Small vessel disease burden in cerebral amyloid angiopathy without symptomatic hemorrhage

Gregoire Boulouis, MD,
MSc
Andreas Charidimou,
MD, PhD
Michael J. Jessel, BS
Li Xiong, MD
Duangnapa
Roongpiboonsopit,
MD, MSc
Panagiotis Fotiadis, BS
Marco Pasi, MD
Alison Ayres, BA
M. Emily Merrill
Kristin M. Schwab, BA
Jonathan Rosand, MD,
MSc
M. Edip Gurol, MD, MSc
Steven M. Greenberg,
MD, PhD
Anand Viswanathan,
MD, PhD

Correspondence to
Dr. Boulouis:
gboulouis@mgh.harvard.edu

ABSTRACT

Objective: Cerebral amyloid angiopathy (CAA) is a common age-related small vessel disease (SVD). Patients without intracerebral hemorrhage (ICH) typically present with transient focal neurologic episodes (TFNEs) or cognitive symptoms. We sought to determine if SVD lesion burden differed between patients with CAA first presenting with TFNEs vs cognitive symptoms.

Methods: A total of 647 patients presenting either to a stroke department ($n = 205$) or an outpatient memory clinic ($n = 442$) were screened for eligibility. Patients meeting modified Boston criteria for probable CAA were included and markers of SVD were quantified, including cerebral microbleeds (CMBs), perivascular spaces, cortical superficial siderosis (cSS), and white matter hyperintensities (WMHs). Patients were classified according to presentation symptoms (TFNEs vs cognitive). Total CAA-SVD burden was assessed using a validated summary score. Individual neuroimaging markers and total SVD burden were compared between groups using univariable and multivariable models.

Results: There were 261 patients with probable CAA included. After adjustment for confounders, patients first seen for TFNEs ($n = 97$) demonstrated a higher prevalence of cSS ($p < 0.0001$), higher WMH volumes ($p = 0.03$), and a trend toward higher CMB counts ($p = 0.09$). The total SVD summary score was higher in patients seen for TFNEs (adjusted odds ratio per additional score point 1.46, 95% confidence interval 1.16–1.84, $p = 0.013$).

Conclusions: Patients with probable CAA without ICH first evaluated for TFNEs bear a higher burden of structural MRI SVD-related damage compared to those first seen for cognitive symptoms. This study sheds light on neuroimaging profile differences across clinical phenotypes of patients with CAA without ICH. *Neurology*® 2017;88:878–884

GLOSSARY

BG = basal ganglia; **CAA** = cerebral amyloid angiopathy; **CI** = confidence interval; **CMB** = cerebral microbleed; **CSO** = centrum semiovale; **cSS** = cortical superficial siderosis; **FLAIR** = fluid-attenuated inversion recovery; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **OR** = odds ratio; **PVS** = perivascular spaces; **SVD** = small vessel disease; **TE** = echo time; **TFNE** = transient focal neurologic episode; **WMH** = white matter hyperintensity.

Sporadic cerebral amyloid angiopathy (CAA) is characterized by progressive deposition of β -amyloid in the walls of cortical and leptomeningeal small arteries, resulting in vessel dysfunction and brain parenchymal injury. CAA is common in older individuals and, when severe, can lead to devastating consequences including intracerebral hemorrhage (ICH) and dementia.^{1,2} While definite diagnosis relies on pathology, clinical and neuroimaging criteria (the Boston criteria) can reliably identify CAA in older patients with lobar hemorrhage.^{3,4} More recently, an updated version of these criteria has demonstrated that the presence of ≥ 2 lobar cerebral microbleeds (CMBs) in patients without large hemorrhage is specific for moderate to severe CAA pathology presence in older individuals seen in a hospital setting.⁵

This group of patients with probable CAA without ICH presents an opportunity to characterize and investigate the consequences of CAA-related small vessel disease (SVD) damage

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From the Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital Stroke Research Center (G.B., A.C., M.J.J., L.X., D.R., P.F., M.P., A.A., K.M.S., J.R., M.E.G., S.M.G., A.V.), MIND Informatics, Massachusetts General Hospital Biomedical Informatics Core (M.E.M., J.R.), and Division of Neurocritical Care and Emergency Neurology, Massachusetts General Hospital (J.R.), Harvard Medical School, Boston, MA; Neuroradiology Department (G.B.), Université Paris Descartes, INSERM S894, Centre Hospitalier Sainte-Anne, Paris, France; and Faculty of Medicine (D.R.), Naresuan University, Phitsanulok, Thailand.

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unambiguously from the destructive effect of large intracerebral bleeds. Distinguishing neuroimaging phenotypes among distinct presentations of CAA would add insight in our understanding of the disease pathophysiology and various clinical expressions.

Characteristic neuroimaging biomarkers of SVD are seen in CAA, including strictly lobar CMBs, enlarged centrum semiovale perivascular spaces (CSO-PVS), cortical superficial siderosis (cSS), and white matter hyperintensities (WMHs).^{4,6–8} However, it remains unclear how the burden of each of these lesions or the combination of them is related to the clinical presentation of the disease.

The 2 main outpatient settings through which patients with CAA without ICH come to medical attention are stroke services (where patients are commonly seen for transient focal neurologic episodes [TFNEs])^{9,10} and memory clinics (where patients are evaluated for cognitive symptoms or subjective cognitive complaints).¹¹ It has been shown that patients with CAA first seen for acute neurologic symptoms often develop recurrent symptoms and are at high risk of developing subsequent ICH,^{12–14} while an association with higher risk of bleeding has not been described in memory clinic patients, who demonstrate cognitive decline over time.¹¹

These data raise the question as to whether the overall microvasculopathic severity influences the type of presentation in patients with CAA without ICH. Better defining these differences may be important to distinguish potential disease phenotypes that may have different prognoses in terms of risk for future ICH and cognitive decline.

We therefore sought to determine whether SVD lesional burden and overall SVD severity differed between patients with CAA first presenting for TFNEs compared to those with cognitive symptoms or complaints, in order to investigate the influence of neuroimaging phenotype on clinical presentation and get further insights into CAA expanding imaging spectrum.

METHODS Local institutional review board approval was obtained for prospective data collection and for retrospective medical record review and analysis.

Study population and group assignment. We analyzed prospectively collected data from consecutive patients meeting modified Boston criteria for probable CAA in the absence of ICH³

admitted to a tertiary care medical center, the Massachusetts General Hospital.

A total of 647 patients with CMBs presenting through the stroke service (and enrolled in an ongoing prospective longitudinal cohort, as described previously,^{14,15} $n = 205$) as well as patients presenting to the memory clinic (and associated with the Massachusetts Alzheimer's Disease Research Center longitudinal study,¹⁶ $n = 442$) were assessed for eligibility between January 1994 and November 2015. MRIs were acquired at the discretion of the clinical team.

Patients with strictly deep microbleeds, mixed (deep and lobar) microbleeds, CAA-related inflammation, or previous cranial irradiation were excluded from this analysis. Patients were then recategorized according to their presenting symptoms: TFNEs vs cognitive symptoms. We aimed at distinguishing TFNEs from TIAs to include patients who presented with symptoms related to CAA pathology. We therefore only included patients with recurrent, stereotyped, and typically spreading focal episodes, or patients with less typical presentations but presence of acute sulcal convexity subarachnoid hemorrhage.

Clinical data. Full medical history (including medication use) was obtained at presentation through in-person interview with patients or surrogates. Baseline neurologic examination was performed as part of standard of care and symptoms recorded prospectively.

Standard protocol approvals, registrations, and patient consents. This study was performed in accordance with the guidelines and with approval of the institutional review boards at our institution.

Neuroimaging acquisition and analysis. Images were obtained using a 1.5T MRI scanner and included whole brain T2-weighted, T2*-weighted gradient-recalled echo (echo time [TE] 750/50 ms, 5 mm slice thickness, 1 mm interslice gap), and fluid-attenuated inversion recovery (FLAIR; repetition time/TE 10,000/140 ms, inversion time 2,200 ms, 1 number of excitations, 5 mm slice thickness, 1 mm interslice gap). Neuroimaging markers of SVD severity were rated according to STRIVE consensus criteria.¹⁷

CMBs were defined on axial blood-sensitive MRI as punctate foci of hypointensity less than 10 mm in diameter, distinct from vascular flow voids and leptomeningeal hemosiderosis. Their presence and number were evaluated according to current consensus criteria¹⁸ and categorized according to the previously validated Microbleed Anatomical Rating Scale.¹⁹

Cortical superficial siderosis was defined as curvilinear hypointensities following the cortical surface, distinct from the vessels, and was assessed on axial blood-sensitive sequences according to a validated scale: absent, focal (restricted to ≤ 3 sulci), or disseminated (affecting 4 or more sulci).⁴

Enlarged PVS were assessed in line with STRIVE recommendations,¹⁷ rated on axial T2-weighted MRI, in the basal ganglia (BG) and CSO, using a validated 4-point visual rating scale (0 = no PVS, 1 = ≤ 10 PVS, 2 = 11–20 PVS, 3 = 21–40 PVS, and 4 = ≥ 40 PVS).²⁰ We prespecified a dichotomized classification of EPVS degree as high (score > 2) or low (score ≤ 2) in line with previous studies.^{21,22}

WMH volumes were calculated on axial FLAIR sequences with a previously described semiautomated planimetric method²³ using MRICron software.²⁴ Periventricular and deep WMH were also classified using the 0–3 Fazekas scale.²⁵ The anteroposterior ratio of WMH lesion distribution was computed using a validated approach.²⁶ As previously shown²⁶ using this method, a lower score reflects more posteriorly distributed WMH lesions.

Global atrophy was rated according to axial brain T1-weighted imaging according to a previously validated 0–3

scale,²⁷ where 3 represents severe atrophy. We dichotomized patients into those with no or mild atrophy (0–1) and those with moderate to severe atrophy (2–3).

Lacunae were defined according to STRIVE criteria⁹ as round or ovoid fluid-filled cavities of between 3 and 15 mm in diameter and were classified as deep, subcortical, or pontine.

We subsequently constructed the total SVD summary score using the principal MRI markers of CAA (lobar CMBs, WMH according to Fazekas,²⁵ CSO-PVS, and cSS) as previously validated.²³ This yielded an ordinal score of total SVD burden (ranging from 0 to 6).

MRI analyses were performed and recorded blinded to all clinical information by 2 trained raters (A.C., G.B.) and consensus was obtained for each case.

As a complementary analysis, we compared the SVD burden of included patients to a cohort of 229 patients with lobar ICH meeting Boston criteria for probable CAA (described fully elsewhere).²⁸

Statistics. Patients were compared in univariate analyses, 2 independent sample *t* tests, Wilcoxon rank sum, Pearson χ^2 , and Fisher exact tests as appropriate.

Multivariable logistic regression analyses were performed to look for independent associations between each of the markers of small vessel disease severity (CMBs, cSS, WMH volumes, lacunes, enlarged PVS, and atrophy) with symptoms at presentation (neurologic vs cognitive), correcting for potential confounders. Stepwise backward variable elimination was subsequently used to generate a minimally adjusted model ($p > 0.05$).

A multivariable ordinal logistic regression model was then used to look for independent associations between the total SVD summary score²³ and symptoms at presentation (neurologic vs cognitive) adjusting for age, sex, hypertension, diabetes mellitus, and hypercholesterolemia, predefined as the core vascular risk factors.

All tests of significance were 2-tailed. Statistical analyses were performed with JMP Pro 12 (SAS Institute Inc., Cary, NC) software; a *p* value of <0.05 was considered statistically significant.

This article was prepared in accordance with Strengthening the Reporting of Observational Studies in Epidemiology guidelines.²⁹

RESULTS A total of 261 patients with probable CAA were included in this analysis. Of these, 93 (35%) were first evaluated for TFNEs and 168 (65%) for cognitive symptoms (figure 1).

Patients were comparable in terms of vascular risk factors, age at presentation, and sex. Patients seen for TFNEs were more likely to have atrial fibrillation or a history of transient neurologic symptoms (including TIAs), compared to patients with cognitive symptoms (19% vs 11%, $p = 0.09$ and 25% vs 5%, $p < 0.001$, respectively). Baseline characteristics are displayed in table 1.

Patients first encountered for TFNEs demonstrated a higher prevalence of individual markers of SVD than those first seen for cognitive symptoms (table 2). Their baseline MRI notably demonstrated a higher prevalence of cSS ($p < 0.0001$), higher WMH volumes ($p = 0.03$), and marginally higher lobar microbleed counts ($p = 0.09$). The rate of lacunes and severe CSO or BG enlarged PVS were comparable.

In a multivariable logistic regression model after adjustment for age and sex, the presence of cSS was independently associated with higher odds of presenting for acute neurologic symptoms (odds ratio [OR] 2.3, 95% confidence interval [CI] 1.5–4.9, $p = 0.003$). Larger WMH volumes (per additional 10 mL, OR 1.1, 95% CI 1–1.24, $p = 0.07$) as well as

Figure 1 Flowchart of patient selection

Other refers to patients excluded for being scanned for unrelated events or as part of a systematic and nonrelated protocol for a different disease (e.g., cancer extension, postcranial irradiation). Mixed refers to patients with lobar and deep cerebral microbleeds (CMBs). CAA = cerebral amyloid angiopathy; ICH = intracerebral hemorrhage.

Table 1 Comparison of demographic and imaging characteristics between presenting symptoms

Variable ^a	Total (n = 261)	Presenting symptoms		
		Cognitive symptoms (n = 168)	TFNE (n = 93)	p Value
Age, y	75.8 ± 8.6	75.5 ± 8	74.6 ± 9.7	0.46
Female	104 (40)	64 (38.1)	40 (43)	0.51
Medical history				
Dyslipidemia	147 (56)	92 (54.8)	55 (59.1)	0.52
Hypertension	171 (66)	108 (64.3)	63 (67.7)	0.59
Atrial fibrillation	37 (14)	19 (11.3)	18 (19.4)	0.09
Diabetes mellitus	34 (13)	23 (13.7)	11 (11.8)	0.71
History of TIA	33 (12.6)	9 (5.4)	24 (25.8)	<0.001 ^b
History of ischemic stroke	28 (11)	15 (8.9)	13 (14)	0.22
Medications				
Warfarin	29 (11)	20 (11.9)	9 (9.7)	0.68
Aspirin	100 (38.3)	67 (39.9)	33 (35.5)	0.51
Statin	126 (48)	81 (48.2)	45 (48.4)	1

Abbreviation: TFNE = transient focal neurologic episodes.

^aVariables are displayed as absolute number (% of total) or mean ± SD.

^bSignificant.

higher counts of CMBs (per additional 5 CMBs, OR 1.1, 95% CI 1–1.06, $p = 0.09$) demonstrated strong trends toward significance (table 3).

Patients first presenting with TFNEs also had a higher total SVD summary score (mean ± SD; 3.5 ± 1.3 vs 2.9 ± 1.2 ; $p < 0.001$) and this remained significant in an ordinal logistic regression, adjusting for age vascular risk factors (adjusted OR per

Table 2 Univariable comparisons of small vessel disease (SVD) severity markers according to presentation

Variable	Total (n = 261)	Cognitive symptoms (n = 168)	TFNE (n = 93)	p Value
Microbleed counts	6 (3–17.5)	5 (3–13)	7 (3–30)	0.09 ^a
WMH volume, mL	20 (8–38)	17 (5–34)	22 (13–42)	0.03 ^a
Lacunes	79 (30)	47 (28)	32 (34)	0.23
cSS (focal or disseminated)	88 (34)	45 (27)	43 (47)	<0.0001 ^a
Severe CSO-PVS	142 (54)	90 (53)	52 (56)	0.79
Severe BG-PVS	18 (7)	15 (9)	3 (3)	0.12
Moderate to severe atrophy	181 (69)	117 (69)	64 (72.3)	0.35
WMH antero-posterior ratio	12 (4–21)	13 (5–23)	11 (4–18)	0.054 ^a
Total SVD score	3.1 ± 1.2	2.9 ± 1.2	3.5 ± 1.3	0.001 ^a

Abbreviations: BG = basal ganglia; CSO = centrum semiovale; cSS = cortical superficial siderosis; PVS = perivascular spaces; TFNE = transient focal neurologic episodes; WMH = white matter hyperintensity.

Variables are displayed as absolute number (% of total), median (IQR), or mean ± SD.

^aSignificant.

additional score point 1.46, 95% CI 1.16–1.84, $p = 0.0013$) (table 4).

Patients first presenting with TFNEs also demonstrated a more posterior distribution of WMH lesions compared to those presenting with cognitive symptoms (median 11 [interquartile range (IQR) 4–18] vs 13 [IQR 5–23], $p = 0.054$, lower values indicating more posterior distribution of WMH).

Patients with CAA without ICH demonstrated a higher total SVD burden than a cohort of 229 patients meeting Boston criteria for probable CAA in the context of an ICH (mean [IQR] total SVD score in ICH = 2 [1–3] vs 3 [2–4] in patients with cognitive symptoms and 3 [3–4] in those with TFNEs, both $p < 0.001$).²⁸ This was almost entirely driven by a higher number of CMBs (1 [1–1] in ICH patients vs 5 [3–13] in patients with cognitive symptoms and 7 [3–30] in those with TFNEs, $p = 0.001$ and $p < 0.001$; see tables e-1 and e-2 and figure e-1 at Neurology.org for details).

DISCUSSION We demonstrated that patients with probable CAA without symptomatic ICH first presenting with TFNEs bore a higher burden of quantifiable SVD-related damage compared to patients with probable CAA first evaluated for cognitive symptoms.

Our results suggest that the first clinical expression of CAA in patients without ICH corresponds to and predicts different degree of underlying SVD pathology. While the aim of this work was to identify disease phenotypes (for prognostic studies investigating the risk of future ICH and incident dementia in patients with CAA), our results may help to explore the main pathologic processes responsible for distinct clinical expression of CAA.

Patients first seen with TFNEs notably presented with a significantly higher burden of cSS and had a higher total SVD summary score. This suggests that these patients harbor more symptomatogenic hemorrhagic manifestation of the disease and more severe SVD pathology than those patients first seen for cognitive symptoms.

Recently, cSS has emerged as a key determinant of recurrent ICH risk in patients with CAA first presenting with hemorrhage^{30,31} and appears to be a strong neuroimaging indicator of CAA-related activity associated with a higher risk of bleeding.³² Being associated with transient focal neurologic episodes and linked to the occurrence of convexity subarachnoid bleeds,³³ the higher prevalence of cSS in patients seen for TFNEs is somewhat expected.³⁴ Nonetheless, this finding supports the hypothesis that clinical expression of the disease is related to the type of underlying SVD changes on MRI. It is possible that those first seen for TFNEs have a more focally active hemorrhagic disease phenotype. By contrast, those seen for

Table 3 Multivariable logistic regression model of small vessel disease (SVD) severity markers for presenting with transient focal neurologic episodes vs cognitive symptoms

Variable	Odds ratio	95% CI	p Value
Age	0.97	0.93-1	0.051
Female sex	0.9	0.51-1.59	0.73
MRI markers of SVD severity			
Microbleed burden (per additional 5 CMBs)	1.09	1-1.06	0.09
WMH volume (per additional 10 mL)	1.1	1-1.24	0.07
cSS presence	2.3	1.5-4.9	0.003

Abbreviations: CI = confidence interval; CMB = cerebral microbleed; cSS = cortical superficial siderosis; WMH = white matter hyperintensity. All variables included in the model are presented.

cognitive symptoms may have a more progressive silent expression of the disease, or may be more frequently associated with neurodegenerative processes including Alzheimer disease.³⁵

Interestingly, patients first seen for TFNEs demonstrated a significantly more posterior distribution of WMH lesions. The posterior distribution of WMH lesions has been described in patients with sporadic CAA without ICH²⁶ but the influence of CAA subtype on WMH distribution had not been previously defined. The differences observed in this study strengthen the hypothesis that these subgroups may indeed represent different disease phenotypes: one being more acutely symptomatogenic leading to first presentation as TFNEs and the other more progressive and participating in/lowering the threshold for cognitive impairment.

The higher burden of SVD in the patients first seen for TFNEs conversely suggests that these patients come to medical attention at a later stage of the disease. Focal symptoms would then be an indicator of advanced CAA disease in this population of patients without cognitive decline or subjective cognitive complaints. It may be that in patients with cognitive complaints, less severe CAA pathology is needed for clinical manifestations because of relative

burden of particular SVD pathologies (e.g., microbleeds vs WMH), because of the topographic location of the SVD pathology,³⁶ or because of the synergistic effect with concomitant neurodegenerative pathology leading to clinical manifestations despite less severe SVD pathology.³⁷

Our findings from the subgroup of patients with cognitive complaints coupled with recent findings from a population-based cohort³⁸ raise the question as to whether neuroimaging could be useful in identifying CAA prior to progression to more severe clinical manifestations. Results from this population-based study suggest that cognitively normal individuals with >4 CAA-related CMBs on MRI scan are at elevated risk to develop cognitive decline. Future studies investigating the risk of cognitive decline and dementia in patients with CAA without ICH are therefore needed.

In our study, the severity of global atrophy was comparable in patients with CAA with TFNEs and cognitive symptoms whereas WMH burden was higher in patients presenting with acute neurologic manifestations. Cortical atrophy has been shown to be a marker of both neurodegeneration³⁹ and SVD-related damage.^{17,40,41} It could be hypothesized that SVD-related damage in patients seen for acute neurologic symptoms more strongly influences cortical atrophy^{41,42} whereas in patients with CAA presenting with cognitive symptoms both SVD pathology and neurodegenerative processes drive atrophy.^{35,43,44} Quantitative cortical atrophy measures coupled with in vivo molecular imaging of amyloid and tau deposition may shed further insight into this possibility.

It has previously been shown that patients with CAA free of ICH (microbleeds only) bear a different neuroimaging profile than those with intracerebral hemorrhage at baseline,¹⁴ and previous work has demonstrated that patients with CAA with ICH differ from microbleeds-only patients.^{44,45} Therefore, in this study, we chose to focus our analysis on the neuroimaging burden of patients free of ICH, further expanding the spectrum of CAA clinical imaging expression in this important and distinct subgroup. Nonetheless, in an ancillary analysis, we found that patients with probable CAA with ICH have lower total SVD burden compared to those without ICH, almost entirely driven by a lower number of CMBs, in line with previous reports.¹⁴

Our study has limitations. First, without pathologic confirmation, we were unable to assess the real proportion of our patients actually having true underlying CAA pathology. While recent evidence has shown that the neuroimaging-based Boston criteria used in this study are highly predictive of moderate to severe CAA even in outpatient memory settings,⁵ those modified criteria have not yet been externally

Table 4 Ordinal logistic regression for total small vessel disease burden score

	Odds ratio	95% CI	p Value
TFNE vs cognitive symptoms	1.46	1.16-1.84	0.0013
Age	1.03	1-1.05	0.0514
Female sex	0.9	0.72-1.13	0.37
Dyslipidemia	0.93	0.74-1.17	0.55
Hypertension	0.9	0.7-1.16	0.39
Diabetes mellitus	0.97	0.69-1.35	0.84

Abbreviations: CI = confidence interval; TFNE = transient focal neurological episodes. All variables in the model displayed.

validated.⁵ It has been shown that the Boston criteria performed less accurately in population-based studies as compared to those seen in a hospital setting due to low prevalence of the disease in the general population.^{5,46} It may be possible that CAA pathology is more truly prevalent in patients with TFNEs compared to patients first seen for cognitive symptoms, thus leading to a potential bias. It is also possible that a portion of patients with TFNEs also experienced subjective cognitive symptoms that we were unable to assess given the retrospective design of this study.

Although there are criteria to distinguish TFNE from TIA,¹⁰ it may not be possible to fully discriminate TIA patients with incidentally discovered CAA from those with TFNE symptoms due to CAA pathology.¹⁰ We aimed at minimizing this potential bias by including patients with typical TFNE symptoms or acute, nonaneurysmal, convexity subarachnoid hemorrhage.

We also acknowledge that the use of a visual scale to assess cortical atrophy is known to be less accurate and reproducible than quantitative methods. Finally, the generalizability of our findings is likely to be influenced by our screening method, at a single academic center with a potential for selection bias. Therefore, replication in an independent cohort is mandated. Future works focusing on longitudinal follow-up, cognitive profiling, and advanced neuroimaging characterization in this subcategory of patients with CAA without ICH are needed.

Patients with probable CAA without ICH first evaluated for neurologic symptoms have a higher burden of quantifiable SVD-related damage compared to those first seen for cognitive symptoms. This study demonstrates the significance of first clinical encounter in patients with CAA without previous ICH and provides further evidence for distinct CAA phenotypes.⁴⁴ Further studies focusing on the relationship between SVD burden and risk of subsequent clinical events, including symptomatic ICH, cognitive decline, and incident dementia, as well as advanced neuroimaging and genetic characterization of this subcategory of patients are needed.

AUTHOR CONTRIBUTIONS

Conception and design of the study: G.B., A.C., M.P., A.V. Acquisition and analysis of data: G.B., A.C., M.J.J., L.X., D.R., P.F., M.P., A.A., M.E.M., K.M.S., J.R., S.M.G., M.E.G., A.V. Data management: A.A., K.M.S. Drafting a substantial portion of the manuscript or figures: G.B., A.C., A.V., S.M.G. Critical revisions: A.C., M.J.J., L.X., D.R., P.F., M.P., A.A., M.E.M., J.R., S.M.G., M.E.G. Funding: J.R., S.M.G., M.E.G., A.V.

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DISCLOSURE

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