Microangiopathy underlying mixed-location intracerebral hemorrhages/microbleeds

A PiB-PET study

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Abstract

Objective

To test the hypothesis that patients with concomitant lobar and deep intracerebral hemorrhages/microbleeds (mixed ICH) have predominantly hypertensive small vessel disease (HTN-SVD) rather than cerebral amyloid angiopathy (CAA), using in vivo amyloid imaging.

Methods

Eighty Asian patients with primary ICH without dementia were included in this cross-sectional study. All patients underwent brain MRI and ¹¹C-Pittsburgh compound B (PiB)-PET imaging. The mean cortical standardized uptake value ratio (SUVR) was calculated using cerebellum as reference. Forty-six patients (57.5%) had mixed ICH. Their demographic and clinical profile as well as amyloid deposition patterns were compared to those of 13 patients with CAA-ICH and 21 patients with strictly deep microbleeds and ICH (HTN-ICH).

Results

Patients with mixed ICH were younger (62.8 ± 11.7 vs 73.3 ± 11.9 years in CAA, $p = 0.006$) and showed a higher rate of hypertension than patients with CAA-ICH ($p < 0.001$). Patients with mixed ICH had lower PiB SUVR than patients with CAA ($1.06 [1.01–1.13]$ vs $1.43 [1.06–1.58]$, $p = 0.003$). In a multivariable logistic regression model, mixed ICH was associated with hypertension (odds ratio 8.9, 95% confidence interval 1.4–58.4, $p = 0.02$) and lower PiB SUVR (odds ratio 0.03, 95% confidence interval 0.001–0.87, $p = 0.04$) compared to CAA after adjustment for age. Compared to HTN-ICH, mixed ICH showed a similar mean age (62.8 ± 11.7 vs 60.1 ± 14.5 years in HTN-ICH) and risk factor profile (all $p > 0.1$). Furthermore, PiB SUVR did not differ between mixed ICH (values presented above) and HTN-ICH ($1.10 [1.00–1.16]$, $p = 0.45$).

Conclusions:

Patients with mixed ICH have much lower amyloid load than patients with CAA-ICH, while being similar to HTN-ICH. Overall, mixed ICH is probably caused by HTN-SVD, an important finding with clinical relevance.

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Glossary

BG = basal ganglia; **CAA** = cerebral amyloid angiopathy; **CMB** = cerebral microbleed; **CSO** = centrum semiovale; **cSS** = cortical superficial siderosis; **EPVS** = enlarged perivascular spaces; **HTN** = hypertension; **ICH** = intracerebral hemorrhage; **NTUH** = National Taiwan University Hospital; **PiB** = Pittsburgh compound B; **SUVr** = standardized uptake value ratio; **SVD** = small vessel disease; **SWI** = susceptibility weighted imaging; **WMH** = white matter hyperintensity.

The majority of spontaneous intracerebral hemorrhages (ICHs) result from the rupture of damaged small vessels of the brain.¹ The 2 main forms of cerebral small vessel disease (SVD) are (1) hypertensive small vessel disease (HTN-SVD) that affects mainly the deep perforators that supply the subcortical gray structures, and (2) cerebral amyloid angiopathy (CAA), which is characterized by the progressive accumulation of β -amyloid in the leptomeningeal and cortical vessels.² Patients with acute and chronic deep hemorrhages not accompanied by bleeds in lobar locations are likely to harbor HTN-SVD as the principal cause of the bleed (HTN-ICH).³ By contrast, patients who present with a lobar ICH and multiple strictly lobar bleeds, such as cerebral microbleeds (CMBs) or cortical superficial siderosis (cSS), are likely to have CAA according to the pathologically validated Boston criteria.⁴ In recent years, cSS has emerged as the strongest predictor of lobar ICH recurrences, highlighting the importance of its recognition for stroke risk stratification in patients with ICH.⁵

However, patients with ICH may have concomitant lobar and deep bleeds (mixed ICH), and the underlying microangiopathy is still controversial in these occurrences. A recent study showed that patients with mixed ICH could be considered as a relatively homogeneous group more similar to patients with HTN-ICH than CAA-related ICH (CAA-ICH).⁶ This is probably because they share a common microangiopathy with HTN-ICH, mainly driven by the presence of vascular risk factors. However, this hypothesis was not tested using neuropathologic analyses or techniques that could detect vascular amyloid deposition in vivo. It thus remains unclear whether mixed ICH is related to a severe vasculopathy similar to HTN-SVD or a combination of both CAA and HTN-SVD. PET imaging with ¹¹C-Pittsburgh compound B (PiB) provides a direct molecular imaging biomarker to identify cerebrovascular amyloid in vivo and has proven to be a valuable tool in detecting CAA in ICH populations.^{7,8} In this perspective, evaluation of patients with mixed ICH using PiB-PET imaging might help to elucidate their relationship with CAA.

To assess the type of microangiopathy underlying mixed ICH, we compared their cerebral PiB retention with both CAA-ICH and HTN-ICH. In addition, we tested the hypothesis that patients with mixed ICH who have cSS have a high PiB retention similar to patients with CAA-ICH, suggesting a common underlying microangiopathy.

Methods

Patient selection

For this cross-sectional study, we prospectively recruited patients who were older than 20 years with symptomatic primary ICH from the National Taiwan University Hospital (NTUH) between September 2014 and March 2017.⁹ We excluded patients with potential causes of secondary hemorrhage, including trauma, structural lesion, brain tumor, severe coagulopathy due to systemic disease or medication, or those who had ischemic stroke with hemorrhagic transformation. Patients who could not tolerate imaging studies because of poor cooperation, hemodynamic instability, and presence of a cardiac pacemaker, or those who had a history of dementia (Clinical Dementia Rating ≥ 1) were also excluded. A total of 82 patients fulfilling enrollment criteria agreed to participate in this study and received brain MRI and ¹¹C-PiB-PET scans (figure 1). Patients with a combination of mixed lobar and deep macrobleed/microbleed were defined as having mixed ICH (n = 43) (figure 2). Patients with ICH in the basal ganglia (BG), thalamus, or infratentorial region (deep locations) with or without deep CMBs but no lobar CMB were defined as having HTN-ICH (n = 21). Patients with lobar ICH(s) involving the cerebral cortex and underlying white matter with strictly lobar CMBs or cSS were defined as having CAA-ICH (n = 15).⁵ Cerebellar bleeds were excluded from the analyses as the type of underlying SVD is less clear for them.⁵ Two patients with a single lobar ICH without any additional lobar CMBs or cSS (possible CAA) were excluded because the possible CAA category has a lower accuracy (approximately 60%) to identify CAA (figure 1). As previously described, baseline clinical data collection was performed through comprehensive review of medical records.^{9,10} The following clinical variables were systemically recorded for each participant: age, sex, presence of hypertension, classes of antihypertensive medication, diabetes mellitus, hypercholesterolemia, history of ICH and ischemic stroke, and values of creatinine clearance (represented by estimated glomerular filtration rate). The presence of left ventricular hypertrophy was recorded by a cardiologist (C.-Y.H.) for patients who had a 12-lead ECG (n = 77).^{11,12}

Standard protocol approvals, registrations, and patient consents

This study was performed with the approval of and in accordance with the guidelines of the institutional review board (201404065MIND) in NTUH and with the written informed consent obtained from all participants or their family members.

Figure 1 Flowchart of patient enrollment and final study sample

Imaging acquisition

MRIs were obtained using a 3-tesla MRI scanner (Siemens Verio, TIM, or mMR; Siemens Medical Solutions, Malvern, PA). Susceptibility weighted imaging (SWI) acquisition was performed with a T2*-weighted gradient echo sequence with flip angle 15°, repetition time/echo time = 28/20 milliseconds, matrix number = 221 × 320, field of view = 23 cm, and slice thickness = 1.6 mm. SWI and minimum intensity projection images were acquired by in-line postprocessing of magnitude and phase images, and these postprocessed images were used for the evaluation of the imaging findings. Other conventional imaging protocols included T1-weighted, T2-weighted, and fluid-attenuated inversion recovery imaging. ¹¹C-PiB was manufactured and handled according to good manufacturing practice at the PET center, NTUH, Taipei, Taiwan (specificity activity: 39 ± 19 GBq/μmol [n = 144]). PET scanning was performed to evaluate brain amyloid deposition within 3 months after the MRI acquisition. Static

PET (Discovery ST; GE Healthcare, Waukesha, WI) was acquired in 3-dimensional mode for 30 minutes starting at 40 minutes after injection of 10 mCi ¹¹C-PiB. PET data were reconstructed with ordered set expectation maximization (5 iterations, 32 subsets, post filter 2.57) and were corrected for attenuation.

MRI analyses

All MRI scans were independently rated between 2 experienced readers (M.P. and H.-H.T.) to determine the diagnosis (CAA-ICH, HTN-ICH, or mixed ICH). If there was disagreement between the 2 readers, a consensus decision was made after discussion. The presence and number of CMBs, macrobleeds, and cSS were evaluated on axial SWI sequences as previously described.^{13,14} The CMB number was counted in lobar (i.e., the frontal, temporal, parietal, occipital, and insular cortices) and in deep regions (i.e., the brainstem, BG, thalamus, internal capsule, external capsule, corpus callosum,

Figure 2 Imaging features of mixed ICH

(A) Patient with deep ICH (thick arrow) and lobar CMB (arrowhead). Some deep CMBs are also seen (thin arrows). (B) Patient with lobar ICH (thick arrow) and deep CMB (arrowhead). (C) Patient with deep (thick arrows) and lobar ICHs (thin arrow). CMB = cerebral microbleed; ICH = intracerebral hemorrhage.

and deep periventricular white matter) for the purpose of this study.¹⁵ White matter hyperintensity (WMH) volume was calculated using an in-house semiautomated algorithm. After registering the T2 fluid-attenuated inversion recovery volume to the T1-weighted volume, a minimum intensity threshold of 1.5 SDs was applied, as previously published.¹⁶ The resulting clusters that fell on the white matter were considered, and their volume was calculated. All results were manually verified to ensure their accuracy and were consistently measured on the hemisphere not affected by ICH. Enlarged perivascular spaces (EPVS) were defined as previously described.¹⁷ The number of EPVS (one side of the brain with more severe involvement) was counted in BG and centrum semiovale (CSO) and were dichotomized as high (count >20) or low (count ≤20) degrees.¹⁸ Lacunes were evaluated in the supratentorial region and were defined as small fluid-filled cavities (between 3 mm and 15 mm) located in the deep gray or white matter according to Standards for Reporting Vascular Changes on Neuroimaging criteria.^{19,20} Each lacune was classified as lobar (when located in CSO, frontal, parietal, insular/subinsular, temporal, and occipital lobes) or deep (when located in thalamus, caudate, BG, and internal and external capsule) based on previously used topographic definitions.²⁰

PET analyses

Each PiB-PET image was realigned, resliced, and manually coregistered to a standardized T1-weighted magnetic resonance template using PMOD software (PMOD Technologies, Zurich, Switzerland). As we have previously described, the PET data were semiquantitatively analyzed and expressed as average mean standardized uptake value ratios (SUVRs) of regions of interest using cerebellar cortex as the reference region.⁹ Regions of interest on these spatially normalized images included the frontal, temporal, parietal, and occipital lobes using the Automated Anatomical Labeling atlas. Areas of macrobleeds were manually excluded for SUVR analyses.

Statistical analysis

Categorical variables are presented as percentages, and the continuous variables are presented as mean ± SD or median (interquartile range) based on their distribution. Baseline demographics, clinical, and neuroimaging variables between the different ICH groups (mixed ICH vs CAA-ICH; mixed ICH vs HTN-ICH) were compared using the independent-sample *t* test for continuous variables and Fisher exact test for categorical variables. Multivariable logistic regression models with a dichotomous dependent variable (mixed ICH vs CAA-ICH or mixed ICH vs HTN-ICH) was built to search for independent associations between the ICH classification and amyloid retention after adjustment for age and presence/absence of hypertension. To characterize patients with coexisting CAA in mixed-ICH patients, MRI SVD markers and amyloid retention (SUVR) were compared between patients with cSS(+) vs cSS(−), and were also adjusted for age. All statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY). All tests of significance were 2-tailed with a threshold for significance of *p* < 0.05.

Data availability

Any data not published within the article are available by request within the NTUH. Such dataset will be shared on request from a qualified investigator.

Results

The table shows a comparison of the baseline characteristics among patients with mixed ICH (*n* = 46), CAA-ICH (*n* = 13), and HTN-ICH (*n* = 21). In mixed ICH, 15 patients had primary lobar ICH with deep CMB(s), 9 patients had primary deep ICH with lobar CMB(s), and 22 patients had both lobar and deep ICHs with or without any CMBs (figures 1 and 2). Figure 3 shows the comparison of PiB SUVR in patients with mixed ICH, CAA-ICH, and HTN-ICH. Figure 4 provides representative MRI and PiB scans for ICH categories.

Comparisons between mixed ICH and CAA-ICH

Compared to patients with CAA-ICH, those with mixed ICH were younger (62.8 ± 11.7 vs 73.3 ± 11.9 years, *p* = 0.006) and showed a higher rate of hypertension (93.5% vs 53.8%, *p* < 0.001). Patients with mixed ICH also had higher WMH volume and higher percentage of high-degree EPVS-BG than patients with CAA-ICH (both *p* < 0.05) but they exhibited a similar rate of lobar and deep lacunes, cSS, and high-degree EPVS-CSO (all *p* > 0.1). PiB SUVR was lower in mixed ICH than in CAA-ICH (1.06 [1.01–1.13] vs 1.43 [1.06–1.58], *p* = 0.003) (figure 3). In a multivariable logistic regression model with a dichotomous dependent variable (CAA-ICH vs mixed ICH), mixed ICH was associated with hypertension (odds ratio 8.9, 95% confidence interval 1.4–58.4, *p* = 0.02) and lower PiB SUVR (odds ratio 0.03, 95% confidence interval 0.001–0.87, *p* = 0.04) after adjustment for age.

Comparisons between mixed ICH and HTN-ICH

Compared to patients with HTN-ICH, patients with mixed ICH had similar mean age (62.8 ± 11.7 vs 60.1 ± 14.5 years in HTN-ICH) and risk factor profile (all *p* > 0.1) but were more often associated with a history of ICH than were patients with HTN-ICH (19.6% vs 0%, *p* = 0.02). Mixed ICH was also associated with higher CMB counts, higher WMH volume, high-degree EPVS-BG, and lobar lacunes compared to HTN-ICH (all *p* < 0.05). PiB retention was not different between mixed ICH and HTN-ICH (1.06 [1.01–1.13] in mixed ICH vs 1.10 [1.00–1.16] in HTN-ICH, *p* = 0.45) (figure 3).

Mixed ICH and cSS

In mixed ICH, 4 of 46 patients (8.7%) had cSS. Patients in the mixed-ICH/cSS(+) group were older than those in the mixed-ICH/cSS(−) group (80.9 ± 9.5 vs 61.1 ± 10.4 years in cSS[−], *p* = 0.005). The PiB SUVR was higher in mixed ICH/cSS(+) compared to mixed ICH/cSS(−) in univariable analyses (1.46 [1.22–1.84] vs 1.06 [1.01–1.12] in cSS[−], *p* = 0.002), and the difference showed a strong tendency for significance after adjustment for age (*p* = 0.051). There was a tendency for higher lobar CMB count in mixed ICH/cSS(+) (28 [7–80] vs 6 [2–12], *p* = 0.06), but none of other MRI

Table Characteristics of patients with mixed ICH, CAA-ICH, and HTN-ICH

	Mixed ICH (n = 46)	CAA-ICH (n = 13)	<i>p</i> Value	HTN-ICH (n = 21)	<i>p</i> Value
Female, n (%)	11 (23.9)	8 (61.5)	0.010 ^a	8 (38.1)	0.232
Age, mean ± SD, y	62.8 ± 11.7	73.3 ± 11.9	0.006 ^a	60.1 ± 14.5	0.414
Hypertension, n (%)	43 (93.5)	7 (53.8)	<0.001 ^a	19 (90.5)	0.664
Diabetes, n (%)	10 (21.7)	2 (15.4)	0.615	4 (19.0)	0.802
Dyslipidemia, n (%)	9 (19.6)	0 (0)	0.083	6 (28.6)	0.412
eGFR, mean ± SD, mL/min/1.73 m ²	88.4 ± 29.2	83.1 ± 17.3	0.539	82.4 ± 19.0	0.394
Previous ischemic stroke, n (%)	11 (23.9)	0 (0)	0.051	3 (14.3)	0.369
Previous ICH, n (%)	9 (19.6)	4 (30.8)	0.389	0 (0)	0.029 ^a
LVH, n (%)	7 (15.2)	0 (0)	0.125	1 (4.8)	0.221
CMB, median (IQR)					
Lobar CMB count	7 (2–17)	3 (1–11)	0.974	None	<0.001 ^a
Deep CMB count	6 (2–13)	None	<0.001 ^a	0 (0–2)	<0.001 ^a
WMH volume, median (IQR), mL	23.0 (10.2–37.1)	19.7 (5.0–25.4)	0.033 ^a	3.8 (2.6–19.3)	<0.001 ^a
Cortical superficial siderosis, n (%)	4 (8.7)	2 (15.4)	0.605	0 (0)	0.231
Enlarged perivascular space (>20), n (%)					
Centrum semiovale	20 (46.5)	6 (46.2)	0.864	6 (28.6)	0.245
Basal ganglia	26 (60.5)	3 (21.1)	0.033 ^a	6 (28.6)	0.034 ^a
Lacune, n (%)					
Presence of lobar lacune	32 (69.6)	6 (46.2)	0.120	2 (9.5)	<0.001 ^a
Presence of deep lacune	17 (39.5)	2 (15.4)	0.142	6 (28.6)	0.502

Abbreviations: CAA = cerebral amyloid angiopathy; CMB = cerebral microbleed; eGFR = estimated glomerular filtration rate; HTN = hypertension; ICH = intracerebral hemorrhage; IQR = interquartile range; LVH = left ventricular hypertrophy; WMH = white matter hyperintensity.

The *p* values reported in the column next to CAA-ICH indicate comparisons between mixed and CAA-ICH patient groups. The *p* values reported in the column next to HTN-ICH indicate comparisons between mixed and HTN-ICH patient groups.

^a Significant.

markers were different between mixed ICH/cSS(+) and mixed ICH/cSS(–) (all *p* > 0.1). The PiB SUVR in mixed ICH/cSS(+) (1.42 [1.24–1.74]) was comparable to CAA-ICH (*p* = 0.365) and was higher than HTN-ICH (*p* = 0.004).

Discussion

Our study confirms in an Asian primary ICH population the hypothesis that mixed ICH is probably due to HTN-SVD rather than CAA. Using amyloid PET imaging, we found that the amyloid retention in mixed ICH was lower than in CAA-ICH and similar to HTN-ICH. Furthermore, patients with mixed ICH and cSS had similar amyloid deposition as patients with CAA-ICH, suggesting that its presence may be helpful to identify those patients with mixed ICH who likely harbor CAA either as dominant microangiopathy or a contributor to ICH/MBs. One of the hallmarks of the present study was the use of amyloid PET to evaluate the relationship between mixed ICH and CAA. This approach provided direct evidence that most cases of mixed ICH do not result from underlying CAA pathology.

Recently, mixed ICH (both macrobleed and microbleed) distribution has been reported to be a relatively common finding in Caucasian patients with ICH (approximately 20%), showing vascular risk factors, clinical, and neuroimaging profiles more similar to HTN-ICH than CAA-ICH.⁶ To validate and expand the association between mixed ICH and HTN-SVD in an Asian population, we analyzed 80 Asian patients with primary ICH, and our data on mixed ICH confirms the hypothesis that hypertension is a major player in the development of a severe arteriopathy of brain vessels that result in hemorrhages in both lobar and deep locations. In line with our findings, previous pathologic studies reported patients with lobar MBs without the pathologic finding of amyloid angiopathy, but with hypertensive arteriolosclerosis.²¹ Similar to our results, a recent observation that patients with negative amyloid imaging who had hypertensive subcortical vascular cognitive impairment (*n* = 92) showed both lobar and deep MBs, also suggesting that lobar MBs can be related to HTN-SVD rather than severe CAA.²² It is also important to remember that ICH and MBs can be caused by

Figure 3 The global amyloid retention in different ICH categories

coexisting different vascular pathologies, and review of multimodality advanced neuroimaging can contribute to better understanding of potential etiologies in these patients.

The understanding of mixed ICH is even more important in Asians, because Asian patients have higher prevalence of MBs and hypertensive burden.²³ Our study confirms this fact

Figure 4 MRI and PiB scan sets representative of different ICH categories

(A) CAA-ICH with right occipital hemorrhage (thick arrow) and superficial siderosis (thin arrows). PiB-PET shows increased cortical amyloid retention (SUVR = 1.57). (B) HTN-ICH with right basal ganglia ICH (thick arrow). PiB-PET shows absent cortical amyloid retention (SUVR = 1.01). (C) Mixed ICH with ICHs in bilateral basal ganglia and right occipital lobe (thick arrows). PiB-PET shows absent cortical amyloid retention (SUVR = 1.06). (D) Mixed ICH with ICH in the right parieto-occipital region (thick arrow) and a microbleed in the right thalamus (arrowhead). Superficial siderosis is also seen (thin arrow). PiB-PET shows mildly increased cortical amyloid retention (SUVR = 1.22). CAA = cerebral amyloid angiopathy; HTN = hypertension; ICH = intracerebral hemorrhage; PiB = Pittsburgh compound B; SUVR = standardized uptake value ratio.

showing that 57.5% in the ICH population who had MRIs were found to have mixed ICH, as opposed to 20% in a mostly Caucasian ICH population from Boston, MA. In our patients with mixed ICH, the presence of HTN-SVD is also supported by a higher prevalence of history of hypertension and BG EPVS, the latter an MRI signature of HTN-SVD,¹⁸ when compared to patients with CAA-ICH. It is of interest that CSO-EPVS severity, which has been previously associated with CAA, was similar between the mixed ICH and CAA-ICH groups in the current study. This finding could also support our hypothesis that a severe HTN-SVD involves not only deep but also subcortical areas in patients with mixed ICH. In contrast to the previous study in Caucasians showing more prevalent CSO-EPVS in patients with CAA-ICH than in those with mixed ICH, the severe involvement of CSO-EPVS was not a unique finding in Asian patients with CAA.⁶ Future studies should evaluate the previously reported relationship between severity of CSO-EPVS and amyloid retention in Asian populations.²⁴

Cortical superficial siderosis is a common finding in CAA: it is found in approximately 40% to 60% of patients depending on patient characteristics and MRI sequences.²⁵ This neuroimaging feature has now been incorporated in the modified Boston criteria, expanding the clinical and imaging spectrum of the disease.⁵ Even if limited by the small sample size and the age difference between these 2 groups, patients with mixed ICH and cSS showed a higher PiB retention value compared to those without cSS and their overall amyloid retention was similar to CAA-ICH. These differences essentially remained even after adjustment for age. Our results suggest a possible relationship between cSS and CAA also in patients with mixed ICH.

The differentiation of CAA and HTN-SVD is crucial in predicting risk of recurrent ICH, especially when antithrombotic decisions should be made. Patients who experience CAA-related ICH have 9% to 10% annual risk of ICH recurrence compared to approximately 2% risk per year in survivors of HTN-SVD.²⁶ Of interest, previous data have shown that among 90-day survivors, the ICH event recurrence rates were 5.1% per year for patients with mixed ICH, which is lower compared to patients with CAA-ICH and higher than in patients with HTN-ICH.⁶ This substantial risk of recurrence highlights the importance to identify mixed ICH, especially in situations that require balancing hemorrhagic and ischemic risks.²⁷ Despite the lack of longitudinal follow-up in the current study, the higher rate of previous ICH in our mixed-ICH group compared to the HTN-ICH group was also in line with these previous observations. Future longitudinal studies will have to evaluate the recurrence rate of mixed ICH in Asian populations.

Our study has some limitations. Although we prospectively recruited consecutive patients with ICH for PiB-PET and MRI, these patients may not be totally representative of the whole ICH population because of early mortality, frequently

seen in ICH. Second, part of cerebral amyloid deposition can be related to Alzheimer disease in addition to CAA.²⁸ We cannot exclude that the PiB-PET values we have reported in all 3 groups reflect not only vascular but also parenchymal amyloid deposition. To minimize the effect of Alzheimer-type pathology on our results, we did not include patients with even mild dementia. Using cognitively healthy patients, amyloid PET imaging was shown to have a 100% sensitivity and 89% specificity in a recent study, but a systematic review showed lower estimates when pooling data from heterogeneous cohorts.^{8,29} The diagnostic accuracy of probable CAA in the Boston criteria was 100% based on a pathologic validation study.⁴ Our current work shows the importance of accuracy of a clinicroadiologic CAA diagnosis, which is commonly used as gold standard for validation of amyloid PET ligands in this context. Even when a single deep MB is missed because of scan parameters or study design, patients with mixed ICH/MB can be misdiagnosed with probable CAA in the setting of lobar ICH/MBs, erroneously lowering the measures of performance of amyloid imaging. On a separate note, we cannot exclude the possibility that all ICH groups have a higher frequency of brain amyloid deposition than the healthy population. The influence of hypertensive SVD on brain amyloid deposition is an important question but beyond the scope of the current study. Finally, our analysis was limited by the small sample size, but this study has one of the largest numbers of amyloid PET imaging in mixed-ICH and HTN-ICH populations. Reproducing the findings in larger cohorts would indeed increase the confidence in the results.

Our study reproduced previous results on mixed ICH in an Asian cohort, while bringing the unique insight that patients with mixed ICH have much lower amyloid load than patients with CAA-ICH, but similar to those with HTN-ICH. Overall, mixed ICH is probably caused by HTN-SVD, an important finding with clinical relevance. Within the mixed-ICH group, patients with cSS showed higher PiB retention than those without, suggesting that they may harbor CAA as the dominant SVD type, supporting that cSS can be a relatively CAA-specific finding even in mixed ICH.

Author contributions

H.-H. Tsai: project concept and design, data collection, imaging analysis, data analysis, write-up. M. Pasi: project concept and design, data collection, imaging analysis, data analysis, write-up. L.-K. Tsai: project concept and design, data collection, data analysis, critical revisions. Y.-F. Chen: data collection, critical revisions. B.-C. Lee: project concept and design, data collection, critical revisions. S.-C. Tang: data collection, critical revisions. P. Fotiadis: data collection, critical revisions. C.-Y. Huang: data collection, critical revisions. R.-F. Yen: data collection, critical revisions. J.-S. Jeng: project concept and design, data collection, critical revisions. M. Edip Gurol: project concept and design, imaging analysis, data analysis, write-up.

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Disclosure

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