ORIGINAL ARTICLE

Clinical significance of amyloid β positivity in patients with probable cerebral amyloid angiopathy markers

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Abstract

Purpose We investigated the frequency and clinical significance of amyloid β (Aβ) positivity on PET in patients with cerebral amyloid angiopathy (CAA).

Methods We recruited 65 patients who met the modified Boston criteria for probable CAA. All underwent amyloid PET, MRI, *APOE* genotyping and neuropsychological testing, and we obtained information on MRI markers of CAA and ischemic cerebral small-vessel disease (CSVD). We investigated the CAA/ischemic CSVD burden and *APOE* genotypes in relation to Aβ positivity and investigated the effect of Aβ positivity on longitudinal cognitive decline.

Results Among the 65 CAA patients, 43 (66.2%) showed Aβ PET positivity (Aβ+). Patients with Aβ+ CAA had more lobar microbleeds (median 9, interquartile range 2–41, vs. 3, 2–8; $P = 0.045$) and a higher frequency of cortical superficial siderosis (34.9% vs. 9.1%; $P = 0.025$), while patients with Aβ− CAA had more lacunes (1, 0–2, vs. 0, 0–1; $P = 0.029$) and a higher frequency of severe white matter hyperintensities (45.5% vs. 20.9%; $P = 0.040$). The frequency of ε4 carriers was higher in Aβ+ patients (57.1%) than in Aβ− patients (18.2%; $P = 0.003$), while the frequency of ε2 carriers did not differ between the two groups. Finally, Aβ positivity was associated with faster decline in multiple cognitive domains including language ($P < 0.001$), visuospatial function ($P < 0.001$), and verbal memory ($P < 0.001$) in linear mixed effects models.

Conclusion Our findings suggest that a significant proportion of patients with probable CAA in a memory clinic are Aβ− on PET. Aβ positivity in CAA patients is associated with a distinct pattern of CSVD biomarker expression, and a worse cognitive trajectory. Aβ positivity has clinical relevance in CAA and might represent either advanced CAA or additional Alzheimer's disease neuropathological changes.

Keywords Cerebral amyloid angiopathy · Amyloid β · Amyloid β PET

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Introduction

Cerebral amyloid angiopathy (CAA) is characterized by amyloid β (Aβ) deposition in the small arteries of the meninges and cortex, leading to vascular dysfunction and brain tissue injury. Magnetic resonance imaging (MRI) markers for CAA including strictly lobar intracerebral hemorrhage (LICH), lobar cerebral microbleeds (CMBs) and cortical superficial siderosis (cSS) have been validated and included in the Boston criteria [1, 2]. A recent study has further suggested that 90% of patients with symptomatic CAA diagnosed by the presence of multiple lobar CMBs without LICH in a hospital setting harbor moderate to severe CAA on neuropathology [3]. Recent studies have investigated the clinical value of Aβ PET in patients with MRI markers of probable CAA. Patients with probable CAA have a significantly higher Pittsburgh compound B (PiB) uptake than normal controls in occipital regions where CAA typically shows a greater predilection [4, 5] than Alzheimer's disease (AD) [6, 7]. It has thus been suggested that Aβ PET has moderate to good accuracy in the diagnosis of CAA, such that an Aβ-negative (Aβ−) PET scan might rule out CAA, at least in patients with symptomatic LICH [4, 5, 8, 9].

CAA is present in the brain of over 80% of patients with AD [10, 11]. By contrast, while CAA can be associated with Aβ parenchymal aggregates such as neuritic and diffuse plaques [12, 13], it can also occur pathologically without evident AD neuropathological changes (ADNC) [10, 14]. Therefore, it might be reasonable to expect that some patients with MRI markers of probable CAA might be Aβ− on PET. By contrast, Aβ positivity in patients with CAA MRI markers might indicate more advanced CAA pathology, or concomitant ADNC, considering that CAA might be more difficult to differentiate from underlying incipient AD in the presence Aβ positivity on PET [8], particularly in the memory clinic.

A large body of evidence emphasizes that Aβ positivity on PET is significantly associated clinically with cognition in neurodegenerative diseases; for example, Aβ-positive (Aβ+) patients with mild cognitive impairment (MCI) are more likely to convert to AD than Aβ− patients [15]. Moreover, we have shown that Aβ burden is associated with cognitive decline in both patients with AD-related cognitive impairment and patients with vascular cognitive impairment, suggesting that Aβ and ischemic cerebral small-vessel disease (CSVD) have additive effects on cognitive decline [16–18]. Although CAA can present with clinical phenotypes other than symptomatic LICH, including cognitive impairment [19], Aβ PET is largely unexplored in such patients.

In the present study, we investigated the clinical significance of Aβ positivity on PET in patients with MRI markers of probable CAA, referred to as CAA patients, who primarily visited a memory clinic. We hypothesized that CAA patients might be classified into Aβ+ and Aβ−

on PET, and that Aβ+ CAA patients might have more MRI-defined CAA markers and worse cognitive function and trajectories than Aβ− CAA patients.

Materials and methods

Study subjects

We included all eligible patients who visited a memory clinic in Samsung Medical Center complaining of cognitive impairment and who underwent either a PiB scan (from July 2007 to July 2011) or a florbetaben scan (from August 2015 to September 2016). A total of 1,027 (253 PiB PET and 774 florbetaben PET) participants were prospectively recruited. Scrutiny of the brain MRI scans of all patients identified only 65 patients (15 PiB PET, 50 florbetaben PET) with probable CAA, who had at least two strictly LICH/lobar CMBs or one strictly LICH/lobar CMB with cSS on MRI according to the modified Boston criteria [2, 20]. Of these 65 CAA patients, 59 (including four with asymptomatic LICH) presented with cognitive impairment and six presented with symptomatic LICH and were referred to our clinic for their cognitive impairment. The remaining 962 patients were diagnosed as cognitively normal (148 patients), Alzheimer's disease-related cognitive impairment [21] (amnestic MCI and AD, 530 patients), subcortical vascular cognitive impairment [21] (184 patients), or other dementia syndrome (101 patients). A control group comprising 129 Aβ+ AD patients was also included. These patients underwent florbetaben PET scans from August 2015 to September 2016 at Samsung Medical Center, and clinically met the criteria for probable AD dementia according to National Institute on Aging and the Alzheimer's Association criteria [22]. Patients with secondary causes for their cognitive deficit (e.g. vitamin B_{12}/folate, syphilis serology, and/or thyroid dysfunction), structural lesions except for LICH (e.g. territorial cerebral infarction and brain tumor), or psychiatric illness (e.g. schizophrenia) were excluded. The Institutional Review Board of Samsung Medical Center approved the study protocol and written consent was obtained from each patient.

MRI acquisition

All participants underwent brain MRI imaging including T2* gradient echo (GRE), T1 three-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) and 3D T1 sequences at Samsung Medical Center using the same type of 3.0T MRI scanner (Philips 3 .0T Achieva; Best, The Netherlands). The T2* GRE images were acquired with the following parameters: axial slice thickness 5.0 mm, interslice thickness 2 mm, repetition time (TR) 669 ms, echo time (TE) 16 ms, flip angle 18°, and matrix size 560 × 560 pixels. The 3D T1 images were acquired with the following parameters: sagittal slice

thickness 1.0 mm, contiguous slices with 50% overlap, TR 9.9 ms, TE 4.6 ms, flip angle 8°, and matrix size 240 × 240 pixels, reconstructed to 480 × 480 over a field of view of 240 mm. The 3D FLAIR images were acquired with the following parameters: axial slice thickness 2 mm, no gap, TR 11,000 ms, TE 125 ms, flip angle 90°, and matrix size 512 × 512 pixels.

Assessment of CAA and ischemic CSVD imaging markers on MRI

Images were analyzed by readers who were trained in neuroimage rating and blinded to the patients' clinical details. All structural imaging markers of CSVD were rated in accordance with consensus guidelines [23]. Lobar CMBs were defined as homogeneous and round lesions with signal loss (≤10 mm in diameter) on T2* GRE images, located exclusively in lobar areas. cSS was defined as linear hypointensities on T2* GRE images consistent with chronic blood residues in the superficial layers of the cerebral cortex [24]. Four experienced neurologists blinded to clinical information rated lobar CMBs and cSS. The interobserver intraclass correlation coefficients ranged from 0.87 to 0.91 for lobar CMBs and from 0.82 to 0.96 for cSS [25].

The severity of white matter hyperintensities (WMH) was rated using the modified scale of Fazekas et al. [26]. Periventricular WMH were classified as P1 (cap or band <5 mm), P2 (cap or band 5 mm to <10 mm) or P3 (cap or band ≥10 mm), and deep WMH were classified as D1 (lesion maximum diameter <10 mm), D2 (lesion 10 mm to <25 mm), and D3 (lesion ≥25 mm). Severe WMH was defined as periventricular WMH of ≥10 mm and deep WMH of ≥25 mm. Lacunes were identified and counted in accordance with standards for reporting vascular changes on neuroimaging (STRIVE) [23].

Aβ PET imaging acquisition

All patients underwent Aβ PET using a Discovery STe PET/CT scanner (GE Medical Systems, Milwaukee, WI) in 3D scanning mode that examined 47 slices of 3.3 mm thickness spanning the entire brain. A 16-slice helical CT scan (140 KeV, 80 mA; 3.75 mm section thickness) was performed for attenuation correction. For ^{11}C-PiB PET, a 30-min static emission PET scan was performed 60 min after a bolus injection of a mean dose of 420 MBq into an antecubital vein. For ^{18}F-florbetaben PET, a 20-min emission PET scan in dynamic mode (consisting of four 5-min frames) was performed 90 min after a bolus injection of a mean dose of 381 MBq into an antecubital vein.

Aβ PET image preprocessing and interpretation

Both MR and PET images were coregistered with each other using rigid-body transformation. The T1-weighted MR image of each patient was aligned with the MNI-152 template using nonlinear deformation including translation, rotation, scaling and shearing. After standard space registration, the gray matter was divided into 116 regions using the Automated Anatomical Labeling atlas [27]. To compute standardized uptake value ratios (SUVR), every voxel intensity was normalized by the mean intensity of the cerebellar gray matter which was regarded as the reference region.

Global Aβ PET (PiB and florbetaben PET) retention ratios were assessed from the volume-weighted average SUVR of 28 bilateral cerebral cortical volumes of interest. Aβ PET was defined as positive (Aβ+) when the global PiB SUVR was greater than 1.5 or when the brain Aβ plaque load on the florbetaben PET scan was visually rated as 2 or 3 on the brain amyloid plaque load scoring system [28]. The regional cortical florbetaben SUVR was obtained, especially for the frontal and occipital regions. The frontal region included the superior and middle frontal gyri, the medial part of the superior frontal gyrus, the opercular part of the inferior frontal gyrus, the triangular part of the inferior frontal gyrus, the supplementary motor area, the orbital part of the superior, the middle and inferior orbital frontal gyri, the rectus, and the olfactory cortex. The occipital region included the superior, middle and inferior occipital gyri, the cuneus, the calcarine fissure, and the lingual and fusiform gyri. The occipital/global and frontal/global SUVRs were then also calculated to demonstrate the distribution of florbetaben retention.

Neuropsychological tests

All patients underwent neuropsychological testing using the Seoul Neuropsychological Screening Battery (SNSB) [25, 29], which consists of tests for attention, language, visuoconstructive function, verbal and visual memory, and frontal/executive function. Retrospective and prospective neuropsychological test results were obtained from these patients, in all of whom the complete SNSB was administered at least once at the time of PET imaging. The following quantitatively scorable tests were included in the analysis: digit span (forward and backward), the Boston Naming Test (BNT), the Rey-Osterrieth Complex Figure Test (RCFT), the Seoul Verbal Learning Test (SVLT), a phonemic and semantic Controlled Oral Word Association Test (COWAT), the Stroop test color reading, Mini-Mental State Examination (MMSE), and Clinical Dementia Rating – Sum of Boxes (CDR-SOB). Detailed explanations of these tests are provided in Supplementary Table 1.

Table 1 Clinical characteristics of Aβ− CAA, Aβ+ CAA, and Aβ+ AD patients

Characteristic	Aβ− CAA (n = 22)	Aβ+ CAA (n = 43)	Aβ+ AD (n = 129)	P value		
				Aβ− CAA vs. Aβ+ CAA	Aβ+ CAA vs. Aβ+ AD	Aβ− CAA vs. Aβ+ AD
Age (years)	75.3 ± 7.1	74.4 ± 8.1	67.1 ± 10.2	0.661	<0.001	<0.001
Gender, female	12 (54.6)	23 (53.5)	71 (55.0)	0.936	0.860	0.966
Education (years)	10.6 ± 6.1	11.3 ± 5.2	12.6 ± 4.4	0.606	0.112	0.060
Vascular risk factors						
Hypertension	10 (45.5)	23 (53.5)	48 (37.2)	0.540	0.016	0.256
Diabetes	8 (36.4)	8 (18.6)	18 (14.0)	0.116	0.461	0.002
Hyperlipidemia	5 (22.7)	7 (16.3)	40 (31.0)	0.526	0.205	0.725
Cardiac disease	3 (13.6)	3 (7.0)	5 (3.9)	0.380	0.166	0.282
Stroke (%)	3 (13.6)	6 (14.0)	1 (0.8)	0.972	0.093	0.153
Clinical manifestation						
Symptomatic LICH	3 (13.6)	3 (7.0)	N/A	0.380	N/A	N/A
Cognitive impairment	19 (86.4)	40 (93.0)	N/A	0.380	N/A	N/A
MMSE score	22.8 ± 5.0	19.7 ± 6.3	16.9 ± 7.1	0.038[a]	0.131[a]	0.003[a]

Values are mean ± standard deviation or number (%)

LICH lobar intracerebral hemorrhage, *MMSE* Mini-Mental State Examination, *N/A* not applicable

[a] After adjusting for age, gender and education

Statistical analyses

Student's *t* test and the chi-squared test were used to evaluate the pairwise differences in demographics and clinical characteristics, including frequency of apolipoprotein E (*APOE*) ε4 or ε2 carriers, among the three groups (Aβ− CAA, Aβ+ CAA, and Aβ+ AD). The chi-squared test was used to compare the frequency of *APOE* ε4 or ε2 carriers among the three groups and between CAA patients with and without hemorrhagic imaging markers. Analysis of covariance (ANCOVA) was used to compare pairwise differences in florbetaben retention distribution among the three groups using age, gender and MMSE as covariates. CAA and ischemic CSVD markers were compared between Aβ− CAA and Aβ+ CAA patients using the Wilcoxon rank sum test for continuous variables (because of the skewed distribution of data) and the chi-squared test for dichotomous variables. Finally, ANCOVA was used to compare cognition between Aβ− and Aβ+ CAA patients using age, gender and education as covariates.

To investigate the effect of Aβ positivity on longitudinal cognitive changes, a linear mixed effects model was applied. Fixed effects were Aβ positivity, time
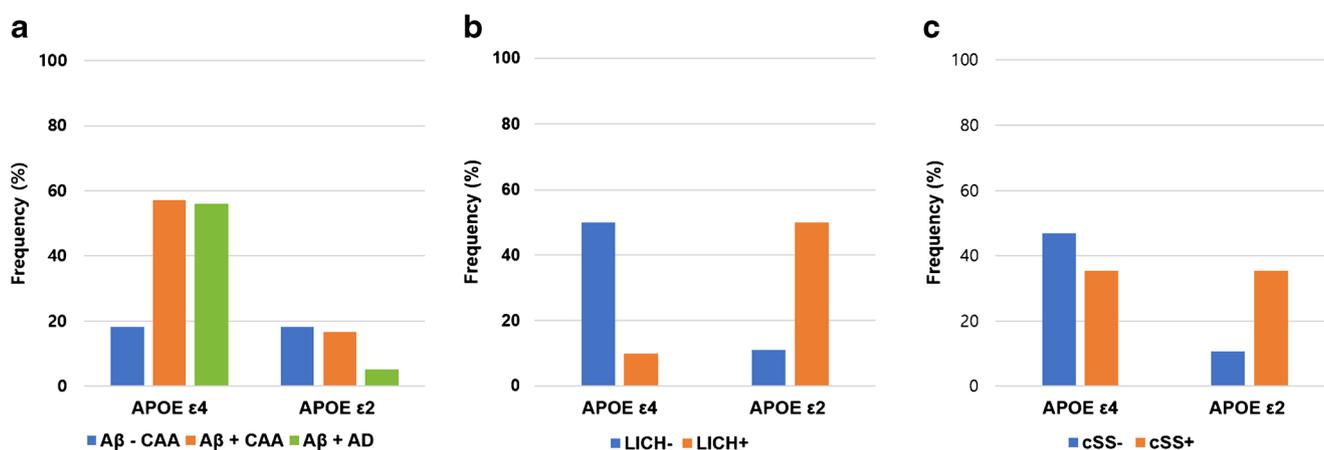

Fig. 1 Frequencies of *APOE* ε4 and ε2 carriers in relation to (**a**) Aβ positivity and the presence of CAA hemorrhagic markers including (**b**) LICH and (**c**) cSS. *APOE* apolipoprotein E, *CAA* cerebral amyloid angiopathy, *Aβ* amyloid β, *AD* Alzheimer's disease, *LICH* lobar intracerebral hemorrhage, *cSS* cortical superficial siderosis

Fig. 2 PET SUVRs in Aβ−
CAA, Aβ+ CAA and Aβ+ AD
patients: **a** occipital/global
SUVR, **b** frontal/global SUVR.
Aβ amyloid β, *SUVR*
standardized uptake value ratio,
CAA cerebral amyloid
angiopathy, *AD* Alzheimer's
disease
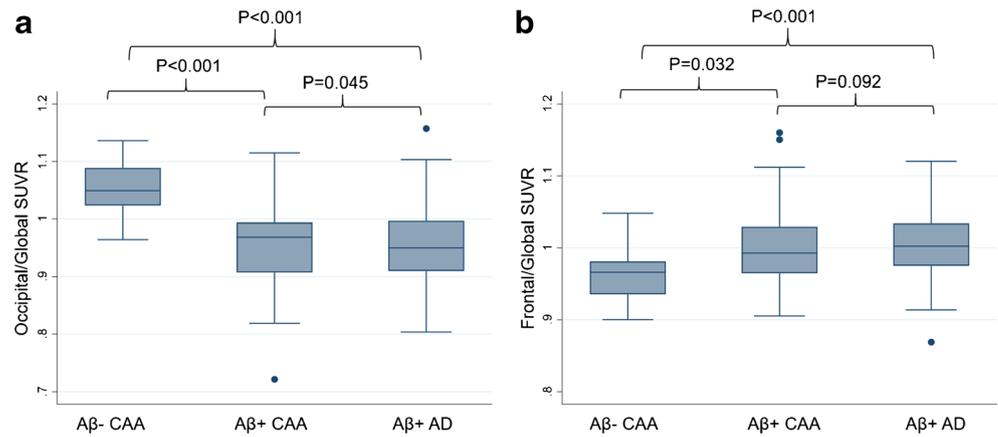
from the PET study, age, gender, education years, and the two-way interaction term for Aβ positivity and time (Aβ positivity × time). Patients were included as random effects. All statistical analyses were performed with STATA/SE version 15.1. Statistical significance was defined as a two-tailed *P* value of <0.05.

Results

Demographics and clinical characteristics of participants

Among the 65 CAA patients, 43 (66.2%) showed Aβ PET positivity (Aβ+ CAA). The frequency of Aβ PET positivity did not differ between the two PET cohorts: 10 of 15 PiB PET patients (66.7%) and 33 of 50 florbetaben PET patients (66%) were Aβ+. Aβ− CAA and Aβ+ CAA patients were older (75.3 ± 7.1 years and 74.4 ± 8.1 years, respectively) than Aβ+ AD patients without CAA imaging markers (67.1 ± 10.2 years; both *P* < 0.001). Aβ+ CAA patients were more likely to have hypertension than Aβ+ AD patients (53.5% vs. 37.2%, respectively; *P* = 0.016), and Aβ− CAA patients were more likely to have diabetes than Aβ+ AD patients

(36.4% vs.14.0%, respectively; *P* = 0.002). There were no differences in other demographic and clinical data across the three groups (Table 1).

The frequency of *APOE* ε4 carriers and ε2 carriers in relation to Aβ positivity and the presence of CAA hemorrhagic markers

The frequency of ε4 carriers was higher in Aβ+ CAA than in Aβ− CAA patients (57.1% vs. 18.2%, respectively; *P* = 0.003) while it did not differ between Aβ+ CAA and Aβ+ AD patients without CAA imaging markers (57.1% vs. 56.3%, respectively; *P* = 0.901). The frequency of ε2 carriers was higher in Aβ− CAA and Aβ+ CAA (18.2% and 14.3%, respectively) than in Aβ+ AD patients (5.2%; *P* = 0.031 and 0.002, respectively), but it did not differ between Aβ− and Aβ+ CAA patients (Fig. 1a).

The frequency of ε2 carriers was higher in LICH+ than in LICH− patients (5/10, 50%, vs. 6/54, 11.1%, respectively; *P* = 0.003) while the frequency of ε4 carriers was higher in LICH− than in LICH+ patients (27/54, 50%, vs. 1/10, 10%, respectively; *P* = 0.019; Fig. 1b). Similarly, the frequency of ε2 carriers was significantly higher in cSS+ than in cSS− patients (6/17, 35.3%, vs. 5/47, 10.6%, respectively; *P* = 0.021), but

Table 2 Comparison of CAA and ischemic CSVD burden between Aβ− and Aβ+ CAA patients

	Aβ− CAA (*n* = 22)	Aβ+ CAA (*n* = 43)	*P* value
CAA markers			
Presence of LICH, *n* (%)	4 (18.2)	6 (14.0%)	0.655
Number of lobar CMBs, median (interquartile range)	3 (2–8)	9 (2–41)	0.045
Presence of cSS, *n* (%)	2 (9.1%)	15 (34.9%)	0.025
Ischemic CSVD markers			
Number of lacunes, median (interquartile range)	1 (0–2)	0 (0–1)	0.029
Presence of severe WMH, *n* (%)	10 (45.5)	9 (20.9)	0.040

CSVD cerebral small vessel disease, *LICH* lobar intracerebral hemorrhage, *CMBs* cerebral microbleeds, *cSS* cortical superficial siderosis, *WMH* white matter hyperintensities

the frequency of $\varepsilon2$ carriers did not differ between cSS+ and cSS− patients (35.3% vs. 46.8%, respectively; P = 0.412; Fig. 1c).

Aβ uptake pattern in CAA patients

Comparing Aβ PET uptake patterns between 33 Aβ+ CAA patients with florbetaben imaging and 129 Aβ+ AD patients with florbetaben imaging without CAA imaging markers, the occipital/global SUVR was higher in Aβ+ CAA than in Aβ+ AD patients (0.97 ± 0.06 vs. 0.95 ± 0.06, respectively; P = 0.045), while the frontal/global SUVR did not significantly differ between these two patient groups (0.99 ± 0.04 vs. 1 ± 0.04, respectively; P = 0.092) after adjusting for age, gender and MMSE score (Fig. 2). Furthermore, comparing Aβ PET uptake patterns between 17 Aβ− CAA with florbetaben imaging and Aβ+ AD patients, the Aβ− CAA patients showed a higher occipital/global SUVR than the Aβ+ AD patients (1.04 ± 0.04 vs. 0.95 ± 0.06, respectively; $P < 0.001$) but a lower frontal/global SUVR (0.96 ± 0.04 vs. 1 ± 0.04, respectively; $P < 0.001$; Fig. 2).

CAA and ischemic CSVD markers in relation to Aβ positivity

Aβ+ CAA patients had more lobar CMBs than Aβ− CAA patients (median 9, interquartile range 2–41, vs. 3, 2–8; P = 0.045) and a higher frequency of cSS (34.9 vs. 9.1%; P = 0.025). In contrast, Aβ− CAA patients had more lacunes than Aβ+ CAA patients (median 1, interquartile range 0–2, vs. 0, 0–1; P = 0.029) and a higher frequency of severe WMH (45.5 vs. 20.9%, P = 0.040). The frequency of LICH did not differ between the two groups (P = 0.655; Table 2). Detailed imaging and clinical characteristics in Aβ− CAA patients are shown in Table 3. Images of typical Aβ− CAA patients are shown in Fig. 3.

Cognitive trajectory in relation to Aβ positivity

In the neuropsychological tests at the time of the PET study, Aβ+ CAA patients had significantly worse performance in the BNT (30.4 ± 12.7 vs. 37.7 ± 9.5, P = 0.014) and the MMSE (19.7 ± 6.3 vs. 22.8 ± 5.0, P = 0.038) than

Table 3 Clinical and imaging characteristics of Aβ− CAA patients

No.	PET ligand	Age (years)	Sex	MMSE score	Location of LICH	Presence of cSS	Number of lobar CMBs	Number of lacunes	Severity of WMH
1	Florbetaben	70	F	17	Frontoparietal	0	16	2	Severe
2	Florbetaben	60	M	18	Parietal	0	3	10	Mild
3	Florbetaben	77	F	17	Parieto-occipital	0	32	0	Moderate
4	Florbetaben	82	F	19	Parietal	0	2	0	Moderate
5	Florbetaben	70	F	30		1	6	0	Moderate
6	Florbetaben	78	F	24		1	1	2	Moderate
7	PiB	71	M	23		0	1	2	Severe
8	PiB	80	M	27		0	2	0	Moderate
9	PiB	78	F	27		0	5	2	Severe
10	PiB	72	F	15		0	12	0	Severe
11	PiB	79	M	18		0	8	7	Severe
12	Florbetaben	87	F	20		0	9	1	Mild
13	Florbetaben	70	F	27		0	7	2	Severe
14	Florbetaben	88	M	18		0	3	2	Mild
15	Florbetaben	78	M	29		0	2	1	Severe
16	Florbetaben	73	M	27		0	3	0	Mild
17	Florbetaben	87	M	25		0	2	1	Severe
18	Florbetaben	73	M	29		0	2	11	Severe
19	Florbetaben	67	F	18		0	2	0	Moderate
20	Florbetaben	75	F	24		0	25	0	Moderate
21	Florbetaben	66	M	19		0	2	0	Mild
22	Florbetaben	76	F	30		0	8	13	Severe

PiB Pittsburgh compound B, *MMSE* Mini-Mental State Examination, *LICH* lobar intracerebral hemorrhage, *cSS* cortical superficial siderosis, *CMBs* cerebral microbleeds, *WMH* white matter hyperintensities

Aβ− CAA patients (Table 3). Of the 65 patients, 42 underwent at least one follow-up visit for neuropsychological testing. The average number of follow-up neuropsychological tests was 3.8 ± 1.4. In linear mixed effects models to investigate the effects of Aβ positivity on cognitive decline, Aβ positivity was associated with faster decline in the following tests: BNT ($P < 0.001$), RCFT copy ($P < 0.001$), SVLT immediate recall ($P < 0.001$), RCFT immediate recall ($P = 0.005$), RCFT delayed recall ($P < 0.001$), COWAT supermarket ($P = 0.001$), Stroop test color reading ($P = 0.001$), MMSE ($P < 0.001$), and CDR-SOB ($P < 0.001$; Table 4, Fig. 4).

Discussion

Using noninvasive amyloid imaging and structural MRI for markers of CSVD, the distinct clinical and MRI characteristics in patients with probable CAA according to Aβ positivity on PET were obtained. The main findings were as follows: first, a significant proportion of patients with probable CAA seen in a memory clinic were Aβ− on PET; second, Aβ positivity in CAA patients was associated with a distinct pattern of MRI CSVD biomarker expression; and third, Aβ positivity in CAA patients was associated with a worse cognitive trajectory. Taken together, our findings suggest that Aβ positivity has
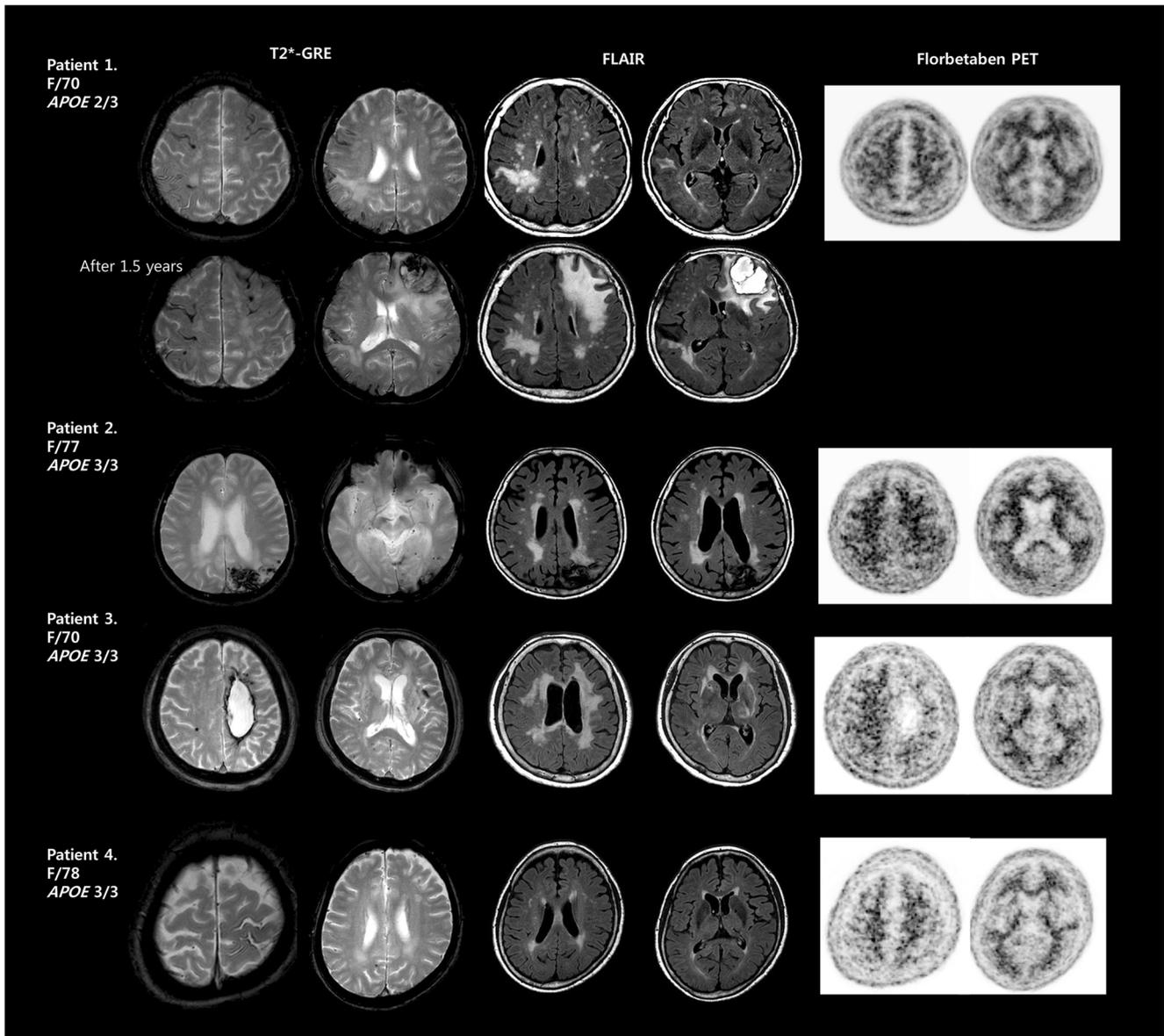

Fig. 3 Imaging in typical Aβ− CAA patients. *Aβ* amyloid β, *CAA* cerebral amyloid angiopathy, *APOE* apolipoprotein E, *GRE* gradient echo, *FLAIR* fluid-attenuated inversion recovery

mechanistic and clinical relevance in CAA and might represent either advanced CAA or additional ADNC.

Aβ positivity was found in 67% of patients with probable CAA. This finding is partially consistent with those of previous studies. Specifically, Aβ PET positivity has been found in 69% [30] and 60% [31] of patients with probable CAA, and other studies have shown even higher values (80% to 100%) [4–6, 32] (Table 5). The discrepancy between the findings of previous studies and those of our study may partly be explained by the smaller sample sizes in previous studies and different study participants (primarily patients with restricted multiple lobar CMBs from a memory clinic in our sample compared with nondemented patients with only symptomatic LICH in the previous studies), as CAA with and without LICH might have different pathophysiological mechanisms [33].

There might be several explanations for the finding that about 30% of patients with characteristic CAA MRI markers were Aβ− on PET. First, current amyloid PET tracers cannot differentiate vascular Aβ from parenchymal Aβ. However, a study has revealed that patients with pathologically proven

CAA have higher occipital/global ratios than those with AD [32]. In the present study, while Aβ− CAA patients had lower frontal/global ratios than Aβ+ AD patients, and Aβ− CAA and Aβ+ CAA patients had higher occipital/global ratios than Aβ+ AD patients. Thus, increased occipital/global ratios in CAA patients regardless of Aβ positivity might reflect vascular Aβ uptake. Second, Aβ− CAA patients might have mild ADNC because Aβ PET shows low accuracy in detecting mild ADNC [34]. Indeed, pathological studies have suggested that less than 50% of CAA patients meet pathological criteria for AD [35, 36].

The frequency of APOE ε2 carriers was significantly higher in Aβ+ CAA and Aβ− CAA patients than in Aβ+ AD patients, although the frequency of APOE ε2 carriers did not differ between Aβ+ CAA and Aβ− CAA patients. Moreover, in CAA patients, the frequency of APOE ε2 carriers was significantly higher in patients with overt hemorrhagic markers including cSS and LICH than in patients without overt hemorrhagic markers. Considering another finding that the frequency of APOE ε4 carriers, but not ε2 carriers,

Table 4 Cognitive trajectory in Aβ− and Aβ+ CAA patients

Test	Baseline cognition			Longitudinal cognitive change		
	Aβ− CAA (n = 22)	Aβ+ CAA (n = 43)	P value[a]	Coefficient	Standard error	P value[b]
Attention						
Digit span forward	5.0 ± 1.2	5.4 ± 1.3	0.344	−0.02	0.06	0.686
Digit span backward	3.1 ± 1.2	3.0 ± 1.3	0.769	−0.14	0.07	0.049
Language						
BNT (60)	37.7 ± 9.5	30.4 ± 12.7	0.014	−2.52	0.40	<0.001
Visuospatial function						
RCFT copy (36)	23.4 ± 11.1	20.5 ± 10.8	0.348	−1.97	0.47	<0.001
Memory						
SVLT immediate recall (36)	13.9 ± 4.7	11.5 ± 5.4	0.095	−1.15	0.26	<0.001
SVLT delayed recall (12)	2.6 ± 2.4	1.6 ± 2.6	0.116	−0.20	0.11	0.062
SVLT recognition (24)	18.5 ± 2.9	17.0 ± 4.3	0.211	6.01	5.58	0.281
RCFT immediate recall (36)	6.3 ± 6.3	3.9 ± 4.8	0.101	−0.08	0.29	0.005
RCFT delayed recall (36)	5.9 ± 5.5	4.2 ± 5.1	0.224	−1.01	0.25	<0.001
RCFT recognition (24)	17.4 ± 3.3	16.8 ± 3.1	0.557	−0.27	0.19	0.144
Frontal/executive function						
COWAT animal	9.5 ± 5.1	9.0 ± 4.4	0.752	−0.29	0.22	0.189
COWAT supermarket	7.3 ± 4.3	9.9 ± 5.8	0.075	−1.17	0.34	0.001
COWAT phonemic	15.0 ± 11.5	13.0 ± 9.1	0.496	−.091	0.56	0.104
Stroop color reading (112)	46.9 ± 29.3	38.2 ± 25.3	0.303	−3.87	1.12	0.001
MMSE (30)	22.8 ± 5.0	19.7 ± 6.3	0.038	−1.46	0.23	<0.001
CDR-SOB	3.5 ± 5.0	4.8 ± 4.1	0.236	0.70	0.16	<0.001

Values are mean ± standard deviation

BNT Boston Naming Test, *RCFT* Rey Copy Figure Test, *SVLT* Seoul Verbal Learning Test, *COWAT* ControlledOral Word Association Test, *MMSE* Mini-Mental State Examination, *CDR-SOB* Clinical Deterioration Rating – Sumof Boxes

[a] Difference between groups by analysis of covariance using age, gender, and education as covariates

[b] Effect of Aβ positivity on longitudinal cognitive changes obtained from linear mixed effects model

was higher in Aβ+ CAA patients than in Aβ- CAA patients, *APOE ε4* in CAA patients predicts Aβ positivity, while *APOE ε2* in CAA patients is related to overt hemorrhagic markers of CAA. The findings of previous studies that *APOE ε4* is related to deposition of Aβ and *APOE ε2* is related to breakdown of blood vessel walls [33, 37] tend to support this suggestion.

Our second finding was that Aβ+ CAA patients had more lobar CMBs and more frequent cSS than Aβ− CAA patients. A previous study has shown that the presence of lobar CMBs is associated with CAA pathology [3]. In addition, cSS is known to be a key hemorrhagic marker of CAA [2] and a previous study has shown that the presence of cSS reflects an Aβ rather than an ischemic etiology [38]. Our findings might therefore indicate that Aβ+ CAA patients have a higher CAA burden than Aβ− CAA patients. In contrast, Aβ− CAA patients are more likely to show markers of ischemic CSVD (or deep perforator arteriopathy) including lacunes and WMH

than Aβ+ CAA. Previous studies by our group have indicated that lobar CMBs might be attributable to CSVD as well as Aβ uptake [21, 39]. CSVD and Aβ uptake have been found to be synergistically associated with the development of lobar CMBs, although these studies included patients with combined lobar and deep CMBs. Our current findings suggest that ischemic CSVD alone or ischemic CSVD combined with CAA might be associated with the presence of some CAA MRI markers (e.g. lobar CMBs) in Aβ− patients who meet the criteria for probable CAA [2] based on MRI markers. For example, chronic hypertension may cause autoregulatory dysfunction of superficial perforating arteries of pial origin and dysfunction of deep perforating arteries [40], resulting in damage to the smooth muscle cells and development of CMBs in lobar areas. It is also possible that an additional hypertensive CSVD burden might affect common pathways of CAA, including endothelial dysfunction and inflammation, which
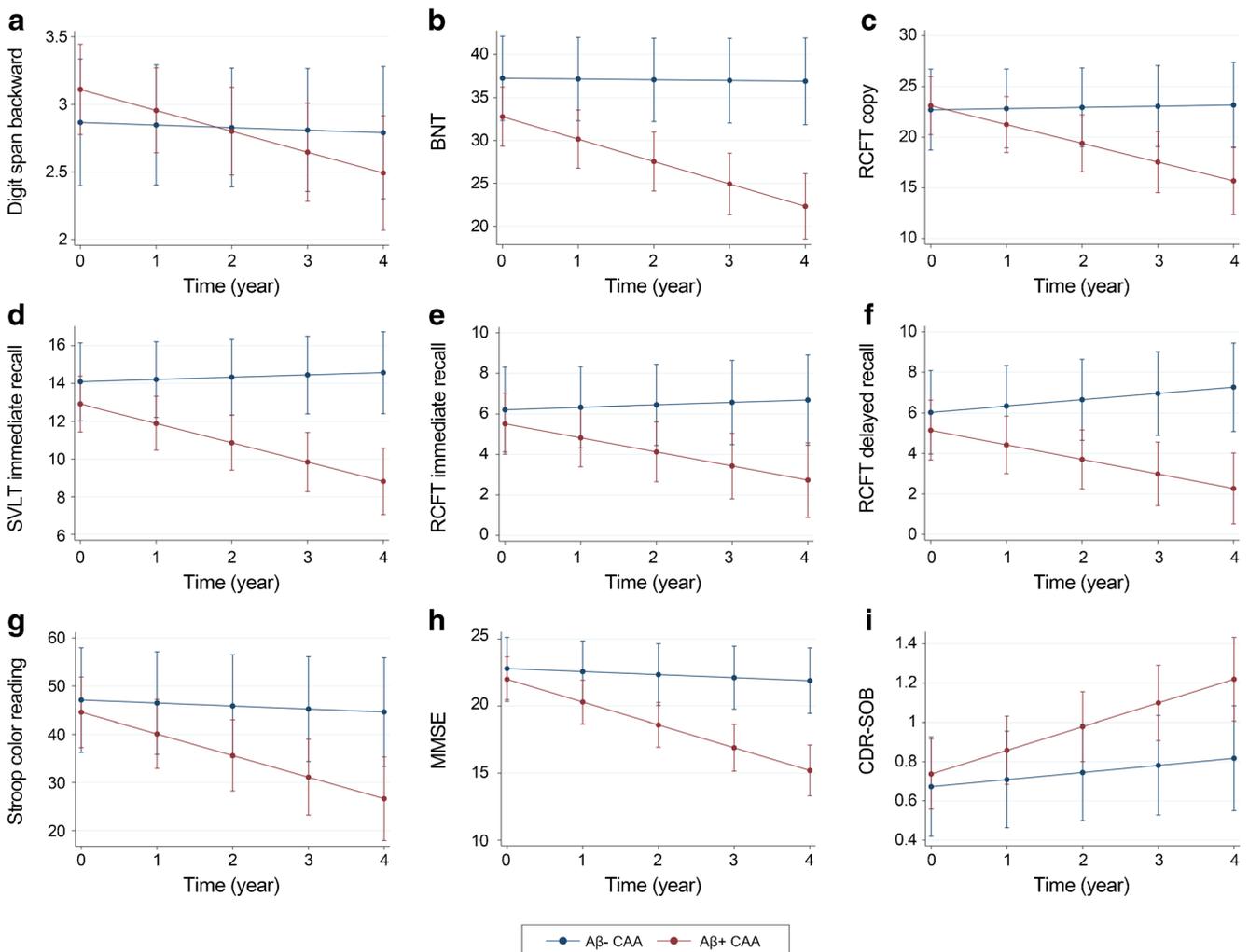

Fig. 4 Cognitive decline according to Aβ positivity (**a** digit span backward, **b** BNT, **c** RCFT copy, **d** SVLT immediate recall, **e** RCFT immediate recall, **f** RCFT delayed recall, **g** Stroop test color reading, **h** MMSE, **I** CDR-SOB). *BNT* Boston Naming Test, *RCFT* Rey Copy Figure Test, *SVLT* Seoul Verbal Learning Test, *MMSE* Mini-Mental State Examination, *CDR-SOB* Clinical Deterioration Rating – Sum of Boxes. The *y* axis represents the predicted neuropsychological scores for each year of follow-up derived from the predicted model equation using a linear mixed effects model

Table 5 Previous studies reporting Aβ positivity in probable CAA

Reference	Number of patients	CAA diagnosis	Clinical manifestation	Aβ PET ligand	Determination of Aβ positivity	Aβ positivity (%)
Current study	65	MRI	Memory impairment (59 patients), LICH (6 patients)	PiB (15 patients), florbetaben (50 patients)	SUVR cutoff 1.5 (PiB), visual (florbetaben)	43/65 (66)
[32]	6	Pathology (4 patients), MRI (2 patients)	Seizure (4 patients), LICH (2 patients)	PiB	Visual	6/6 (100)
[6]	8	MRI	LICH	PiB	DVR cutoff 1.44	7/8 (88)
[30]	42	MRI + supporting pathology (14 patients), MRI (28 patients)	LICH (23 patients), other (19 patients, including gait disorder and seizures)	PiB	DVR cutoff 1.22	29/42 (69)
[4]	11	MRI	LICH	PiB	DVR cutoff 1.22	9/11 (82)
[5]	10	MRI	LICH	Florbetapir	Visual	10/10 (100)
[31]	15	MRI + supporting pathology (2 patients), MRI (13 patients)	LICH	Florbetapir	Visual	9/15 (60)

LICH lobar intracerebral hemorrhage, *PiB* Pittsburgh compound B, *SUVR* standardized uptake value ratio, *DVR* distribution volume ratio

could lead to synergistically increased vulnerability to hemorrhage in patients with a less severe CAA burden.

Our final major finding was that Aβ+ CAA patients showed more rapid decline in multiple cognitive domains than Aβ− CAA patients. A previous study by our group has shown that the presence of CAA hemorrhagic markers have an adverse influence on cognition [41]. In the current study, we built on these observations by showing that Aβ positivity is associated with cognitive decline in CAA patients. These findings are consistent with those of a previous autopsy study, which demonstrated that CAA and AD pathologies synergistically contribute to cognitive impairment [42], although a recent study has shown that the relative contributions of mixed neuropathologies to cognitive impairment vary [43]. A possible explanation is that CAA causes ischemic injury by decreasing cerebral blow flow and hypoxia, which could increase vulnerability to neuronal death due to ADNC [43]. It is also possible that a severe CAA burden alone contributed to worse cognitive decline, as Aβ positivity might represent advanced CAA pathology even without parenchymal Aβ.

The strengths of this study include standardized Aβ PET, MRI and neuropsychological protocols. Although the sample size was not large, compared to previous studies, our study included a larger cohort of CAA patients from a memory clinic [4–6, 30–32] (Table 5). We are not aware of similar studies in this field that focused on probable CAA. However, some limitations need to be acknowledged. The main limitation of this study was the lack of pathological data. Thus, CAA markers were defined using only the modified Boston criteria for probable CAA. In addition, we did not use Aβ PET for the diagnosis of CAA because current amyloid PET ligands cannot differentiate vascular Aβ from parenchymal Aβ burden. Therefore, the findings of this study need to be validated in pathological studies. Finally, we included patients who underwent Aβ PET scans using PiB or florbetaben, which might have affected the findings. However, there was no difference in the frequency of Aβ positivity between CAA patients imaged with PiB and those imaged with florbetaben (10/15, 66.7%, vs. 33/50, 66%; $P = 0.962$). Also, a previous head-to-head study using two Aβ tracers has indicated that the binding of the two tracers is highly correlated ($R^2 = 0.96$) [44]. Therefore, we expect that the use of different Aβ ligands did not greatly affect the classification of parenchymal Aβ positivity. However, further studies are needed to investigate differences in intensity and pattern of uptake between the two ligands in CAA patients.

Conclusion

Our findings suggest that Aβ+ CAA patients have a distinct neuroimaging signature suggesting advanced CAA or ADNC burden, which lead to a worse cognitive status and trajectory. Our findings suggest that Aβ PET has mechanistic and clinical relevance in patients with clinically diagnosed probable CAA. In particular, our findings demonstrate the potential

clinical value of Aβ PET in predicting the prognosis of CAA patients who primarily visited a memory clinic. Aβ PET might also have value in the design, patient selection and interpretation in future CAA treatment trials.

Compliance with ethical standards

Conflicts of interest None.

Role of the funder The funders had no role in the design or conduct of the study; in the collection, management, analysis or interpretation of the data; in the preparation, review or approval of the manuscript; or in the decision to submit the manuscript for publication.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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