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

Hyemin Jang[1,2], Young Kyoung Jang[1,2], Hee Jin Kim[1,2], David John Werring[3], Jin San Lee[4], Yeong Sim Choe[1], Seongbeom Park[1], Juyeon Lee[5], Ko Woon Kim[6], Yeshin Kim[7], Soo Hyun Cho[1,2], Si Eun Kim[8], Seung Joo Kim[1,2], Andreas Charidimou[9], Duk L. Na[1,2,10], Sang Won Seo, MD, PhD[1,2,10]

[1]Departments of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Neuroscience Center, Samsung Medical Center, Seoul, Korea; [3]UCL Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London, UK; [4]Departments of Neurology, KyungHee University School of Medicine, Seoul, Korea; [5]Department of neurology, Chungnam National University School of Medicine, Daejeon, Korea; [6] Department of neurology, Chonbuk National University Hospital, Chonbuk National University Medical school, Jeonju, Korea; [7]Department of Neurology, Kangwon National University Hospital, Kangwon National University College of Medicine, Chuncheon, Korea; [8]Departments of Neurology, Inje University College of Medicine, Haeundae Paik Hospital, Busan, Korea; [9]Department of Neurology, Massachusetts General Hospital Stroke Research Center, Harvard Medical School, Boston, MA, USA; [10]Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University

Corresponding author:

Sang Won Seo, MD, PhD

Department of Neurology, Sungkyunkwan University School of Medicine, Samsung Medical Center, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea

Tel.: +82-2-3410-6147, Fax: +82-2-3410-0052

E-mail: sangwonseo@empal.com or sw72.seo@samsung.com

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ABSTRACT

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

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

Results Among 65 CAA patients, 43(66.2 %) showed Aβ PET positivity(+). Aβ+ CAA had more lobar microbleeds(9(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 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+(57.1%) than in Aβ- CAA(18.2%) (p=0.003) while the frequency of ε2 carriers did not differ between 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.

Conclusions Our findings suggest that a significant proportion of probable CAA patients in a memory clinic are Aβ PET negative. 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 neuropathologic changes.

Keywords: Cerebral amyloid angiopathy, Amyloid β, Amyloid β PET

Introduction

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

CAA is present in over 80% of the brains 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 neuropathologic changes (ADNC)[14, 15]. Therefore, it might be reasonable to expect that some patients with probable CAA MRI markers might be Aβ- on PET. By contrast, Aβ positivity in patients with CAA MRI markers might identify more advanced CAA pathology, or concomitant ADNC considering that it might be more difficult to differentiate from underlying incipient AD if Aβ PET positive (+)[8], particularly in memory clinic.

A large body of evidence has emphasized the clinical significance of Aβ+ PET scans on cognition in neurodegenerative diseases; for example, Aβ+ mild cognitive impairment (MCI) patients are more likely convert to AD than Aβ- patients [16]. Moreover, we have shown that Aβ burden is associated with cognitive decline in patients with both AD related

and vascular cognitive impairment, suggesting that Aβ and ischemic cerebral small vessel disease (CSVD) have additive effects on cognitive decline[17-19]. Although CAA can present with clinical phenotypes other than symptomatic LICH, including cognitive impairment[20], Aβ PET is largely unexplored in such patients.

In the present study, we investigated clinical significance of Aβ positivity on PET in patients with probable CAA MRI markers, referred 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 underwent either PiB (from July 2007 to July 2011) or florbetaben (from August 2015 to September 2016) scans. A total of 1,027 (253 for PiB and 774 for florbetaben) participants were prospectively recruited. Then, we scrutinized brain MRI of all patients and identified only 65 patients (15 PiB PET, 50 florbetaben PET) with probable CAA, who have at least two strictly LICH/lobar CMBs or one strictly LICH/lobar CMB with cSS on MRI as according to modified Boston criteria[21, 22]. Among 65 CAA patients, 59 patients (including four patients with asymptomatic LICH) presented with cognitive impairment and six patients presented with symptomatic LICH and were referred to our clinic for their cognitive impairment. The remaining 962 patients were diagnosed as cognitively normal (n=148), Alzheimer's disease related cognitive impairment[23] (amnestic MCI and AD, n=530), subcortical vascular cognitive impairment[23] (n=184), or other dementia syndrome (n=101). As a control group in this study, we included 129 Aβ+ AD patients. 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[24].We excluded patients with the presence of secondary causes of cognitive deficits (e.g., vitamin B_{12}/folate, syphilis serology, and/or thyroid dysfunction), or structural lesions except for LICH (e.g., territorial cerebral infarctions and brain tumors), or with psychiatric illnesses such as schizophrenia. 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 including T2* GRE, T1, three-dimensional (3D) FLAIR and 3D T1 images at Samsung Medical Center using the same kind of 3.0T MRI scanner (Philips 3.0T Achieva; Best, the Netherlands). The following parameters were used for the T2* GRE images: axial slice thickness 5.0 mm; inter-slice thickness 2 mm; repetition time (TR) 669 ms; echo time (TE) 16 ms; flip angle 18°; matrix size 560x560 pixels. We acquired 3D T1 images with the following parameters: sagittal slice thickness 1.0 mm, over contiguous slices with 50% overlap; TR 9.9 ms; TE 4.6 ms; flip angle8°; and matrix size 240 × 240 pixels, reconstructed to 480 × 480 over a field of view of 240 mm. 3D FLAIR images were obtained with the following parameters: axial slice thickness 2 mm; no gap; TR 11,000 ms; TE 125 ms; flip angle 90°; and matrix size 512x512 pixels.

Assessment of CAA and ischemic CSVD imaging markers on MRI

Imaging analysis was carried out by individuals who were trained in neuroimaging rating and blinded to the participant clinical details. All structural imaging markers of CSVD were rated in accordance with consensus guidelines [25]. Lobar CMBs were defined as homogenous and round lesions with signal loss (≤10mm in diameter) on T2* GRE images, with location in exclusively 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 [26]. Four experienced neurologists, who were blinded to clinical information rated lobar CMBs and cSS. The inter-observer intra-class correlation coefficient ranged from 0.87 to 0.91 for lobar CMBs and from 0.82 to 0.96 for cSS [27].

White matter hyperintensities (WMH) severity was rated using the modified Fazekas scale [28]. Periventricular WMH (PWMH) were classified as P1 (cap and band<5 mm), P2 (5 mm≤cap or band<10 mm), or P3 (10 mm≤cap or band); and deep WMH (DWMH) were classified as D1 (maximum diameter of deep white matter lesion <10 mm), D2 (10 mm≤lesion<25 mm), and D3 (≥25 mm). Severe WMH was defined as periventricular WMH ≥ 10mm and deep WMH ≥ 25mm. Lacunes were identified and counted in accordance with STRIVE (STandards for ReportIng Vascular changes on nEuroimaging) [25].

Aβ PET imaging acqusition

All patients underwent Aβ PET using a Discovery STe PET/CT scanner (GE Medical Systems, Milwaukee, WI) in a 3D scanning mode that examined 47 slices of 3.3 mm thickness spanning the entire brain. A 16-slice helical CT (140 KeV, 80 mA; 3.75 mm section width) was performed for attenuation correction. For ^{11}C-PiB PET, a 30-minute emission static PET scan was performed 60 minutes after injection into an antecubital vein as a bolus of a mean dose of 420 MBq. For ^{18}F-Florbetaben PET, a 20-minute emission PET scan with dynamic mode (consisting of 4 x 5 min frames) was performed 90 minutes after injection into an antecubital vein as a bolus of a mean dose of 381 MBq.

Aβ PET image preprocessing and interpretation

Both MR and PET images were co-registered with each other using the rigid-body transformation. The T1-weighted MR image of each subject was aligned with the MNI-152 template using a non-linear deformation including translation, rotation, scaling and shearing. After standard space registration, we divided grey matter into 116 regions using the

Automated Anatomical Labeling (AAL) atlas [29]. In order to compute standardized uptake value ratios (SUVR), every voxel intensity was normalized by the mean intensity of cerebellar gray matter which was regarded as reference region.

Global Aβ PET (PiB and florbetaben PET) retention ratios were assessed from the volume-weighted average SUVR of 28 bilateral cerebral cortical volume of interests (VOIs). We defined Aβ PET to be positive (Aβ+) when the global PiB SUVR was greater than 1.5 or when florbetaben PET was visually rated as 2 or 3 on the brain Aβ plaque load (BAPL) scoring system [30].

We also obtained regional cortical florbetaben SUVR, especially frontal (superior and middle frontal gyri, medial part of superior frontal gyrus, opercular part of inferior frontal gyrus, triangular part of inferior frontal gyrus, supplementary motor area, orbital part of superior, middle, and inferior orbital frontal gyri, rectus and olfactory cortex) and occipital (superior, middle, and inferior occipital gyri, cuneus, calcarine fissure, and lingual and fusiform gyri) SUVR, and calculated occipital/global and frontal/global SUVR ratio to demonstrate the distribution of florbetaben retention.

Neuropsychological tests

All patients underwent neuropsychological tests using the Seoul neuropsychological Screening Battery (SNSB) [27, 31], which consists of tests for attention, language, visuoconstructive function, verbal and visual memory, and frontal/executive function. We obtained retrospective and prospective neuropsychological test results from these patients, all of whom conducted the complete SNSB at least once at time of PET imaging. We used quantitatively scorable tests in the analysis; therefore,digit span forward (total: 9) and backward (total:8) scores for attention domain, the Boston Naming Test (BNT) scores (total: 60) for language domain, the Rey-Osterrieth Complex Figure Test (RCFT) copy score (total: 36) for visuospatial domain, the Seoul Verbal Learning Test (SVLT)/RCFT immediate score (total:36), delayed recall score (total: SVLT 12, RCFT 36) and recognition score (total: 24)

for memory domain, a phonemic and semantic Controlled Oral Word Association Test (COWAT) score (total: unlimited), a Stroop test color reading score (total: 120) for frontal/executive domain, Mini-mental state examination (MMSE, total:30), and clinical dementia rating - sum of boxes (CDR-SOB) were included in the analysis.

Statistical analyses

To investigate the pairwise differences in demographics and clinical characteristics (including frequency of apolipoprotein E *(APOE)* ε4 or ε2 carriers) between three groups (Aβ - CAA, Aβ+ CAA, and Aβ+ AD), student's t-tests and $\chi 2$ tests were used. In order to compare the frequency of *APOE* ε4 or ε2 carriers between three groups (Aβ - CAA, Aβ+ CAA, and Aβ+ AD) or between CAA patients with and without hemorrhagic imaging markers, we performed χ^2 tests. To compare pairwise differences in florbetaben retention distribution between three groups (Aβ - CAA, Aβ+ CAA, and Aβ+ AD), we performed analysis of covariance (ANCOVA) using age, gender and MMSE as covariates. Comparison of CAA and ischemic CSVD markers between Aβ- CAA and Aβ+ CAA were performed using wilcoxon ranksum tests for continuous variables (because of the skewed distribution of data) and χ^2 tests for dichotomous variables. Finally, to compare cognition (SNSB scores) between Aβ- and Aβ+ CAA, we also performed ANCOVA using age, gender and education as covariates.

To investigate the effect of Aβ positivity on longitudinal cognitive changes, linear mixed effect model was conducted. Fixed effects were Aβ positivity, time 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 two-tailed $P < 0.05$.

Results

Demographics and clinical characteristics of participants

Among 65 CAA patients, 43 (66.2 %) showed Aβ PET positivity (Aβ+ CAA). The frequency of Aβ PET positivity did not differ between two PET cohorts; 10 of 15 PiB PET (66.7%) and 33 of 50 florbetaben PET (66%) were Aβ+.

Aβ- CAA (75.3 ± 7.1) and Aβ+ CAA (74.4 ± 8.1) were older than Aβ+ AD without CAA imaging markers (67.1 ± 10.2) ($P < 0.001$ and $P < 0.001$). Aβ+ CAA (53.5 %) were more likely to have hypertension than Aβ+ AD (37.2 %) ($P = 0.016$), and Aβ- CAA (36.4%) were more likely to have diabetes than Aβ+ AD (14.0%) ($P = 0.002$). There were no differences in other demographics and clinical data across three groups (Table 1).

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

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

The frequency of ε2 carriers was higher in LICH+ (5/10, 50%) than in LICH- group (6/54, 11.1%) ($P = 0.003$) while the frequency of ε4 carriers was higher in LICH- (27/54, 50%) than in LICH+ group (1/10, 10 %) ($P = 0.019$) (Fig. 1b). Similarly, the frequency of ε2 carriers was significantly higher in cSS+ (6/17, 35.3%) than in cSS- group (5/47, 10.6%) ($P = 0.021$) but the frequency of ε2 carriers did not differ between cSS+ (35.3%) and cSS- group (46.8%) ($P = 0.412$) (Fig. 1C)

Aβ uptake pattern of CAA

When we compared Aβ PET uptake patterns between Aβ+ CAA (n=33, florbetaben only) and Aβ+ AD without CAA imaging markers (n=129, florbetabepn), occipital/global ratio was higher in Aβ+ CAA (0.97±0.06) than in Aβ+ AD (0.95±0.06) ($P = 0.045$), while frontal/global ratio did not differ between Aβ+ CAA (0.99±0.04) and Aβ+ AD (1±0.04) ($P =$

0.092) after adjusting for age, gender and MMSE scores (Fig. 2). Furthermore, when we compared Aβ PET uptake patterns between Aβ- CAA (n=17, florbetaben only) and Aβ+ AD, Aβ- CAA (1.04±0.04) showed a higher occipital/global ratio than Aβ+ AD (0.95±0.06) (P < 0.001) while Aβ- CAA (0.96±0.04) showed lower frontal/global ratio than Aβ+ AD (1±0.04) (P < 0.001) (Fig. 2).

CAA and ischemic CSVD markers by Aβ positivity

Compared with Aβ- CAA, Aβ+ CAA patients had more lobar CMBs (9 (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 (1 (0, 2) vs. 0 (0, 1), P = 0.029) and a higher frequency of severe WMH (45.5% vs. 20.9, P = 0.040) than Aβ+ CAA patients. The frequency of LICH did not differ between the two groups (P = 0.655) (Table 2). Detailed imaging and clinical characteristics of Aβ- CAA patients are shown in Table 3. Images from typical $A\beta^-$ CAA patients are shown in Fig. 3.

Distinct cognitive trajectory by Aβ positivity

Neuropsychological tests at time of PET study showed that Aβ+ CAA patients had significantly worse performances on 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 Aβ- CAA patients (Table 3).

A total of 42 of 65 patients underwent at least one follow-up visit for neuropsychological tests. The average number of neuropsychological tests follow-up 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, we report distinct clinical and MRI characteristics of patients with probable CAA according to Aβ positivity status on PET. Our main findings are that: first, a significant proportion of patients with probable CAA seen in a memory clinic are Aβ PET negative; second, Aβ positivity in CAA patients is associated with a distinct pattern of MRI small vessel disease biomarker expression; and third, Aβ positivity in CAA is associated with a worse cognitive trajectory. Taken together, our findings suggested that Aβ positivity has mechanistic and clinical relevance in CAA and might represent either advanced CAA or additional ADNC.

Our first major finding was that Aβ positivity was found in 67% of patients with probable CAA. Our finding is partially consistent with previous studies. Specifically, some studies suggested that about 60% [32] or 70 %[33] of probable CAA patients had Aβ PET positivity while other studies showed relatively high sensitivity (80% to 100%) of Aβ PET in probable CAA [4-6, 34] (Table 5). The discrepancy between previous studies and our study may be partly explained by smaller sample size of previous studies and different study participants (primarily patients with restricted multiple lobar CMBs from memory clinic in our sample compared with non-demented patients with only symptomatic LICH in those studies) as CAA with and without LICH might have different pathophysiologic mechanisms [35].

The reason that about 30% of patients who have characteristic CAA MRI markers were Aβ- on PET was important. There might be several explanations. First, current amyloid PET tracers cannot differentiate vascular Aβ from parenchymal Aβ. However, a previous study revealed that pathologically proven CAA cases had increased occipital/global ratio relative to AD cases [34]. In fact, in the present study, while Aβ- CAA had lower frontal/global ratio than Aβ+ AD, Aβ- CAA as well as Aβ+ CAA had higher occipital/global ratio than Aβ+ AD. Thus, increased occipital/global ratio in CAA patients regardless of Aβ positivity might reflect vascular Aβ uptake. Second, Aβ- CAA patients might have mild ADNC because Aβ PET has a limitation that it shows low accuracy in detecting mild ADNC [36]. Indeed, pathologic studies suggested that less than 50% of CAA patients meet

pathological criteria for AD [37, 38].

We found that frequency of *APOE* ε2 carriers was significantly higher in Aβ+ CAA or Aβ- CAA patients than in Aβ+ AD patients, although the frequency of *APOE* ε2 carriers did not differ between Aβ+ CAA and Aβ- CAA groups. Moreover, in CAA patients, the frequency of *APOE* ε2 carriers was significantly higher in a group with overt hemorrhagic markers such as cSS or LICH than in a group without overt hemorrhagic markers. Considering another finding that the frequency of *APOE* ε4, but not ε2, carriers was higher in Aβ+ CAA than in Aβ- CAA, *APOE* ε4 in CAA predict Aβ positivity while *APOE* ε2 in CAA is related to overt hemorrhagic markers of CAA. In fact, our suggestion might be supported by previous studies showing that *APOE* ε4 is related to deposition of Aβ burdens and *APOE* ε2 is related to breakdown of blood vessel walls [35, 39].

Our second finding was that Aβ+ CAA patients had more lobar CMBs and more frequent cSS than Aβ- CAA patients. A previous study showed that increasing lobar CMB count may increase the ability to identify CAA pathology [40]. In addition, cSS is known to be a key hemorrhagic marker of CAA [21] and a previous study demonstrated that cSS reflects an Aβ rather than ischemic etiology [41]. Our findings might therefore indicate that Aβ+ CAA have more CAA burdens than Aβ- CAA. In contrast, Aβ- CAA have more ischemic CSVD (or deep perforator arteriopathy) markers including lacunes and WMH than Aβ+ CAA. Previous studies from our group suggested that lobar CMBs might be attributed to CSVD as well as Aβ uptake [42, 43]. CSVD and Aβ uptake were 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 contribute to some CAA MRI markers (e.g. lobar CMBs) in Aβ- patients who meet criteria [21] for probable CAA based on MRI markers. For example, chronic hypertension may cause autoregulatory dysfunction of superficial perforating arteries of pial origin as well as deep perforating arteries [44], resulting in damage to the smooth muscle cells and development of CMBs in lobar areas. It is also possible that additional hypertensive CSVD burden might affect common pathways of CAA, including

endothelial dysfunction or inflammation, which could lead to synergistically increased vulnerability to hemorrhage with less severe CAA burden.

Our final major finding was that Aβ+ CAA patients showed more rapid decline in multiple cognitive domains, compared with Aβ- CAA patients. A previous study from our group showed that CAA hemorrhagic markers had an adverse influence on cognition [45]. In the current study, we build on these observations by showing that Aβ positivity is associated with cognitive decline in CAA patients. These findings are consistent with a previous autopsy study, which demonstrated that CAA and AD pathologies synergistically contribute to cognitive impairment [46], although relative contributions of mixed neuropathologies to cognitive impairment varied according to a recent study [47]. It is also possible that severe CAA burden alone contributed to worse cognitive decline as Aβ positivity might represent advanced CAA pathology even without parenchymal Aβ. A possible explanation is that CAA causes ischemic injury by decreased cerebral blow flow and hypoxia, which could increase vulnerability to neuronal death due to ADNC [47].

The strengths of our study include standardized Aβ PET, MRI and neuropsychological protocols. Although a sample size is not large, our study has a relatively large CAA cohort from a memory clinic compared with previous studies[4-6, 32-34] (Table 5). We are not aware of similar studies in this field that focus on probable CAA. However, some limitations need to be acknowledged. The main limitation of our study is the lack of pathological data. Thus, CAA markers were defined using only the modified Boston criteria for probable CAA. In addition, we did not utilize Aβ PET for diagnosis of CAA because current amyloid ligands for PET cannot differentiate vascular Aβ from parenchymal Aβ burdens. Therefore, it needs to be validated in pathological studies. Finally, we included patients who underwent Aβ PET scans using PiB or florbetaben, which might affect our findings. However, there was no difference in the frequency of Aβ positivity in CAA patients with PiB and florbetaben PET (10/15 (66.7%) vs. 33/50 (66%), $p = 0.962$). Also, a previous head-to-head study using two Aβ tracers suggested that two tracers binding were highly correlated with each other ($R^2 = 0.96$)[48]. Therefore, we expect that use of different Aβ

ligands does not much affect the classification of parenchymal Aβ positivity. However, further studies should be needed to investigate a difference in intensity or pattern of uptake between two ligands in CAA patients.

Conclusions

In conclusion, our findings suggest that Aβ+ CAA patients have a distinct neuroimaging signature suggesting advanced CAA or ADNC burdens, which lead to a worse cognitive status and trajectory. Our findings suggest that Aβ PET has mechanistic and clinical relevance in a clinically diagnosed probable CAA population; In particular, our findings demonstrate potential clinical utility of Aβ PET in predicting the prognosis of CAA patients who primarily visited a memory clinic. Aβ PET might also have value for the design, patient selection and interpretation in future CAA treatment trials.

Compliance with ethical standards

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Conflict of interest All authors have no conflicts of interest to disclose.

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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 1964 Helsinki declaration 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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Table 1

Clinical characteristics of Aβ- CAA, Aβ+ CAA, and Aβ+ AD

	Aβ- CAA (n = 22)	**Aβ+ CAA (n = 43)**	**Aβ+ AD (n = 129)**	*p* (Aβ- CAA vs. Aβ+ CAA)	*p* (Aβ+ CAA vs.Aβ+ AD)	*p* (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*	22.8 ± 5.0	19.7±6.3	16.9 ± 7.1	0.038	0.131	0.003

Abbreviation: Aβ, amyloid β; CAA, cerebral amyloid angiopathy; AD, Alzheimer's disease dementia; n, number; LICH, lobar intracerebral hemorrhage; MMSE, Mini mental status examination; N/A, non-applicable

Values are expressed as means ± standard deviations or numbers (%)

*p value after adjusting for age, gender and education

Table 2

Comparison of CAA and ischemic CSVD burden between Aβ- and Aβ+ CAA

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

Abbreviation: CAA, cerebral amyloid angiopathy; CSVD, cerebral small vessel disease; Aβ, amyloid β; n, number; LICH, lobar intracerebral hemorrhage; CMBs, cerebral microbleeds; cSS, cortical superficial siderosis; WMH, white matter hyperintensities

Values are expressed as median (interquartile range) or numbers (%)

Table 3

Detailed clinical and imaging characteristics of Aβ- CAA patients

No	PET ligand	Age	Sex	MMSE	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

Abbreviation: Aβ, amyloid β; CAA, cerebral amyloid angiopathy; PET, Positron emission tomography; PiB, Pittsburg B compound; MMSE, mini-mental state examination; LICH, lobar intracerebral hemorrhage; cSS, cortical superficial siderosis; CMBs, cerebral microbleeds; WMH, white matter hyperintensities

Table 4

Comparison of cognitive trajectory between Aβ- and Aβ+ CAA

	Baseline cognition			**Longitudinal cognitive change**		
	Aβ- CAA (n = 22)	**Aβ+ CAA (n = 43)**	***p****	**B**	**SE**	***p*†**
Attention						
Digit span forward (9)	5.0±1.2	5.4±1.3	0.344	-0.02	0.06	0.686
Digit span backward (8)	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

Abbreviation: Aβ, amyloid β; CAA, cerebral amyloid angiopathy; n, number; SE, standard error; BNT, Boston naming test; RCFT, Rey copy figure test; SVLT, Seoul Verbal Learning Test; COWAT, Controlled Oral Word Association Test; MMSE, mini-mental state examination; CDR-SOB, clinical deterioration rating-sum of boxes

Values are expressed as means ± standard deviations

* Difference between groups by analysis of covariance using age, gender, and education as covariates

† Effect of Aβ positivity on longitudinal cognitive changes obtained from linear mixed effect model

Table 5

Previous studies reporting Aβ positivity in probable CAA

Study	Number of patients	CAA diagnosis	Clinical manifestation	Aβ PET ligand	Determination of Aβ positivity	Aβ positivity (%)
Current study	n=65	MRI	Memory impairment (n=59) LICH (n=6)	PiB (n=15) florbetaben (n=50)	SUVR cutoff: 1.5 (PiB) Visual (florbetaben)	43/65 (66%)
Johnson et al[34], Ann Neurology, 2007	n=6	Pathology (n=4) MRI (n=2)	Seizure (n= 4), LICH (n=2)	PiB	Visual	6/6 (100%)
Ly et al, Neurology, 2010[6]	n=8	MRI	LICH	PiB	DVR cutoff: 1.44	7/8 (88%)
Gurol et al, Ann Neurology, 2013[32]	n=42	MRI + supporting pathology (n=14) MRI (n=28)	LICH (n=23), other (n=19) such as gait disorder or seizures	PiB	DVR cutoff: 1.22	29/42 (69%)
Baron et al, JCBFM, 2014[4]	n=11	MRI	LICH	PiB	DVR cutoff: 1.22	9/11 (82%)
Gurol et al, Neurology, 2016[5]	n=10	MRI	LICH	florbetapir	Visual	10/10 (100%)
Raposo et al. Neurology, 2017[33]	n=15	MRI + supporting pathology (n=2) MRI (n=13)	LICH	florbetapir	Visual	9/15 (60%)

Abbreviation: Aβ, amyloid β; CAA, cerebral amyloid angiopathy; PET, positron emission tomography; n, number; MRI, magnetic resonance imaging; LICH, lobar intracerebral hemorrhage; PiB, Pittsburg B compound; SUVR, standardized uptake value ratio; DVR, distribution volume ratio

Figure legends

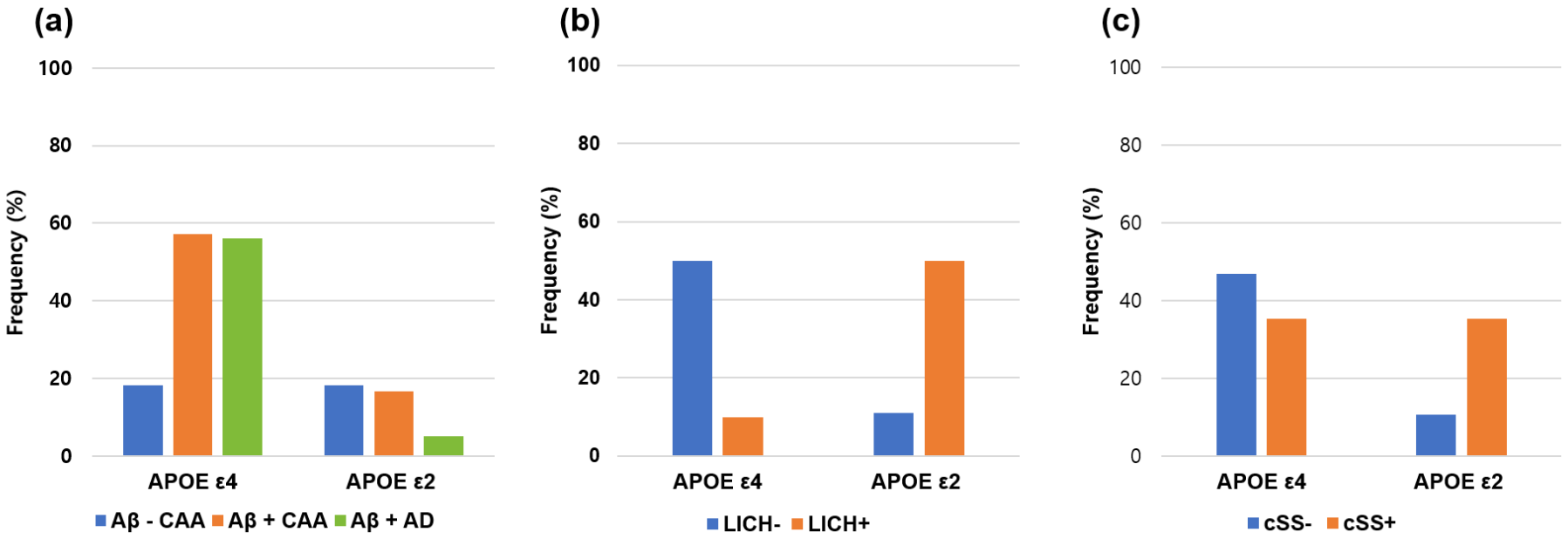

Fig. 1 The frequency of *APOE* ε4 or ε2 carriers by (a) Aβ positivity and the presence of CAA hemorrhagic markers such as (b) LICH and (c) cSS

Abbreviation: APOE, apolipoprotein E; CAA, cerebral amyloid angiopathy markers; Aβ, amyloid β; AD, Alzheimer's disease dementia; LICH, lobar intracerebral hemorrhage; cSS, cortical superficial siderosis

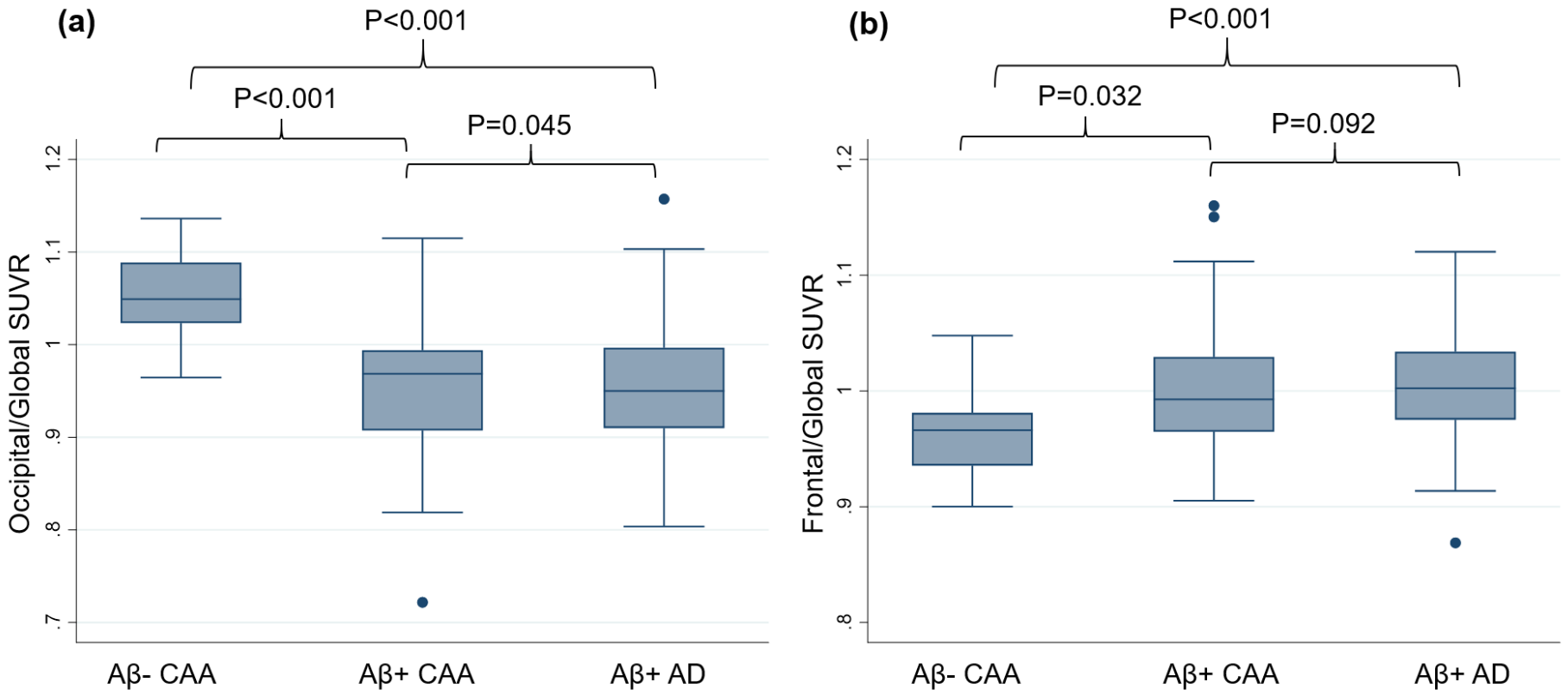

Fig. 2 (a) Occipital/global and (b) frontal/global PET SUVR ratio of Aβ- CAA, Aβ+ CAA and Aβ+ AD

Abbreviation: Aβ, amyloid β; PET, positron emission tomography; SUVR, standardized uptake value ratio; CAA, cerebral amyloid angiopathy; AD, Alzheimer's disease dementia

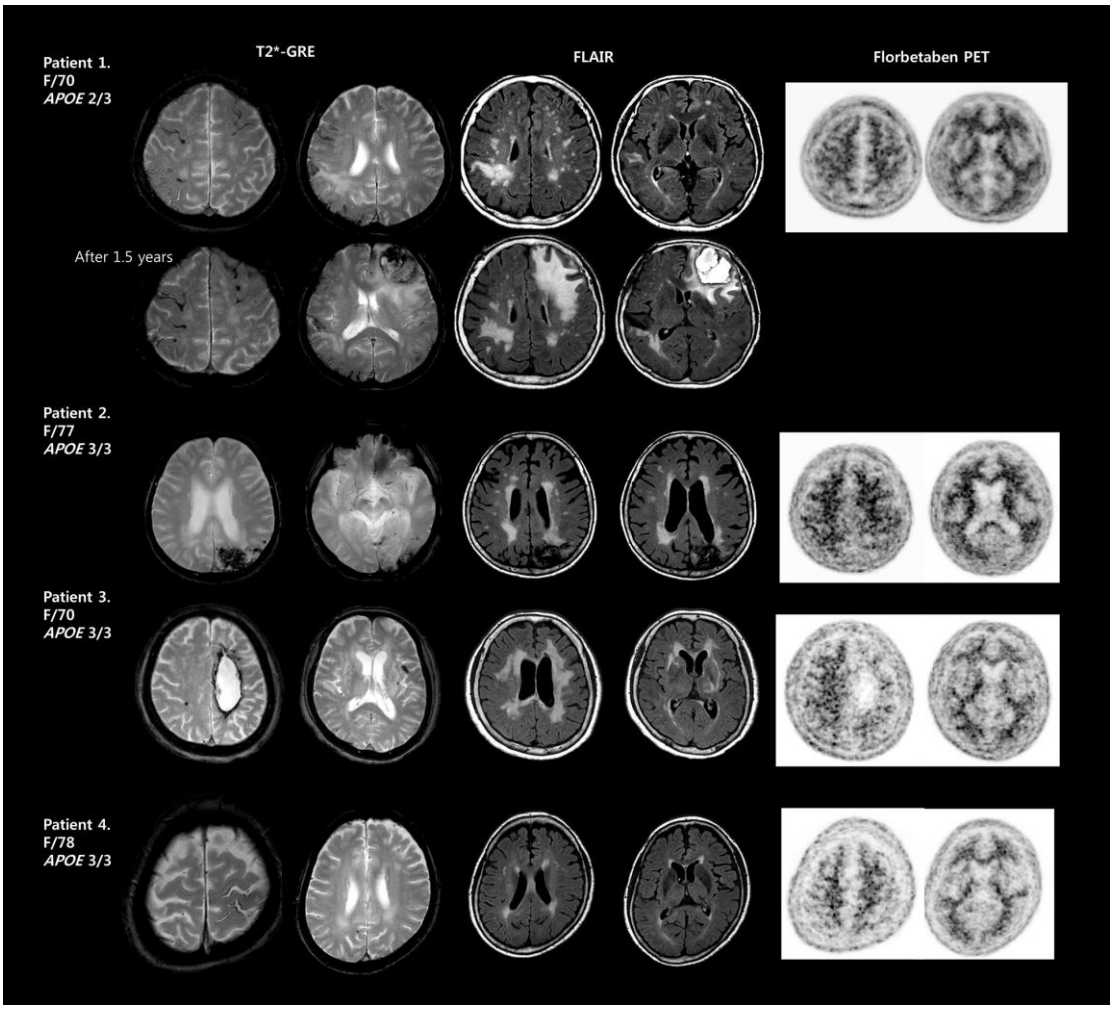

Fig. 3 Typical cases of Aβ- CAA patients

Abbreviation: Aβ, amyloid β; CAA, cerebral amyloid angiopathy; APOE, apolipoprotein E; GRE, gradient echo; FLAIR, Fluid-attenuated inversion recovery; PET, positron emission tomography

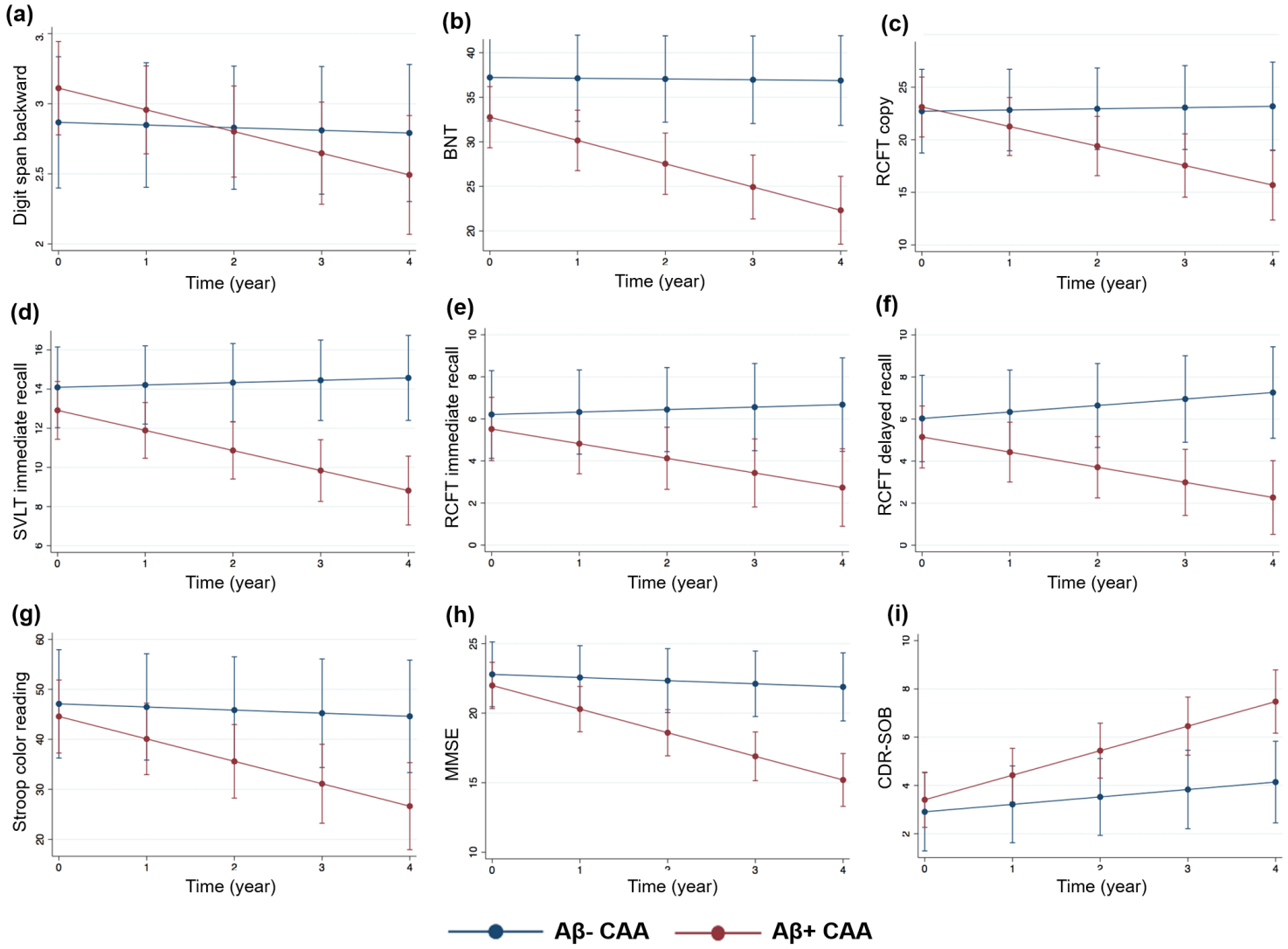
(a)
Digit span backward
Time (year)
(b)
BNT
Time (year)
(c)
RCFT copy
Time (year)
(d)
SVLT immediate recall
Time (year)
(e)
RCFT immediate recall
Time (year)
(f)
RCFT delayed recall
Time (year)
(g)
Stroop color reading
Time (year)
(h)
MMSE
Time (year)
(i)
CDR-SOB
Time (year)
Aβ- CAA
Aβ+ CAA

Fig. 4 Distinctive 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)).

Abbreviation: Aβ, amyloid β; CAA, cerebral amyloid angiopathy; 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 box

Y axis represents the predicted neuropsychological scores for each follow up year derived from the predicted model equation using a linear mixed effect model