%], MCI [43.5%], and dementia [76.2%]), whereas it decreased as the severity of WMH increased (minimal [54.5%], moderate [53.9%], and severe [41.0%]) or the number of lacunes (0 [59.0%], 1–3 [42.0%], and >3 [23.4%]) increased. Aβ positivity was associated with higher education, absence of diabetes, and presence of *APOE* ε4 after controlling for cognitive and WMH status.

Conclusion

Our analysis of Aβ positivity involving a large sample classified according to the stratified cognitive states and WMH severity indicates that Alzheimer and cerebral small vessel diseases lie on a continuum. Our results offer clinicians insightful information about the association among Aβ, WMH, and cognition.

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Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADCI** = Alzheimer disease–related cognitive impairment; **aMCI** = amnestic mild cognitive impairment; **BAPL** = brain amyloid–plaque load; **CI** = confidence interval; **CL** = Centiloid; **CREDOS** = Clinical Research Center for Dementia of South Korea; **CSVD** = cerebral small vessel disease; **CTX VOI** = Centiloid global cortical target volume of interest; **DM** = diabetes mellitus; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; **EH** = elderly healthy participants; **FBB** = ^{18}F-florbetaben; **FLAIR** = fluid-attenuated inversion recovery; **FMM** = ^{18}F-flutemetamol; **ICV** = intracranial volume; **MCI** = mild cognitive impairment; **OR** = odds ratio; **PiB** = Pittsburgh compound B; **RCTU** = regional cortical tracer uptake; **SCD** = subjective cognitive decline; **SMC** = Samsung Medical Center; **SUVR** = standardized uptake ratio; **SVaD** = subcortical vascular dementia; **SVCI** = subcortical vascular cognitive impairment; **svMCI** = subcortical vascular mild cognitive impairment; **WMH** = white matter hyperintensities.

β-amyloid (Aβ) deposition is regarded a hallmark of Alzheimer disease (AD)–related cognitive impairment (ADCI),[1] while white matter hyperintensities (WMH) caused by cerebral small vessel disease (CSVD) are considered the hallmark of subcortical vascular cognitive impairment (SVCI).[2] Although ADCI and SVCI have different treatments and prognoses, there may be substantial overlap between these 2 conditions in terms of clinical and radiologic findings. Therefore, ADCI and SVCI are considered to lie on a continuum, where ADCI with nonischemia lies on one end and SVCI without AD pathology on the other end. Previous studies investigated the prevalence of Aβ pathology after dichotomizing patients into groups with either AD or SVCI,[3,4] and, therefore, failed to cover the whole spectrum of ADCI and SVCI, not addressing mixed pathology cases with different levels of Aβ and CSVD burden.

The first goal of our study was to investigate the frequency of Aβ positivity in a large sample of individuals classified into 9 groups based on the combination of different levels of cognition and WMH. The second goal was to explore the association between Aβ positivity and the severity of cognitive impairment in 3 stratified WMH groups and the association between Aβ positivity and severity of WMH in 3 stratified cognitive levels. The third goal was to explore the association between Aβ positivity and other CSVD burden, including lacunes and microbleeds, in 3 stratified cognitive levels. Finally, we aimed to evaluate the clinical and genetic factors associated with Aβ markers in this large memory clinic cohort.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The institutional review boards at Samsung Medical Center (SMC) approved this study. Written informed consent was obtained from the patients or caregivers of patients with advanced dementia and all procedures were executed in accordance with approved guidelines.

Study Participants

We retrospectively enrolled 1,047 participants with subjective cognitive decline (SCD), mild cognitive impairment (MCI), or dementia who underwent Aβ PET at the memory clinic in the Department of Neurology at SMC in Seoul, Korea, between August 2015 and December 2018. As previously described,[5] all participants underwent comprehensive dementia evaluation, including a standardized neuropsychological test (Seoul Neuropsychological Screening Battery, 2nd edition[6,7]), blood tests including *APOE* genotyping, and brain MRI. We excluded participants who had any of the following conditions: (1) WMH due to etiologies other than vascular pathology, including radiation injury, multiple sclerosis, leukodystrophy, or metabolic/toxic disorders; (2) traumatic brain injury; (3) normal pressure hydrocephalus; (4) territorial infarction; (5) neurodegenerative disorders other than AD or ischemic etiologies such as progressive supranuclear palsy, corticobasal syndrome, frontotemporal dementia, or Lewy body/Parkinson disease dementias; or (6) rapidly progressive dementias and treatable dementias.

All participants with SCD fulfilled the following criteria: (1) subjective memory complaints by participants or caregivers; (2) no objective cognitive dysfunction, as assessed by scores from evaluations on any cognitive domain; (3) no history of medical diseases likely to affect cognitive function; and (4) no significant impairment in activities of daily living. All patients diagnosed with MCI fulfilled Petersen criteria for MCI.[8] Patients with dementia satisfied diagnostic criteria for dementia according to the DSM-IV.[9]

Brain MRI Acquisition and WMH Visual Rating

All participants underwent fluid-attenuated inversion recovery (FLAIR) imaging using the 3.0 T MRI scanner (Philips 3.0T Achieva) according to the following imaging measures: sagittal slice thickness, 2 mm; no gap; repetition time, 11,000 ms; echo time, 125 ms; flip angle, 90°; and matrix size, 512 × 512 pixels.

The WMH visual rating scale proposed by the Clinical Research Center for Dementia of South Korea (CREDOS) was used to investigate WMH in the deep subcortical and periventricular regions in FLAIR images by one experienced neurologist, as reported in the literature.[10] Briefly, deep WMH were classified as D1 (<10 mm), D2 (10–25 mm), or D3 (≥25 mm) based on the longest diameter of the lesions. Periventricular WMH were classified as P1 (cap and band

Table 1 Amyloid Positivity in 9 Groups (3 Cognition States × 3 White Matter Hyperintensity Severity Levels) Classified According to the Clinical Research Center for Dementia of South Korea Diagnostic Matrix

	White matter hyperintensity		
Cognition	**Minimal**	**Moderate**	**Severe**
SCD	I-1: Healthy or SCD (30/207, 14.5%)	I-2: Mixed NCI (14/62, 22.6%)	I-3: svNCI (2/25, 8.0%)
MCI	II-1: aMCI (54/106, 50.9%)	II-2: Mixed MCI (31/71, 43.7%)	II-3: svMCI (18/60, 30.0%)
Dementia	III-1: AD dementia (232/267, 86.9%)	III-2: Mixed dementia (99/134, 73.9%)	III-3: SVaD (62/115, 53.9%)

Abbreviations: aMCI = amnestic mild cognitive impairment; MCI = mild cognitive impairment; NCI = noncognitive impairment; SCD = subjective cognitive decline; SVaD = subcortical vascular dementia; svMCI = subcortical vascular mild cognitive impairment; svNCI = subcortical vascular noncognitive impairment.

<5 mm), P2 (5–10 mm), or P3 (cap or band ≥10 mm) based on the maximum length measured perpendicular (cap) and horizontal (band) to the ventricle. The combination of these D and P ratings yielded 9 cells, and the overall WMH severity (minimal, moderate, and severe) was defined based on the following combination of D and P ratings: minimal (D1P1, D1P2), moderate (D1P3, D2P1, D2P2, D2P3, D3P1, D3P2), and severe (D3P3).[10] To test the interrater reliability of our WMH visual rating, we randomly selected 100 FLAIR images, and 3 experienced neurologists (1 experienced neurologist as mentioned above and 2 additional neurologists) performed a visual rating of the WMH severity. Interrater agreement was excellent for the overall WMH severity (Fleiss k = 0.84).

Three Cognition Levels × 3 WMH Levels Diagnostic Matrix

We classified participants into 9 groups according to the diagnostic matrix proposed by the CREDOS[11,12]: the combination of 3 different levels of cognition (SCD, MCI, and dementia) and 3 distinct levels of WMH (minimal, moderate, and severe), as illustrated in table 1.

Measurement of WMH Volume

In addition to the visual rating of WMH, as has already been described, we also quantified WMH volume (in mL) on FLAIR images using an automated method as previously described.[13] Extracted WMHs were localized and quantified according to the brain lobes (frontal, parietal, temporal, and occipital) by applying the prelabeled 3D probabilistic anatomical atlases using a nonlinear registration-based technique.[14] We could not analyze the volume of WMH in 23 of 1,047 participants because of technical problems.

Assessment of the Number of Lacunes and Microbleeds

We counted the number of lacunes on 80 axial slices of FLAIR images, as has been proposed by Wardlaw et al[15]: (1) small lesions (≤15 mm and ≥3 mm in diameter) with low signal on T1-weighted images, (2) high signal on T2-weighted images, and (3) a perilesional halo. Similar to the WMH categorization, we divided participants into 3 groups based on the median (0), tercile (1), and 90% (4) of the lacune counts: grade 1 (lacune count = 0), grade 2 (1–3), and grade 3 (>3).

We also counted the number of microbleeds, defined as ≤10 mm in diameter on 20 axial slices of T2 gradient recalled echo MRI.[16] Likewise, we divided participants into 3 groups based on the median (0), tercile (0), and 90% (3) of the microbleed counts: grade 1 (microbleed count = 0), grade 2 (1–3), and grade 3 (>3).

Aβ PET Acquisition and Definition of Aβ Positivity

All 1,047 participants underwent Aβ PET: ^{18}F-florbetaben (FBB) PET in 651 patients and ^{18}F-flutemetamol (FMM) PET scans in 396 patients at SMC using a Discovery STe PET/CT scanner (GE Medical Systems, Milwaukee, WI). For FBB PET and FMM PET, a 20-minute emission PET scan with dynamic mode (consisting of 4 × 5 minute frames) was performed 90 minutes after injection of a mean dose of 311.5 MBq FBB and 197.7 MBq FMM, respectively. We reconstructed 3D PET images in a 128 × 128 × 48 matrix with 2 × 2 × 3.27 mm voxel size using the ordered-subsets expectation maximization (OSEM) algorithm (^{18}F-florbetaben, iteration = 4 and subset = 20; ^{18}F-flutemetamol, iteration = 4 and subset = 20).

Aβ PET images were reviewed by 2 experienced doctors (1 nuclear medicine physician and 1 neurologist) who were blinded to clinical information and the images were dichotomized as either Aβ-positive or -negative using visual reads.[17] The reviewers discussed discrepant results of Aβ positivity to achieve a consensus. FBB PET was classified as positive when interpreters scored visual assessment as 2 or 3 on the brain amyloid–plaque load (BAPL) score.[17,18] Specifically, the regional cortical tracer uptake (RCTU) score was used in 4 brain areas (lateral temporal cortex, frontal cortex, posterior cingulate cortex/precuneus, and parietal cortex). An RCTU score of 1, 2, and 3 were defined as no tracer uptake, moderate tracer uptake, and pronounced tracer uptake, respectively. An RCTU score of 1 in each brain region corresponded to a BAPL score of 1, RCTU score of 2 in any brain region and no score 3 corresponded to a BAPL score of 2, and RCTU score of 3 in any of the 4 brain regions corresponded to a BAPL score of 3. In the visual assessment of FMM PET, interpreters reviewed 5 brain regions (frontal, parietal, posterior cingulate/precuneus, striatum, and lateral temporal

Table 2 Demographics and Clinical Characteristics of Study Participants

	SCD (n = 294)	MCI (n = 237)	Dementia (n = 516)	*p* Value
Demographics				
Age, y	69.9 ± 8.4	73.0 ± 8.5[c]	70.9 ± 10.5[d]	0.001
Sex, female	182 (61.9)	140 (59.1)	316 (61.2)	0.786
Education, y	11.3 ± 4.9	10.9 ± 5.3	10.9 ± 5.3	0.469
Clinical characteristics				
MMSE	28.1 ± 1.9	25.6 ± 3.8[c]	18.8 ± 5.6[cd]	<0.001
Hypertension	123/278 (41.8)	127/228 (54.0)[c]	238/513 (46.2)[d]	<0.001
DM	48/278 (17.3)	55/228 (24.1)	104/513 (20.3)	0.162
Hyperlipidemia	100/278 (36.0)	80/228 (35.1)	150/512 (29.3)	0.099
***APOE*, ε4 carrier**	64/276 (23.2)	69/215 (32.1)[c]	230/483 (47.6)[cd]	<0.001
Aβ positivity	46 (15.6)	103 (43.5)[c]	393 (76.2)[cd]	<0.001
Aβ CL value[a]	12.74 ± 26.61	39.37 ± 47.34[c]	76.43 ± 49.85[cd]	<0.001
Severe WMH	25 (8.5)	60 (25.3)[c]	115 (22.3)[c]	<0.001
WMH volume, mL[b]	8.10 ± 13.86	17.62 ± 19.74[c]	15.86 ± 18.64[c]	<0.001
Lacunes, n	0.4 ± 1.1	1.4 ± 3.1[c]	1.5 ± 3.2[c]	<0.001
Microbleeds, n	0.7 ± 3.4	2.1 ± 6.5	2.3 ± 10.3[c]	<0.001

Abbreviations: Aβ = β-amyloid; CL = Centiloid; DM = diabetes mellitus; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; SCD = subjective cognitive decline; WMH = white matter hyperintensities.
Values are presented as mean ± SD or number (%). *p* Values were obtained by analysis of variance model and χ^2 test.
[a] Aβ CL values were obtained from 1,026 (98.0%) of the 1,047 participants who underwent Aβ PET.
[b] WMH volume was obtained in 1,024 (97.8%) of the 1,047 participants.
[c] $p < 0.05$ compared to SCD.
[d] $p < 0.05$ compared to MCI.

lobes). If any one of the brain regions was positive in either hemisphere, the scan was considered positive.[17]

Aβ Quantification on PET Images Using Centiloid Values

To standardize the quantification of Aβ on PET images scanned with different ligands, Centiloid (CL) methods have recently been developed.[19,20] Our group also previously developed a CL method for FBB and FMM PET, which enables the transformation of the standardized uptake ratio (SUVR) values of FBB and FMM PETs to CL values directly without conversion to the ^{11}C-labeled Pittsburgh compound SUVR.[21]

There are 3 steps to obtain CL values[21]: (1) preprocessing of PET images, (2) determination of CL global cortical target volume of interest (CTX VOI), and (3) conversion of SUVR to CL values. First, to preprocess the Aβ PET images, PET images were coregistered to each participant MRI, and then were normalized to a T1-weighted Montreal Neurological Institute 152 template through the SPM8 unified segmentation method.[19] We used T1-weighted MRI correction with the N3 algorithm only for intensity nonuniformities,[22] without applying corrections to the PET images for brain atrophy or partial volume effects. Second, we used the FBB–FMM CTX VOI defined as areas of AD-specific brain Aβ deposition in our previous article.[21] Briefly, to exclude areas of aging-related brain Aβ deposition, the FBB–FMM CTX VOI was generated by comparing SUVR parametric images (with the whole cerebellum as a reference area) among 20 patients with typical ADCI (AD-CTX) and 16 elderly healthy participants (EH-CTX) who underwent both FBB and FMM PET scans. To generate the FBB–FMM CTX VOI, the average EH-CTX image was subtracted from the average AD-CTX image. Then, we defined the FBB–FMM CTX VOI as areas of AD-related brain Aβ accumulation common to both FBB and FMM PET. Finally, the SUVR values of the FBB–FMM CTX VOI were converted to CL units using the CL conversion equation. The CL equation was derived from the FBB–FMM CTX VOI separately for FBB and FMM PET and applied to each of the FBB and FMM SUVR. As CL values from 21 participants could not be calculated due to technical errors, 1,026 participants were included in the CL analysis.

Statistical Analysis

We used analysis of variance with Bonferroni post hoc tests and χ^2 test to compare the demographic and clinical characteristics of the 3 cognitive groups (SCD, MCI, and dementia). To investigate the association between Aβ positivity and the

Table 3 Characteristics of Participants According to 9 Groups Derived From the Combination of 3 Cognitive States and 3 White Matter Hyperintensity (WMH) Severity Levels

	SCD WMH severity level			MCI WMH severity level			Dementia WMH severity level			
	Minimal	Moderate	Severe	Minimal	Moderate	Severe	Minimal	Moderate	Severe	Total
N	207	62	25	106	71	60	267	134	115	1,047
Age, y[a]	68.3 ± 8.2	73.8 ± 7.8	73.2 ± 7.8	69.1 ± 8.5	75.1 ± 6.5	77.3 ± 7.8	66.1 ± 10.3	74.4 ± 7.8	78.0 ± 7.4	71.1 ± 0.9.6
Sex, female	124 (60.0)	41 (66.1)	17 (68.0)	58 (54.7)	44 (62.0)	38 (63.3)	156 (58.4)	82 (61.2)	77 (67.0)	637 (60.8)
Education, y[a]	11.8 ± 4.7	10.4 ± 4.9	10.3 ± 5.7	12.2 ± 4.7	10.2 ± 5.5	9.5 ± 5.4	11.5 ± 4.7	10.5 ± 5.5	10.0 ± 5.9	11.0 ± 5.2
MMSE[a]	28.4 ± 1.6	27.7 ± 2.4	27.1 ± 2.4	26.7 ± 2.9	25.0 ± 3.8	24.3 ± 4.5	18.9 ± 5.9	19.4 ± 5.1	18.2 ± 5.4	23.3 ± 6.0
Hypertension[a,b]	73 (37.8)	37 (60.7)	13 (54.2)	41 (41.4)	43 (61.4)	43 (72.9)	92 (34.8)	71 (53.0)	75 (65.2)	488 (47.9)
DM[a,b]	31 (16.1)	12 (19.7)	5 (20.8)	21 (21.2)	13 (18.6)	21 (35.6)	37 (14.0)	36 (26.9)	31 (27.0)	207 (20.3)
Hyperlipidemia[c]	74 (38.3)	19 (31.1)	7 (29.2)	32 (32.3)	31 (44.3)	17 (28.8)	75 (28.4)	41 (30.6)	34 (29.8)	330 (32.4)
***APOE*, ε4 carrier**[a,d]	41 (20.9)	18 (32.1)	5 (20.8)	37 (38.5)	20 (31.7)	12 (21.4)	127 (50.0)	70 (55.1)	33 (32.4)	363 (37.3)
Aβ positivity	30 (14.5)	14 (22.5)	2 (8.0)	54 (50.9)	31 (43.7)	18 (30.0)	232 (86.9)	99 (73.9)	62 (53.9)	542 (51.8)

Abbreviations: Aβ = β-amyloid; DM = diabetes mellitus; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; SCD = subjective cognitive decline.
Values are presented as mean ± SD or n (%). *p* Values were obtained by analysis of variance model and χ^2 test.
[a] $p < 0.05$.
[b] History of hypertension and DM was collected in 1,019 (97.3%) of the 1,047 participants.
[c] History of hyperlipidemia was collected in 1,018 (97.2%) of the 1,047 participants.
[d] *APOE* genotyping was performed in 974 (93.0%) of the 1,047 participants.

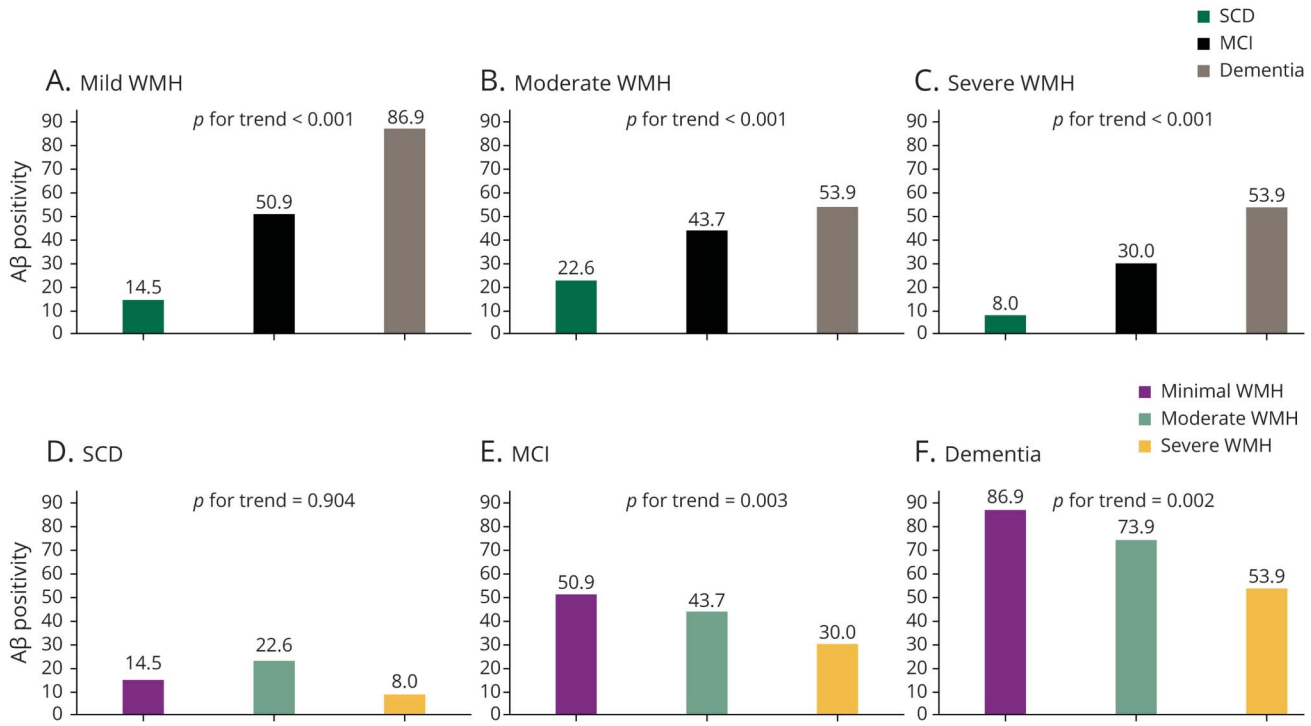
cognitive state within the same level of WMH severity, we performed linear trend tests using logistic regression analysis, with the cognitive state (SCD, MCI, and dementia) as a continuous variable in each WMH group (minimal, moderate, and severe WMH), after controlling for age. To investigate the association between Aβ positivity and the WMH severity in the same cognitive state, we also performed linear trend tests using logistic regression analysis, with the WMH severity category (minimal, moderate, and severe WMH) as a continuous variable in each cognitive group (SCD, MCI, and dementia), after controlling for age. To further validate the relationship between Aβ and WMH burden, we also investigated the relationship using automatically quantified values of CL and WMH/intracranial volume (ICV) rather than using visually rated categorical values. In this analysis, we used Pearson correlation analysis with CL values as dependent variables and log-transformed WMH/ICV as an independent variable.

In addition, for the association between Aβ positivity and other CSVD burdens (lacunes and microbleeds) in the same cognitive state, we performed linear trend tests using logistic regression analysis, with the 3 categories based on the number of lacunes (0, 1–3, and >3) or the number of microbleeds (0, 1–3, and >3) as a continuous variable in each cognitive group (SCD, MCI, and dementia), after controlling for age. To further validate the relationship between Aβ and lacune or microbleed burdens, we also investigated the relationship between CL values and the number of lacunes or microbleeds rather than categorical values. In this analysis, we used Pearson correlation analysis with CL values as dependent variables and log-transformed lacune or microbleed counts as independent variables.

Finally, to determine the factors associated with Aβ positivity, we used multivariable logistic regression analysis, including age, sex, year of education, hypertension, diabetes mellitus (DM), hyperlipidemia, and presence of *APOE* ε4 genotype as independent variables, after controlling for the cognitive state (SCD, MCI, and dementia) and the severity of WMH (minimal, moderate, and severe).

All reported *p* values were 2-sided, and the significance level was set at 0.017 in each analysis for linear trend. Three comparisons were made in each analysis for linear trend. To reduce the risk of type 1 error, we performed the Bonferroni correction for multiple comparisons, with resulting $\alpha = 0.017$ (0.05/3). The significance level in the analysis of factors associated with Aβ positivity was set at 0.05. All analyses were performed using SPSS version 25.0 and R version 3.6.1 (Institute for Statistics and Mathematics, Vienna, Austria; R-project.org).

Figure 1 Association Between β-Amyloid (Aβ) Positivity, White Matter Hyperintensity (WMH) Burden, and Cognition



Values depicted in the bar plot represent Aβ positivity. Aβ positivity significantly increased as the severity of cognitive impairment (subjective cognitive decline [SCD], mild cognitive impairment [MCI], dementia) increased in all participants of minimal (A, *p* for trend <0.001), moderate (B, *p* for trend <0.001), and severe WMH (C, *p* for trend <0.001) groups, assessed using the linear trend tests after adjusting for age. Aβ positivity significantly decreased as the severity of WMH (minimal, moderate, and severe) increased in the MCI (E, *p* for trend = 0.003) and dementia (F, *p* for trend = 0.002) groups, while this trend was not significant in the SCD (D, *p* for trend = 0.904) group, accessed using the linear trend tests after adjusting for age.

Data Availability

Anonymized data for our analyses presented in this report are available upon request from the corresponding authors.

Results

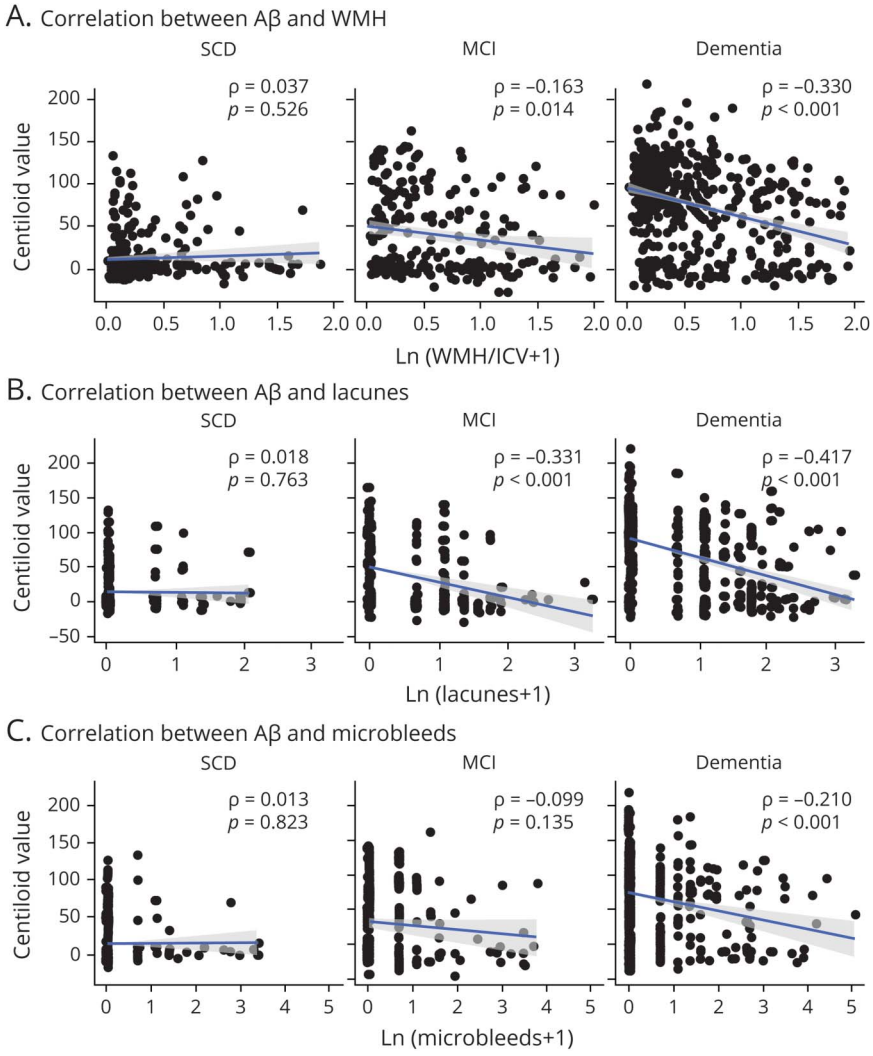
Clinical Characteristics of Study Participants

Among the 1,047 participants, there were 294 individuals with SCD, 237 with MCI, and 516 with dementia (table 2). The female ratio ($p = 0.786$) and years of education ($p = 0.469$) were not different across the 3 cognitive groups. The mean ages were different across the groups ($p = 0.001$); specifically, participants with MCI were more likely to be older (73.0 ± 8.5) than those with SCD (69.9 ± 8.4) or dementia (70.9 ± 10.5). The frequency of *APOE* ε4 carriers also differed across the groups ($p < 0.001$); participants with dementia had the highest frequency of *APOE* ε4 genotypes (47.6%), followed by MCI (32.1%), and SCD (23.2%). In terms of the Aβ positivity, only 15.6% of participants with SCD showed Aβ positivity compared with 43.5% of patients with MCI and 76.2% of patients with dementia, with a significant difference between groups ($p < 0.001$). Mean CL values of Aβ PET scans also differed across the 3 groups ($p < 0.001$): participants with dementia had the highest CL values (76.43 ± 49.85), followed by MCI (39.37 ± 47.34) and SCD (12.74 ± 26.61). When participants in each cognitive group were categorized into minimal, moderate, and severe WMH, the frequency of severe WMH was 8.5% in SCD, 25.3% in MCI, and 22.3% in the dementia group, and the difference between groups was significant ($p < 0.001$). The mean WMH volumes in participants with MCI (17.62 ± 19.74) or dementia (15.86 ± 18.64) were higher than those of SCD (8.10 ± 13.86, $p < 0.001$). Regarding other CSVD markers, the number of lacunes in participants with MCI (1.4 ± 3.1) or dementia (1.5 ± 3.2) was higher than that of SCD (0.4 ± 1.1, $p < 0.001$). The number of microbleeds in participants with dementia (2.3 ± 10.3) was higher than that of SCD (0.7 ± 3.4, $p = 0.023$), while the number of microbleeds in participants with MCI (2.1 ± 6.5) did not differ from that of SCD.

Aβ Positivity in the 9 Cells (3 Cognition × 3 WMH Levels)

The demographics and clinical characteristics of participants in 9 groups categorized according to the combination of 3 cognitive states and 3 WMH severity levels are presented in table 3. Aβ positivity for all participants was 51.7% (542/1,047). The Aβ positivity in the SCD group ranged from 8.0% to 14.5% and was relatively low, regardless of the severity of WMH, compared with other groups (figure 1 and table 1). All MCI groups had mid-level Aβ positivity regardless of the severity of WMH, and all dementia groups had the highest Aβ

Figure 2 Correlations Between β-Amyloid (Aβ) PET Centiloid (CL) Values and Cerebral Small Vessel Disease (CSVD) Burdens in the 3 Stratified Cognitive Groups



(A) Values depicted in the scatterplot represent log-transformed WMH/intracranial volume (ICV) on x-axis and Aβ PET CL values on y-axis. (B) Values depicted in the scatterplot represent log transformed lacune count on x-axis and Aβ PET CL values on y-axis. (C) Values depicted in the scatterplot represent log transformed microbleed count on x-axis and Aβ PET CL values on y-axis. MCI = mild cognitive impairment; SCD = subjective cognitive decline.

positivity compared with the other groups. In particular, the group of dementia with minimal WMH severity showed the highest Aβ positivity at 86.9% (232/267).

Association Between Aβ and Cognition According to WMH Severity

We investigated the association between Aβ positivity and cognitive status based on the WMH severity using linear trend tests (figure 1). The analyses showed that Aβ positivity increased as the severity of cognitive impairment (SCD, MCI, and dementia) increased in all 3 WMH groups (minimal, moderate, and severe) (p for trend < 0.001 in all groups).

Association Between Aβ and WMH According to Cognitive Status

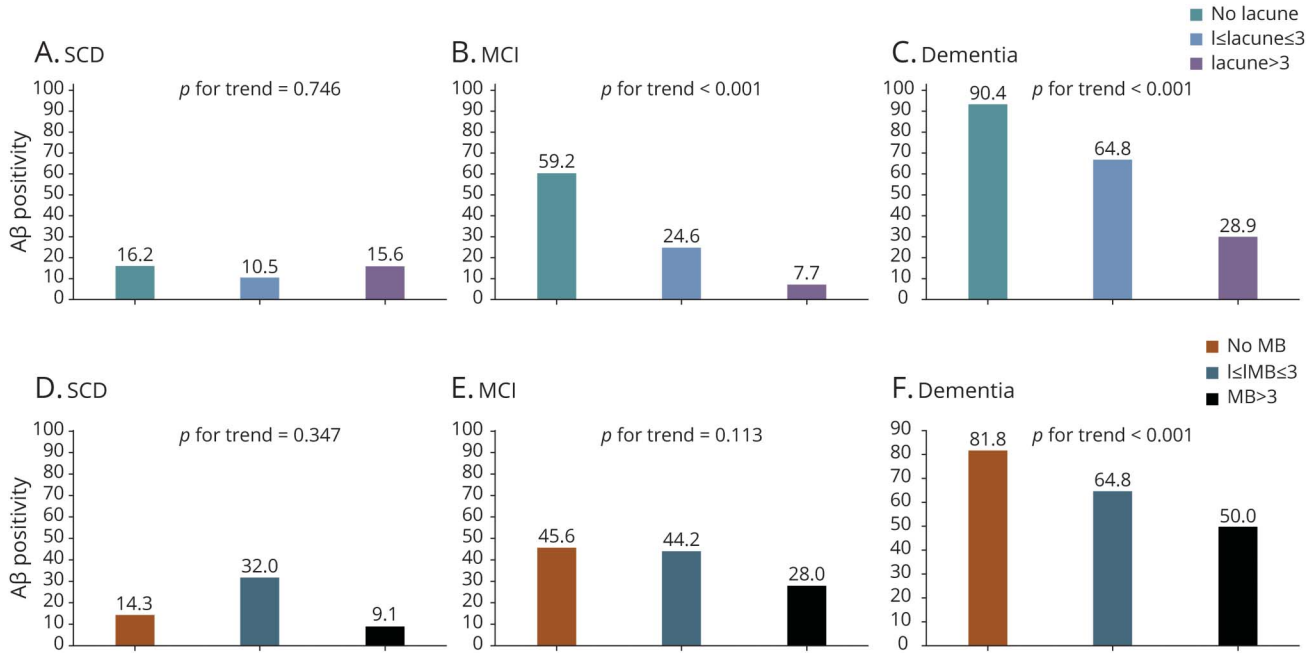
We also investigated the association between Aβ positivity and the severity of WMH based on the cognitive state using linear trend tests (figure 1). A linear trend test showed that Aβ positivity decreased as the WMH severity (minimal, moderate, and severe WMH) increased in the MCI (p for trend = 0.003) and dementia (p for trend = 0.002) groups. However, this trend was not significant in the SCD group (figure 1).

To further validate these findings, we analyzed the correlation between Aβ and WMH burden using continuous rather than categorical values of Aβ and WMH. Figure 2 shows the correlations between the Aβ PET CL values and WMH volumes. CL values negatively correlated with the WMH volume in the dementia (ρ = −0.330, p < 0.001) and MCI (ρ = −0.163, p = 0.014) groups, while CL values did not correlate with the WMH volume in the SCD (p = 0.526) group (figure 2A).

Association Between Aβ and Lacunes or Microbleeds According to Cognitive Status

We investigated the association between Aβ positivity and lacune counts in 3 cognitive groups using the linear trend tests (figure 3). The results showed that Aβ positivity decreased as

Figure 3 Association Between β-Amyloid (Aβ) Positivity and Lacunes/Microbleed (MB) Burden Values Depicted in the Bar Plot Represent Aβ Positivity



Aβ positivity significantly decreased as the number of lacunes (0, 1–3, and >3) increased in the mild cognitive impairment (MCI) (A, *p* for trend <0.001) and dementia (C, *p* for trend <0.001) groups, while this trend was not significant in the subjective cognitive decline (SCD) (A, *p* for trend = 0.746) group, accessed using the linear trend tests after adjusting for age. Aβ positivity significantly decreased as the number of microbleeds (0, 1–3, and >3) increased only in the dementia (F, *p* for trend <0.001) group, while this trend was not shown in the MCI (E, *p* for trend = 0.113) or SCD (D, *p* for trend = 0.347) groups. WMH = white matter hyperintensities.

the number of lacunes (0, 1–3, and >3) increased in the MCI (p for trend < 0.001) and dementia (p for trend < 0.001) groups, which, however, was not the case with the SCD group (figure 3). To further validate these findings, we analyzed the correlation between Aβ PET CL values and lacune counts using continuous rather than categorical values of Aβ and lacunes. As illustrated in figure 2, CL values negatively correlated with the number of lacunes in the dementia ($\rho = -0.417$, $p < 0.001$) and MCI ($\rho = -0.331$, $p < 0.001$) groups, while there was no correlation in the SCD ($p = 0.763$) group (figure 2B).

We also investigated the association between Aβ positivity and microbleed counts in 3 cognitive groups using linear trend tests (figure 3). The results showed that Aβ positivity decreased as the number of microbleeds (0, 1–3, and >3) increased only in the dementia (p for trend < 0.001) group, which was not the case with the MCI and SCD groups (figure 3). To further validate these findings, we analyzed the correlation between Aβ PET CL values and microbleed counts using continuous rather than categorical values of Aβ and microbleeds. As illustrated in Figure 2, CL values negatively correlated with the number of microbleeds only in the dementia ($\rho = -0.210$, $p < 0.001$) group, while CL values did not correlate with the number of microbleeds in the MCI ($p = 0.135$) and SCD ($p = 0.823$) groups (figure 2C).

Clinical and Genetic Factors Associated With Aβ Positivity

Table 4 shows the results of multivariable linear regression analysis for the independent clinical predictors for Aβ positivity in our Alzheimer/subcortical-vascular spectrum cohort. Presence of *APOE* ε4 (odds ratio [OR] 4.90, 95% confidence interval [CI] 3.35–7.18), absence of DM (OR 1.76, 95% CI 1.14–2.72), and higher education (OR 1.06, 95% CI 1.03–1.10) were independently associated with Aβ positivity, whereas age was not associated with Aβ positivity after adjusting for cognitive status and WMH severity.

Discussion

We systematically investigated Aβ positivity in a large sample with varying degrees of cognition and WMH, which is rarely presented in the literature. Specifically, we enrolled individuals with Alzheimer/subcortical-vascular spectrum and investigated the Aβ positivity in the 9 groups derived from the combination of 3 different cognition states and 3 WMH severity levels. The major findings in this study were as follows: (1) Aβ positivity varied across 9 groups with different levels of cognition and WMH burden; (2) Aβ positivity was associated with cognitive impairment in the presence of the same level of WMH severity, and inversely associated with severity of WMH in cognitively impaired groups; (3) Aβ positivity was also inversely associated

Table 4 Adjusted Odds Ratio (OR) for β-Amyloid (Aβ) Positivity

	Aβ positivity		
	OR[a]	CI	*p* Value
Age	0.998	0.978–1.019	0.845
Sex	1.025	0.699–1.501	0.901
Education	1.063	1.025–1.102	0.001
Hypertension	0.789	0.543–1.147	0.214
Absence of DM	1.759	1.139–2.717	0.011
Hyperlipidemia	0.710	0.486–1.036	0.076
***APOE* ε4 carrier**	4.903	3.348–7.181	<0.001

Abbreviations: CI = confidence interval; DM = diabetes mellitus.
[a] Adjusted OR for Aβ positivity: adjusted for cognitive state and white matter hyperintensity severity.

with the lacune counts in MCI and dementia groups, and with the microbleed counts in the dementia group; (4) distinctive clinical factors such as *APOE* ε4, absence of DM, and higher education were associated with Aβ positivity.

The first major finding was that Aβ positivity was variable in the 9 groups. The SCD, MCI, and dementia groups with minimal WMH severity revealed 14.5%, 50.9%, and 86.9% of Aβ positivity, respectively. Considering that patients with MCI and dementia with minimal WMH are likely to be diagnosed with amnestic MCI (aMCI) and AD dementia in memory clinic settings, the frequencies in our study are similar to those reported previously that ranged from 46.6% to 62.2% for aMCI and from 85.0% to 89.9% for AD dementia.[23-25] Likewise, MCI with severe WMH is likely to be clinically referred to as subcortical vascular MCI (svMCI), a prodromal stage of subcortical vascular dementia (SVaD); meanwhile, dementia with severe WMH is likely to be referred to as SVaD. The Aβ positivity in svMCI was 30%, which was similar to our previous reports,[4,26] while the Aβ positivity in SVaD was 53.9%, which was higher than previous reports (31.1% and 32.8%).[3,27] This discrepancy might be due to the use of different PET ligands in the 2 studies: FBB or FMM ligands were used in the present study, while the ^{11}C Pittsburgh compound B (PiB) ligand was used in the previous studies. In fact, a recent study using FBB PET reported Aβ positivity of 40% in SVaD,[28] which was higher than 30% on PiB PET. Another possible explanation for the discrepancy may be due to greater flexibility with regard to diagnostic criteria favoring pure SVaD in the present study than previous studies. More specifically, SVaD criteria in the previous studies required focal neurologic symptoms or signs suggestive of cerebrovascular disease, whereas in the present study, we clinically categorized all dementia with severe WMH into SVaD, regardless of focal symptoms or signs.

The second major finding was that Aβ positivity was associated with cognitive impairment in the presence of same level of WMH severity, and inversely associated with severity of WMH in cognitively impaired groups. That is, Aβ positivity increased as the severity of cognitive impairment increased in each WMH severity category. Although the association between Aβ positivity and cognitive impairment was what was expected, this was again replicated in our groups with various WMHs and cognition, a finding suggestive of the importance of Aβ on cognitive impairment. More importantly, we found that the Aβ positivity decreased as a function of WMH severity in both the MCI and dementia groups. This inverse correlation between Aβ and WMH burden was further replicated in the quantitative analysis where continuous values of Aβ CL values and WMH volume rather than categorical values were used. These findings suggest that Aβ and WMH may exert an additive effect on cognitive impairment, in line with previous findings,[29] and that Aβ positivity can be the main predictor of cognitive impairment after controlling for the severity of WMH. In addition, as cognitive impairment increased from MCI to dementia, Aβ positivity and mean Aβ CL values increased, but the severity of WMH and mean WMH volume did not, which also supports the hypothesis that Aβ has a greater effect on cognitive impairment than WMH.

We reviewed the literature regarding the relationship between amyloid and WMH and found that positive correlations were mainly observed in cognitively normal participants,[30-33] while the correlations were not shown in cognitively impaired patients diagnosed with MCI or dementia.[32,34] Even studies of cognitively normal groups reported mixed results. Of the 7 studies we reviewed, 4 reported positive correlations,[30-33] while the other 3 reported null results.[34-36] In the present study, we did not observe an association between Aβ positivity and the severity of WMH even in the cognitively unimpaired group, suggesting that the contribution of WMH to cognitive impairment might be additive but independent of the Aβ pathway.

The third major finding was that Aβ positivity was inversely associated with the severity of the lacune burden in cognitively impaired groups. This inverse correlation between Aβ and the number of lacunes was further replicated in the quantitative analysis. Regarding microbleeds, however, Aβ positivity was inversely associated with the severity of microbleeds burden only in the dementia group. Again, this inverse correlation between Aβ and the number of microbleeds was replicated in the quantitative CL analysis. Given that lacunes are known to be associated with Aβ-negative SVCI rather than mixed pathology[14,37] among CSVD markers, the inverse relationship between Aβ and lacunes in participants with cognitive impairment also supports the concept that Aβ and CSVD burden had an additive effect on cognitive impairment. Unlike lacunes, microbleeds were known to be associated with CSVD as well as Aβ burden,[38,39] which may explain our finding that the inverse correlation between Aβ and microbleeds was not as robust as in the case of lacunes.

The fourth major finding was that the presence of *APOE* ε4, higher levels of education, and absence of DM were associated with Aβ positivity after controlling for cognitive status and

severity of WMH. It is well known that *APOE* ε4 is associated with increased Aβ burden.[40,41] Regarding level of education, participants with higher educational attainment tended to have higher Aβ positivity after controlling for the cognitive state. These results suggest that higher education may mitigate cognitive dysfunction, despite the presence of significant amyloidosis. A previous study showed that higher education may guard against cognitive decline by mitigating the effect of Aβ pathology,[42] which was also compatible with the concept of cognitive reserve.[43] Regarding the effect of DM on Aβ positivity, there have been conflicting results between epidemiologic studies and pathologic studies. Several studies reported that the incidence of clinically diagnosed AD is higher in patients with DM.[44-46] However, autopsy studies showed that fewer Aβ plaques were found in patients with dementia and DM than in those without DM.[47-50] These results suggest that neuronal damage other than that associated with Aβ pathology might also contribute to cognitive impairment in patients with dementia and DM.

In this study, we investigated Aβ positivity in a large memory clinic cohort by establishing classifications of cognitive state and extent of WMH. Our study has several limitations. First, because of cross-sectional study design that invalidates any claim of causality, the temporal relationship between WMH and Aβ remains unclear. Second, we used Aβ PET and WMH on MRI instead of pathologic confirmation. Nevertheless, our study is noteworthy because we reported Aβ positivity in the largest number of participants in the Korean population from a cohort obtained from a memory clinic that encompasses the whole spectrum of ADCI and SVCI. The inverse relationship of Aβ deposition and CSVD found in cognitively impaired patients in our memory cohort may suggest their additive roles on cognitive impairment. Also, it demonstrated that there was a large portion of patients presenting with mixed dementia, in which Aβ and CSVD burdens coexisted. Considering the importance of Aβ on cognition, evaluation of Aβ biomarkers is warranted in cognitively impaired patients even with severe CSVD, in aiding diagnoses, predicting the prognosis, and determining the optimal treatment option.

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Monica Eunseo Kim, MS	Chicago College of Osteopathic Medicine, Midwestern University, IL	Major role in the acquisition of data
Hyemin Jang, MD, PhD	Samsung Medical Center, Seoul, Korea	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content
Hojeong Kwon	New York University, New York	Major role in the acquisition of data
Hyejoo Lee, PhD	Samsung Medical Center, Seoul, Korea	Analyzed the data
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Amyloid Positivity in the Alzheimer/Subcortical-Vascular Spectrum

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