Cerebral amyloid angiopathy with and without hemorrhage

Evidence for different disease phenotypes

Andreas Charidimou, MD, PhD
Sergi Martinez-Ramirez, MD
Ashkan Shoamanesh, MD
Jamary Oliveira-Filho, MD
Matthew Frosch, PhD
Anastasia Vashkevich, BA
Alison Ayres, BA
Jonathan Rosand, MD, MSc
Mahmut Edip Gurol, MD
Steven M. Greenberg, MD, PhD
Anand Viswanathan, MD, PhD

Correspondence to
Dr. Charidimou:
acharidimou@mgh.harvard.edu

ABSTRACT

Objective: To gain insight into different cerebral amyloid angiopathy (CAA) phenotypes and mechanisms, we investigated cortical superficial siderosis (CSS), a new imaging marker of the disease, and its relation with *APOE* genotype in patients with pathologically proven CAA, who presented with and without intracerebral hemorrhage (ICH).

Methods: MRI scans of 105 patients with CAA pathologic confirmation and MRI were analyzed for CSS (focal, ≤ 3 sulci; disseminates, ≥ 4 sulci) and other imaging markers. We compared pathologic, imaging, and *APOE* genotype data between subjects with vs without ICH, and investigated associations between CSS and *APOE* genotype.

Results: Our cohort consisted of 54 patients with CAA with symptomatic lobar ICH and 51 without ICH. *APOE* genotype was available in 53 patients. More than 90% of pathology samples in both groups had neuritic plaques, whereas neurofibrillary tangles were more commonly present in the patients without ICH (87% vs 42%, $p < 0.0001$). There was a trend for patients with CAA with ICH to more commonly have *APOE* $\epsilon 2$ (48.7% vs 21.4%, $p = 0.075$), whereas patients without ICH were more likely to be *APOE* $\epsilon 4$ carriers (85.7% vs 53.9%, $p = 0.035$). Disseminated CSS was considerably commoner in patients with ICH (33.3% vs 5.9%, $p < 0.0001$). In logistic regression, disseminated CSS was associated with *APOE* $\epsilon 2$ (but not *APOE* $\epsilon 4$) (odds ratio 5.83; 95% confidence interval 1.49–22.82, $p = 0.011$).

Conclusions: This neuropathologically defined CAA cohort suggests that CSS and *APOE* $\epsilon 2$ are related to the hemorrhagic expression of the disease; *APOE* $\epsilon 4$ is enriched in nonhemorrhagic CAA. Our study emphasizes the concept of different CAA phenotypes, suggesting divergent pathophysiologic mechanisms. *Neurology*® 2015;84:1206–1212

GLOSSARY

AD = Alzheimer disease; **BG** = basal ganglia; **CAA** = cerebral amyloid angiopathy; **CI** = confidence interval; **CMB** = cerebral microbleed; **CSO** = centrum semiovale; **CSS** = cortical superficial siderosis; **EPVS** = enlarged perivascular spaces; **FLAIR** = fluid-attenuated inversion recovery; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **MGH** = Massachusetts General Hospital; **NFT** = neurofibrillary tangle; **OR** = odds ratio; **PVS** = perivascular spaces; **STRIVE** = Standards for Reporting Vascular Changes on Neuroimaging; **SWI** = susceptibility-weighted imaging; **T2*-GRE** = T2*-weighted gradient-recalled echo; **WMH** = white matter hyperintensities.

Sporadic cerebral amyloid angiopathy (CAA) is a small vessel disease that preferentially involves small cortical and leptomeningeal arteries due to progressive amyloid- β deposition in their walls.^{1,2} CAA occurs frequently in elderly people, and is a common and important cause of symptomatic lobar intracerebral hemorrhage (ICH).^{1–3} However, CAA might present without major lobar ICH, but instead with cognitive impairment (either chronic or rapidly progressive), or transient focal neurologic symptoms.⁴ CAA is almost invariably found in Alzheimer disease (AD), but in most cases is relatively mild.⁵

CAA is also associated with characteristic MRI biomarkers, including strictly lobar cerebral microbleeds (CMBs), cortical superficial siderosis (CSS),⁶ centrum semiovale (CSO) perivascular spaces (PVS), and white matter hyperintensities (WMH).^{1,7} These neuroimaging markers

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From the Department of Brain Repair and Rehabilitation (A.C.), UCL Institute of Neurology and The National Hospital for Neurology and Neurosurgery, London, UK; and the Hemorrhagic Stroke Research Program, Stroke Research Center, Department of Neurology (A.C., S.M.-R., A.S., J.O.-F., A. Vashkevich, A.A., J.R., M.E.G., S.M.G., A. Viswanathan), C.S. Kubik Laboratory for Neuropathology (M.F.), Division of Neurocritical Care and Emergency Neurology (J.R.), and Center for Human Genetic Research (J.R.), Massachusetts General Hospital, Harvard Medical School, Boston.

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probably reflect related but distinct aspects of CAA pathophysiology. CSS in particular is an interesting recently recognized form of CAA-related hemorrhage, which likely reflects repeated episodes of blood leaking into the subarachnoid space from brittle and fragile CAA-affected vessels. CSS has been shown to carry a high risk of future symptomatic lobar ICH.^{6,8,9}

Genetic factors, such as *APOE* genotype, are important in the pathophysiology of CAA.^{10,11} *APOE* $\epsilon 4$ appears to enhance vascular amyloid- β deposition in a dose-dependent fashion,¹² while *APOE* $\epsilon 2$ promotes vasculopathic changes that can lead to vessel rupture.¹³ To gain further insights into different CAA phenotypes and potential mechanisms,¹⁴ we investigated associations between neuroimaging markers of the disease, *APOE* genotype, and pathologic findings in patients with CAA presenting with and without symptomatic ICH. We hypothesized that (1) hemorrhagic markers of CAA (CSS and lobar CMBs) would be more strongly associated with *APOE* $\epsilon 2$ genotype; (2) hemorrhagic markers of disease severity in CAA (CSS and lobar CMBs) and *APOE* $\epsilon 2$ genotype would be more common in patients presenting with symptomatic ICH than in those presenting without ICH; and (3) neurofibrillary tangles (NFTs) will be more common in nonhemorrhagic compared to hemorrhagic CAA, whereas amyloid plaques might be invariably present in the 2 groups due to their close molecular pathogenesis.

METHODS Case selection and clinical data collection.

We included all eligible patients from Massachusetts General Hospital (MGH) identified retrospectively by a systematic keyword search of pathology reports and prospective clinical databases. Cases were defined as subjects with both pathology-proven CAA (from routinely collected brain biopsy, biopsy at hematoma evacuation, or autopsy) and adequate brain MRI sequences for the study. Data search covered patients seen at the hospital between 1997 and 2012. An additional overlapping search through established prospective datasets of patients with lobar hemorrhages (ICH or CMB) was performed to confirm identification of all potential eligible cases for the study. Among more than 3,200 retrieved cases, we initially included those having (1) a pathology report containing explicit information regarding CAA assessment and (2) available brain MRI sequences of adequate quality including T2-weighted, T2*-weighted gradient-recalled echo (T2*-GRE), or susceptibility-weighted imaging (SWI) and fluid-attenuated inversion recovery (FLAIR) sequences. After reviewing all neuroimaging, pathologic, and clinical data available, we excluded subjects with (1) small brain biopsy samples (greater diameter

<1 cm) or samples from clot evacuations not containing any assessable vessels; (2) autopsy studies not grading CAA; and (3) known alternative causes for lobar ICH. A total of 192 patients were eligible for analysis. Patients with no pathologic evidence of CAA ($n = 54$), clinical/imaging presentations not characteristic of CAA (3 cases with deep ICH and 9 with ischemic stroke at baseline), no T2 or T2*-GRE MRI ($n = 18$), T2/T2*-GRE MRI of insufficient quality ($n = 2$), and irretrievable sequences ($n = 1$) were excluded.

Demographic and clinical information was obtained from prospective databases and medical records using standardized data collection forms. Variables of interest were age, sex, history of hypertension, antithrombotic drug use, and clinical presentation at baseline. *APOE* genotype was determined in a subset of patients who provided blood samples and consented to genetic testing as previously described,¹⁵ and without knowledge of clinical or neuroimaging data.

The original clinical presentation of patients was ascertained from all available neuroimaging, pathologic, and clinical data, and was determined as either symptomatic lobar ICH confirmed on neuroimaging or nonhemorrhagic (including cognitive impairment, transient focal neurologic episodes, or other neurologic symptoms). Cases of inflammatory CAA were included in the analysis when an MRI outside the acute phase (≥ 1 month) was available. To investigate the stability of the non-ICH CAA clinical phenotypes, we extrapolated follow-up information from prospective databases and medical records on incident symptomatic ICH.

Standard protocol approvals, registrations, and patient consents. The study received ethical approval by the institutional review board of MGH.

Pathologic data collection. Morphologic assessment was performed in routine hematoxylin & eosin staining and the presence or absence and severity of vascular amyloid- β deposition was confirmed by immunohistochemical detection or Congo red staining. CAA presence and severity was assessed in all available vessels. Cases were considered positive for CAA when they had at least 1 leptomeningeal or cortical vessel with amyloid- β reported, providing enough information to reliably classify CAA severity using the Vonsattel grading system^{16,17} and were classified as mild (Vonsattel grade 1) or moderate to severe (Vonsattel grades 2–4). Where available from neuropathology reports, we also systematically extracted information on neuritic plaques and NFTs assessed in routinely immunostained sections for amyloid- β and phosphorylated tau and recorded as present or absent.

Neuroimaging data and analysis. Imaging for all patients included T2-weighted, FLAIR, T2*-GRE, or SWI. MRI were reviewed blinded to clinical, histopathologic, and genetic data by trained observers, according to Standards for Reporting Vascular Changes on Neuroimaging (STRIVE).¹⁸

The presence and number of CMBs was evaluated on axial T2*-GRE or SWI images according to current consensus criteria⁷ and categorized as lobar (i.e., cortical-subcortical), deep (i.e., basal ganglia [BG], thalami, brainstem), or cerebellar. The presence and number of macro ICHs (> 5 mm in diameter on T2*-GRE/SWI)¹⁹ was also noted.

CSS was defined as linear residues of chronic blood products in the superficial layers of the cerebral cortex showing a characteristic gyriform pattern of low signal on T2*-GRE/SWI; T1-weighted and FLAIR images were used for anatomical confirmation of the gyral location of these signal hypointensities.²⁰ The distribution and severity of CSS was classified as focal (restricted to ≤ 3 sulci) or disseminated (≥ 4 sulci).⁶ Areas of CSS were ≥ 2 unaffected sulci away from any

lobar ICH, at multiple axial levels; CSS contiguous or potentially anatomically connected with any lobar ICH were not included in these categories.²⁰

PVS were assessed in line with STRIVE definitions¹⁸ and rated on axial T2-weighted MRI, using a validated 4-point visual rating scale in the BG and CSO as previously described.^{21,22}

Periventricular and deep WMH were visually assessed on axial FLAIR images on the 4-point Fazekas rating scale for each, adding up to a total score on a 7-point scale.²³

Statistical analysis. Categorical variables were analyzed using Pearson χ^2 or Fisher exact test, and continuous variables by the 2-sample *t* test (for normal distributions) and Wilcoxon rank sum (for non-normal distributions). We compared demographic, genetic, pathologic, and imaging characteristics of CAA patients with and without ICH. Variables for *APOE* ϵ 2 and ϵ 4 were each coded as the number of alleles per participant (0, 1, or 2). Separate logistic regression models were used to assess the relationship between *APOE* genotype and CSS (presence or burden), as well as CMB count (linear regression). As sensitivity analyses, these models were predetermined to adjust for age and clinical presentation of CAA. Significance level was set at 0.05. Stata software (version 11.2, StataCorp., College Station, TX) was used. The manuscript was prepared with reference to the STROBE guidelines.²⁴

RESULTS Our final cohort consisted of 105 patients with pathologic evidence of CAA: 52 from autopsies, 22 from brain biopsies, and 31 with pathologic samples from hematoma evacuations. Fifty-four patients were admitted with symptomatic, spontaneous lobar ICH, while 51 patients were admitted without any symptomatic ICH. Patients without ICH presented with cognitive impairment ($n = 42$), transient focal neurologic episodes ($n = 3$), or a combination of other symptoms ($n = 6$, including altered mental status, or seizures, with findings consistent with inflammatory CAA). The median Clinical Dementia Rating score of patients without ICH and available data ($n = 27$) was 1 (interquartile range [IQR] 0.5–2).

Table 1 indicates the severity of CAA and the presence or absence of neuritic plaques and NFTs in the 2 groups. In general, mild (Vonsattel grade 1) or moderate to severe (Vonsattel grades 2–4) CAA were equally represented in the cohorts ($p > 0.2$ for both comparisons). There was no difference in the presence of vasculopathic changes (vessel-within-vessel appearance and vessel wall necrosis) in the 2 groups (29.6% vs 24%,

$p = 0.336$). Although the prevalence of neuritic plaques was similar in the 2 groups, neuritic plaques in isolation (i.e., with no tangles) were much more frequent in the ICH patients than in the patients with CAA without ICH (53% vs 13%, $p < 0.0001$). More than 90% of pathology samples in both groups had neuritic plaques, whereas NFTs were more commonly present in the patients without ICH (87% vs 42%, $p < 0.0001$). These associations remained consistent in logistic regression models controlling for age.

Comparisons of clinical and imaging characteristics between patients with CAA with vs without ICH are summarized in table 2. There was a trend for patients with CAA and ICH to more often have *APOE* ϵ 2 (48.7% vs 21.4%, $p = 0.075$), whereas patients without ICH were more likely to be carriers of *APOE* ϵ 4 (85.7% vs 53.9%, $p = 0.035$). The 2 groups were similar in imaging markers of cerebral small vessel disease, including WMH burden, high degree of CSO–enlarged PVS (EPVS) and BG-EPVS, and lobar CMB counts (table 2). However, the prevalence of CSS was higher in patients with ICH (51.9% vs 19.6%, $p = 0.001$), especially disseminated CSS (33.3% vs 5.9%, $p < 0.0001$). Representative MRIs are shown in the figure.

Among subjects with available genetic testing ($n = 53$), *APOE* ϵ 2 (but not ϵ 4) allele was overrepresented in cases with disseminated CSS, in the whole cohort ($p = 0.013$), and in the CAA subgroup with ICH (table 3). In logistic regression, disseminated CSS was associated with *APOE* ϵ 2 (odds ratio [OR] 5.83; 95% confidence interval [CI] 1.49–22.82, $p = 0.011$). These results remained consistent and of similar effect size in a sensitivity analysis adjusting for age and clinical presentation with symptomatic ICH (OR 4.97; 95% CI 1.11–22.21, $p = 0.036$) and in models further adjusting for the presence of vasculopathic changes on pathology. There was no association between CSS (burden or presence) and *APOE* ϵ 4. There was no association between CMB counts and *APOE* genotype.

Follow-up data were available in all patients presenting without ICH at baseline. During a median

Table 1 Cerebral amyloid angiopathy with and without intracerebral hemorrhage: Severity and associations with neuritic plaques and tangles^a

	CAA severity (Vonsattel grade)		Vasculopathic changes	NP alone	NT alone	NP and NT	No NP or NT
	Grade 1	Grade 2–4					
CAA with ICH, n (%)	7 (13)	47 (87)	16 (29.6)	19 (52.8)	0	15 (41.7)	3 (5.6)
CAA without ICH, n (%)	11 (21.6)	40 (78.4)	12 (24)	6 (13)	1 (2.2)	39 (84.8)	0

Abbreviations: CAA = cerebral amyloid angiopathy; ICH = intracerebral hemorrhage; NP = neuritic plaques; NT = neuritic tangles.

^aData on neuritic plaques and tangles were available in 36/54 patients with ICH and 46/51 patients without ICH.

Table 2 Comparison of clinical, imaging, and genetic characteristics between pathologically proven CAA with vs without ICH cohorts

	Whole CAA cohort (n = 105)	CAA with ICH (n = 54)	CAA without ICH (n = 51)	p Value
Age, y, mean (95% CI)	72.7 (71.1–74.2)	71.6 (69.4–73.7)	73.9 (71.5–76.2)	0.148
Female, n (%)	55 (52.4)	33 (63.1)	22 (43.1)	0.065
Hypertension, n (%)	66 (64.7)	30 (57.8)	36 (72)	0.131
Antithrombotic drug use, n (%)	40 (44.4)	15 (36.6)	25 (51)	0.170
APOE ϵ 2, n (%) ^a	22 (41.5)	19 (48.7)	3 (21.4)	0.075
APOE ϵ 4, n (%) ^a	33 (62.3)	21 (53.9)	12 (85.7)	0.035
Time from MRI to pathology, mo, median (IQR)	5.3 (0.3–31.4)	1.3 (0.2–11)	23.3 (1.4–50.7)	0.0002
Severe (Fazekas 5–6) WMH, n (%)	21 (20)	13 (24.1)	8 (15.7)	0.283
High-grade CSO-EPVS (>20), n (%)	57 (54.8)	29 (54.7)	28 (54.9)	0.985
High-grade BG-EPVS (>20), n (%)	25 (24)	11 (20.8)	14 (27.5)	0.424
Lobar CMB presence, n (%)	63 (60)	36 (66.7)	27 (52.9)	0.151
Lobar CMB count, median (IQR)	2 (0–27)	3 (0–23)	2 (0–31)	0.411
Presence of CSS, n (%)	38 (39.2)	28 (51.9)	10 (19.6)	0.001
Focal CSS, n (%)	17 (16.2)	10 (18.5)	7 (13.7)	0.505
Disseminated CSS, n (%)	21 (20)	18 (33.3)	3 (5.9)	<0.0001

Abbreviations: BG = basal ganglia; CAA = cerebral amyloid angiopathy; CI = confidence interval; CMB = cerebral microbleed; CSO = centrum semiovale; CSS = cortical superficial siderosis; EPVS = enlarged perivascular spaces; ICH = intracerebral hemorrhage; IQR = interquartile range; WMH = white matter hyperintensities.

^a APOE genotype was available in 53 CAA patients: 39 with ICH and 14 without ICH.

follow-up time of 3 years (IQR 1.1–5.6 years), 2 of 51 patients (3.9%, 95% CI 0.5–13.5%) experienced a symptomatic lobar ICH. One of these 2 patients had focal CSS at baseline MRI.

DISCUSSION The major findings from this study show that patients with CAA presenting with ICH are more likely to have CSS (particularly disseminated) and the APOE ϵ 2 genotype compared to CAA patients presenting without ICH. By contrast, APOE ϵ 4 is enriched in nonhemorrhagic CAA. In addition, there was an overall higher burden of NFT pathology in the non-hemorrhagic CAA group. APOE genotype might partly influence these relationships: APOE ϵ 2 was found to be associated with both symptomatic ICH clinical phenotype and disseminated CSS.

Our results provide new insights into the clinical and imaging spectrum of sporadic CAA, pointing to different disease phenotypes.¹⁴ While sporadic CAA is commonly found in the elderly, it is currently unknown why only a fraction of people with CAA pathology develop symptomatic disease, and why some present with symptomatic ICH, while others only develop cognitive impairment or other clinical symptoms. A previous comparative postmortem histopathologic study found that the brain features from patients with CAA that are most consistently related to ICH are severe degree of vascular amyloid deposition and the presence of fibrinoid necrosis (with or without microaneurysms).¹⁶ However, cases

of CAA with symptomatic ICH in our study had a fairly similar vascular amyloid burden and prevalence of CAA-associated vasculopathic changes compared to cases without ICH, although this could have been influenced by sampling bias. In addition, the 2 groups had a similar profile of putative neuroimaging biomarkers of CAA severity, including lobar CMBs, WMH, and CSO-EPVS. It thus seems likely that additional biological pathways from those involved in amyloid- β accumulation in cortical and leptomeningeal vessels play a role in determining clinical expression.

The most distinctive neuroimaging feature between the 2 groups was the much higher prevalence of disseminated CSS in patients with CAA and ICH. The prevalence of CSS in our histopathology-confirmed CAA-ICH group is in line with the reported prevalence in a previous imaging study of CAA-ICH.²⁰ In addition, the presence of CSS in the group without ICH (10%) is more in line with recent imaging studies evaluating CSS in a memory clinic setting and AD.²⁵

Although the pathophysiologic mechanisms underlying CSS in CAA are not yet fully understood, observational data suggest that CSS represents blood residues related to blood leaking episodes into the subarachnoid space from CAA-affected vessels.^{6,20,26} A secondary mechanism due to leakage or expansion of a lobar ICH into the subarachnoid space cannot be fully excluded; however, similar to other studies, CSS was mostly found distant from any ICH (and often in

(A) A 73-year-old woman with cerebral amyloid angiopathy (CAA)-intracerebral hemorrhage (ICH) and disseminated cortical superficial siderosis on T2*-weighted gradient-recalled echo (T2*-GRE) MRI (left). Her APOE genotype was $\epsilon 2/\epsilon 4$. (B) Multiple strictly lobar cerebral microbleeds (but no siderosis) on T2*-GRE MRI (left) in a 73-year-old woman with cognitive impairment and $\epsilon 4/\epsilon 4$ APOE genotype. Note the comparable white matter hyperintensities burden on fluid-attenuated inversion recovery MRI (middle panels) and centrum semiovale perivascular spaces on T2-weighted images (right panels) in the 2 patients. Both cases had severe CAA with vasculopathic changes (vessel-within-vessel appearance) on pathology.

the opposite hemisphere), and was also detected even in cases without any ICH. Two recent studies have identified CSS as a particular risk factor for subsequent ICH in CAA.^{8,9} In a cohort of 51 patients with CAA-related CSS and a median follow-up of 35.3 months, new intracranial hemorrhages were observed

in 24 patients (47.1%).⁸ A European multicenter study of patients with probable or possible CAA ($n = 118$) found that CSS was a significant predictor of time until ICH.⁹ The ICH risk at 4 years was 28.9% (95% CI 7.7–76.7%) and 74% (95% CI 44.1–95.7) for patients with focal and disseminated CSS, respectively, compared to 25% (95% CI 7.6–28.3%) for patients without siderosis (log-rank test: $p = 0.0031$).⁹ A small autopsy series of 6 CAA cases showed that multiple leptomeningeal arteries (and not parenchymal cortical vessels) can rupture into the subarachnoid space and the brain parenchyma, leading to large lobar hemorrhages.^{27,28} These observations might explain the relationship between disseminated CSS and CAA with ICH, as well as why patients with disseminated CSS have the highest risk of future ICH.⁹

Our study demonstrates that there might be APOE genotype-specific effects on the imaging and clinical expression of CAA-related disease. While APOE $\epsilon 4$ seems to be more associated with CAA without ICH, APOE $\epsilon 2$ is linked more strongly with bleeding and CSS. The APOE $\epsilon 2$ allele is reported to be associated with CAA-related lobar ICH, possibly due to the disease-related vasculopathic changes seen with this allele,^{13,29} and recently with CSS in a cohort

Table 3 APOE allele prevalences according to cortical superficial siderosis burden in patients with cerebral amyloid angiopathy with or without intracerebral hemorrhage

	CSS burden		
	No CSS	Focal CSS	Disseminated CSS
Whole CAA cohort, n (%)			
APOE $\epsilon 2$	7 (29.2)	3 (25)	12 (70.6)
APOE $\epsilon 4$	18 (75)	6 (50)	9 (52.9)
CAA with ICH, n (%)			
APOE $\epsilon 2$	7 (46.7)	1 (11.1)	11 (73.3)
APOE $\epsilon 4$	9 (60)	4 (44.4)	8 (53.3)
CAA without ICH, n (%)			
APOE $\epsilon 2$	0 (0)	2 (66.7)	1 (50)
APOE $\epsilon 4$	9 (100)	2 (66.7)	1 (50)

Abbreviations: CAA = cerebral amyloid angiopathy; CSS = cortical superficial siderosis; ICH = intracerebral hemorrhage.

of CAA defined by clinicoradiographic criteria.³⁰ *APOE* $\epsilon 4$ (presence and number) is also associated with sporadic CAA and ICH risk.^{31–33} Our study raised the interesting possibility that *APOE* $\epsilon 2$ influences pathways causing both CSS and ICH. After accounting for the presence of vasculopathic changes, the apparent relation of *APOE* $\epsilon 2$ to CSS was not reduced, suggesting that vascular amyloid load and how extensively the vessel wall architecture is disrupted is not the sole driving force underlying these pathways and hence, clinical phenotypes. However, any mechanistic links are clearly complex and need to be treated with caution, as *APOE* genotype alone might not be necessary or sufficient to drive these effects. It is important to note that links may differ according to the presence or absence of AD pathology, particularly for *APOE* $\epsilon 2$, which has been associated with a reduced risk of late-onset Alzheimer dementia.³¹ This observation is in line with the differential associations between neuritic plaques and NFTs in our patients with CAA with and without ICH. There is significant variation in the pathologic appearance of CAA and its influence on AD pathology,^{34,35} further highlighting the concept of different phenotypes of CAA. It is important to acknowledge though that the overrepresentation of NFTs among the patients with CAA without ICH might also reflect a bias issue, since by definition these cases presented with cognitive impairment, partly driven by NFT pathology.

Although the natural history of patients with symptomatic CAA mainly presenting with cognitive impairment (i.e., without ICH at baseline) has not been fully investigated, our data suggest that this CAA phenotype may have a lower risk of developing ICH compared to CAA cases with a history of ICH. It is important to note that patients with CAA without major ICH (microbleeds or CSS-only CAA) presenting to stroke services with symptoms other than cognitive impairment (e.g., transient focal neurologic episodes) might still be at significant risk of future bleeding.^{9,36,37} This topic requires further investigation in prospective studies.

Major strengths of the study include the large sample of patients with histopathologically confirmed CAA and available MRI sequences, the systematic evaluation of MRI scans for a range of neuroimaging biomarkers of small vessel disease, and the testing of a prespecified hypothesis. The main limitations, inherent to any clinical-pathology series in CAA, include (1) the difference in pathology sampling between autopsied brains and biopsies/hematomas; (2) the biases regarding which patients get biopsied or autopsied, which might be skewed towards end stage or advanced disease; and (3) potential selection bias due to the requirement for both pathology and MRI and the

unavailability of *APOE* genotype data in all patients. The differences in Alzheimer pathology between groups could potentially be explained by a longer duration of disease (taking time from MRI to pathology as a surrogate for disease duration) in patients with CAA without ICH or the different characteristics between the 2 groups (including *APOE* $\epsilon 4$ prevalence). Molecular imaging studies assessing amyloid and tau burden in vivo³⁸ may help resolve this question. Furthermore, the degree and evolution of cognitive impairment in patients with CAA without ICH (data limited in our study) could influence pathologic findings, especially NFTs and amyloid plaques presence. Finally, the cross-sectional design of the current study did not allow us to assess potential causality of the reported associations.

Results from this neuropathologic-defined cohort of patients with CAA with and without ICH provide evidence for distinct disease phenotypes, and suggest that CSS and *APOE* $\epsilon 2$ are related to the hemorrhagic expression of the disease. Our study emphasizes the widening spectrum of CAA, with clinical phenotypes reflecting different neuroimaging and genetic features, and suggests divergent pathophysiologic mechanisms. Although these findings require external validation in larger CAA cohorts, they may be relevant for future biomarker studies and disease-modifying CAA trials.

AUTHOR CONTRIBUTIONS

A. Charidimou: project concept and design, imaging and data analysis, write up. S. Martinez-Ramirez: data collection, imaging analysis, critical revisions. A. Shoamanesh: critical revisions. J. Oliveira-Filho: data collection, critical revisions. M. Frosch: data collection, critical revisions. Anastasia Vashkevich: data collection and management. Alison Ayres: data collection and management. J. Rosand: funding, data collection, critical revisions. Mahmut Edip Gurol: data collection. Steven M. Greenberg: funding, data collection, critical revisions. A. Viswanathan: project concept and design, write up, critical revisions.

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