Cortical superficial siderosis and first-ever cerebral hemorrhage in cerebral amyloid angiopathy

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ABSTRACT

Objective: To investigate whether cortical superficial siderosis (cSS) is associated with increased risk of future first-ever symptomatic lobar intracerebral hemorrhage (ICH) in patients with cerebral amyloid angiopathy (CAA) presenting with neurologic symptoms and without ICH.

Methods: Consecutive patients meeting modified Boston criteria for probable CAA in the absence of ICH from a single-center cohort were analyzed. cSS and other small vessel disease MRI markers were assessed according to recent consensus recommendations. Patients were followed prospectively for future incident symptomatic lobar ICH. Prespecified Cox proportional hazard models were used to investigate cSS and first-ever lobar ICH risk adjusting for potential confounders.

Results: The cohort included 236 patients with probable CAA without lobar ICH at baseline. cSS prevalence was 34%. During a median follow-up of 3.26 years (interquartile range 1.42–5.50 years), 27 of 236 patients (11.4%) experienced a first-ever symptomatic lobar ICH. cSS was a predictor of time until first ICH ($p = 0.0007$, log-rank test). The risk of symptomatic ICH at 5 years of follow-up was 19% (95% confidence interval [CI] 11%–32%) for patients with cSS at baseline vs 6% (95% CI 3%–12%) for patients without cSS. In multivariable Cox regression models, cSS presence was the only independent predictor of increased symptomatic ICH risk during follow-up (HR 4.04; 95% CI 1.73–9.44, $p = 0.001$), after adjusting for age, lobar cerebral microbleeds burden, and white matter hyperintensities.

Conclusions: cSS is consistently associated with an increased risk of future lobar ICH in CAA with potentially important clinical implications for patient care decisions such as antithrombotic use.

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GLOSSARY

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; **HR** = hazard ratio; **ICH** = intracerebral hemorrhage; **OR** = odds ratio; **STRIVE** = Standards for Reporting Vascular Changes on Neuroimaging; **SWI** = susceptibility-weighted imaging; **T2*-GRE** = T2*-weighted gradient recalled echo; **TE** = echo time; **TFNE** = transient focal neurologic episode; **TR** = repetition time; **WMH** = white matter hyperintensity.

Cortical superficial siderosis (cSS) on T2*-weighted gradient recalled echo (T2*-GRE) or susceptibility-weighted imaging (SWI) is a strong hemorrhagic signature of cerebral amyloid angiopathy (CAA)¹—a common small vessel disease characterized by cerebrovascular amyloid deposition affecting superficial cortical microvascular networks, leading to spontaneous lobar intracerebral hemorrhage (ICH). cSS results from bleeding episodes within or adjacent to cortical sulci, presumably from amyloid-laden superficial cortical and leptomeningeal arterioles. cSS is a common manifestation of CAA, being found in 40%–60% of patients, and has distinct clinical and prognostic implications in this setting.¹

cSS increases the sensitivity of the Boston criteria for clinical–radiologic CAA diagnosis and is associated with characteristic clinical symptoms, including transient focal neurologic episodes (amyloid spells).² In CAA cohorts with ICH, cSS was demonstrated to be the most important

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prognostic risk factor for future recurrent ICH.^{3,4} In these studies, cSS remained the main driver of ICH recurrence in CAA after adjusting for the presence of multiple lobar cerebral microbleeds (CMBs) (a putative hemorrhagic marker of CAA^{5,6} previously shown to influence ICH risk)⁷ and white matter hyperintensities (WMHs) (another small vessel damage biomarker).

Lobar ICH is the most common symptomatic CAA presentation and lobar ICH survivors are at high risk of a recurrent event (up to 10%–15% per year). CAA is now often diagnosed on MRI in the setting of isolated lobar CMBs or cSS in patients with non-ICH neurologic presentations in stroke or memory clinics.^{5,8} However, little is known about the effects of cSS on the risk of future first-ever lobar ICH in patients with CAA presenting with neurologic symptoms and without lobar ICH. Small case series indicate that in these patients with CAA, cSS might still be a warning sign for subsequent lobar ICH,^{9,10} but data from large cohort studies with sufficient power are lacking.

We tested the hypothesis that in patients with CAA presenting with neurologic

symptoms without lobar ICH, cSS is associated with an increased risk of future incident (first-ever) symptomatic lobar ICH in a large cohort study.

METHODS Study population and patient selection. We analyzed prospectively collected data from consecutive patients meeting modified Boston criteria for probable CAA in the absence of ICH (symptomatic or asymptomatic) seen by the Massachusetts General Hospital Stroke Service (including stroke unit and outpatient clinics) or Memory Disorders Unit (March 2000–November 2015). Detailed inclusion criteria included (1) diagnosis of probable CAA by modified Boston criteria; (2) clinical presentation other than hemorrhagic (or ischemic) stroke; and (3) available MRI sequences, including T2*-weighted/SWI, T2-weighted, fluid-attenuated inversion recovery (FLAIR) sequences, and diffusion-weighted imaging. Patients without ICH but with strictly deep CMBs, mixed (deep and lobar) and cerebellar CMBs, or single strictly lobar CMBs were also excluded.

Full medical history, including demographic and clinical information, was obtained at presentation using standardized data collection forms. Baseline neurologic examination and symptoms were recorded prospectively. Diagnosis of mild cognitive impairment and dementia at presentation was determined based on the clinical assessment of daily living function status in line with the recommendations from the National Institute on Aging and Alzheimer's Association workgroup.^{11,12}

Two fellows independently reviewed and classified baseline clinical presentations based on all available information as follows: transient focal neurologic episodes (TFNEs) (episodes of positive or negative neurologic symptoms lasting for minutes with subsequent complete resolution, without a cause other than CAA after adequate evaluation, including angiography studies and carotid imaging, as previously suggested),^{13,14} cognitive complaints, or nonfocal neurologic symptoms.

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 data acquisition and analysis. Images were obtained using a 1.5T MRI scanner and included whole brain T2-weighted, T2*-GRE (echo time [TE] 750/50 ms, 5 mm slice thickness, 1 mm interslice gap), and FLAIR (repetition time [TR]/TE 10,000/140 ms, inversion time 2,200 ms, 1 number of excitations, 5 mm slice thickness, 1 mm interslice gap). For a subset of patients (n = 77), the T2*-weighted MRI sequences included SWI, TR/TE 27/20 ms, 1.5 mm slice thickness. In the rare scenario of a patient having both T2*-GRE and SWI available, we reviewed the SWI. All MRI were reviewed blinded to clinical and follow-up data by 2 trained observers, according to Standards for Reporting Vascular Changes on Neuroimaging (STRIVE).¹⁵

CMB presence and number were evaluated on axial T2*-GRE or SWI images using current consensus criteria.^{16,17} cSS was defined and jointly assessed by 2 trained raters in line with recent consensus recommendations (intrater κ = 0.87).¹ cSS was defined as curvilinear hypointensities following the cortical surface distinct from vessels, and was assessed on axial T2*-weighted sequences according to a validated scale: absent, focal (restricted to ≤3 sulci), or disseminated (affecting 4 or more sulci).^{18,19} cSS ratings were performed independently of the rating of other imaging markers.

Figure 1 Flowchart of patient selection

CAA = cerebral amyloid angiopathy; CMB = cerebral microbleed; ICH = intracerebral hemorrhage; MGH = Massachusetts General Hospital.

Enlarged perivascular spaces (EPVS) were assessed on axial T2-weighted MRI separately in the basal ganglia and centrum semiovale (CSO), using a validated 4-point visual rating scale (0 = no EPVS, 1 = <10 EPVS, 2 = 11–20 EPVS, 3 = 21–40 EPVS and 4 = >40 EPVS).²⁰ We prespecified a dichotomized classification of EPVS degree as high (score >2) or low (score ≤2) in line with previous studies.

WMH volumes were calculated on axial FLAIR sequences with a previously described semi-automated planimetric method using MRICron software.²¹ WMH were also classified using the 0–3 Fazekas scale.²² The antero-posterior ratio of WMH lesion distribution was computed using a validated approach,²³ in which a lower score reflects more posteriorly distributed WMH lesions.²³ Lacunes were defined according to STRIVE criteria.¹⁵

Follow-up data. Prospective follow-up (including follow-up phone calls at 3 months after enrollment and every 6 months thereafter) was supplemented by a comprehensive systematic chart review of all available information (including discharge summaries, follow-up outpatient and general practitioner letters, and death certificates), using standardized data collection forms. We collected information on clinically symptomatic ICH, defined as a symptomatic stroke syndrome associated with neuroimaging evidence of a corresponding ICH. The anatomical location of ICH was defined as lobar if the hematoma was in the

cerebral cortex or at the junction of the cortex and white matter (including subcortical white matter). Outcome events were assessed using all clinical and radiologic information available, blinded to the presence of cSS at baseline MRI or other imaging findings. All patients were followed from their date of baseline presentation until the occurrence of ICH, death, or the end of follow-up.

Statistics. Baseline demographic, clinical, and neuroimaging characteristics of patients with probable CAA with vs without incident ICH during follow-up were compared in univariate analyses, using 2-sample *t* test, Wilcoxon rank sum, Pearson χ^2 , and Fisher exact tests, as appropriate.

We determined the presence of cSS as a univariable predictor of incident lobar ICH risk using the Kaplan-Meier plot with significance testing by the log-rank test. Survival time was calculated from date of baseline MRI scan until the date of lobar ICH at follow-up or the last known date without the outcome event of interest. For individuals experiencing multiple lobar ICHs during follow-up, data were censored at the time of first ICH. Data were also censored at the time of death from causes other than documented symptomatic ICH. Prespecified Cox proportional hazards regression analyses were performed to calculate the multivariable hazard ratio (HR) of cSS presence (and burden, i.e., focal and disseminated) in relation to first-ever CAA-related

Table 1 Comparison of demographic, clinical, and imaging characteristics of patients with probable cerebral amyloid angiopathy (CAA) according to first-ever symptomatic lobar intracerebral hemorrhage (ICH) during follow-up

Characteristics	Whole CAA cohort (n = 236)	CAA with ICH at follow-up (n = 27)	CAA without ICH at follow-up (n = 209)	p Value
Age at MRI, y, mean (95% CI)	81.8 (66.6–97)	73.6 (70.3–76.9)	82.9 (65.7 to 100)	0.703
Female, n (%)	94 (40)	12 (44)	82 (39)	0.603
Hypertension, n (%)	154 (65)	17 (63)	137 (66)	0.790
Hypercholesterolemia, n (%)	135 (57)	17 (63)	118 (57)	0.520
Warfarin use, n (%)	28 (12)	1 (4)	27 (13)	0.398
Statin use, n (%)	117 (50)	13 (48)	104 (50)	0.875
Dementia diagnosis, n (%) ^a	74 (32)	5 (19)	69 (33)	0.237
MCI diagnosis, n (%)	98 (42)	12 (44)	86 (41)	
Severe (Fazekas 5–6) WMH, n (%)	78 (33)	9 (33)	69 (33)	0.974
WMH volume, mL, median (IQR)	19.5 (7.9–37.5)	21.7 (15.2–44.2)	18.5 (6.5 to 36.24)	0.033
Log WMH volume, mean (95% CI)	2.84 (2.70–2.98)	3.33 (3.04–3.62)	2.77 (2.62 to 2.93)	0.014
WMH antero-posterior ratio, mean (95% CI)	13.6 (11.9–15.3)	9.7 (5.9–13.6)	14.1 (12.3 to 16)	0.101
Lacunes, n (%)	70 (30)	7 (26)	63 (30)	0.652
High-grade CSO-EPVS (>20), n (%)	126 (53)	11 (41)	115 (55)	0.161
Lobar CMB count, median (IQR)	5 (2–17)	5 (1–14)	5 (2 to 17)	0.288
Log CMB count, mean (95% CI)	2.2 (2–2.4)	1.9 (1.3–2.4)	2.2 (2 to –2.4)	0.209
>5 CMBs, n (%)	109 (46)	12 (44)	97 (46)	0.847
cSS, n (%)	80 (34)	18 (67)	62 (30)	<0.0001
Focal	41 (17)	12 (44)	29 (14)	<0.0001 ^b
Disseminated	39 (17)	6 (22)	33 (16)	
DWI lesion presence, n (%)	20 (8.5)	3 (11)	17 (8)	0.601

Abbreviations: CI = confidence interval; CMB = cerebral microbleed; CSO = centrum semiovale; cSS = cortical superficial siderosis; DWI = diffusion-weighted imaging; EPVS = enlarged perivascular spaces; IQR = interquartile range; MCI = mild cognitive impairment; WMH = white matter hyperintensity.

^aData available in 235/236 patients.

^bOverall p value.

lobar ICH. In these models, we included biologically plausible potential predictors identified in previous studies for recurrent CAA-related lobar ICH, including age, lobar CMBs, and WMH burden.^{7,24} Other covariates demonstrating a univariable association with the outcome in Cox regression analysis ($p < 0.1$) were also considered for inclusion. The main full model included cSS presence, age at MRI (dichotomized by the median age of the cohort at 80 years), presence of >5 lobar CMBs, and severe (Fazekas 5–6) WMH. In a sensitivity analysis multivariable Cox regression model, we included cSS presence and continuous covariates (age, log-transformed lobar CMB number, and log-transformed WMH volume to assure normal distributions) to assess any potential dose-effect relationship between these covariates and the outcome. In further sensitivity analyses, we also adjusted for blood-sensitive MRI sequence parameters (SWI vs T2*-GRE). The proportional hazard assumption in unadjusted and adjusted models was tested using graphical checks and Schoenfeld residuals-based tests.

All tests of significance were 2-tailed and significance level was set at 0.05 for all analyses. Stata software (version 11.2,

StataCorp., College Station, TX) was used for all analyses. The manuscript was prepared with reference to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.²⁵

RESULTS A total of 260 potentially eligible patients with probable CAA according to the Boston criteria were screened for this analysis. A flowchart of patient selection is provided in figure 1. Reliable follow-up data were available for 237 patients. Patients without follow-up information were not different from patients with CAA included in the longitudinal analysis in baseline clinical characteristics or imaging markers of the disease (all $p > 0.05$, data not shown). One patient was excluded post hoc because of a deep ICH during follow-up, leaving 236 patients for our analysis. Of these, 51 (22%) presented with TFNEs, 163 (68%) cognitive complaints, and 23 (10%) other neurologic symptoms prompting the baseline MRI investigation. Among these patients, 75 (32%) and 161 (68%) were referred to the Stroke Service and Memory Clinics, respectively. Eighty-one patients (34%) had cSS at baseline. cSS presence was associated with clinical presentation with TFNEs (odds ratio [OR] 2.74, 95% confidence interval [CI] 1.55–4.85; $p = 0.001$).

During a median follow-up time of 3.26 years (interquartile range 1.42–5.50 years; 1,878.8 person-years of follow-up), 27 of 236 patients (11.4%, 95% CI 7.7–16.2) experienced a first symptomatic CAA-related lobar ICH (incidence rate 1.44; 95% CI 0.99–2.10 per 100 patient-years). Three of these 27 patients experienced multiple (>1) sequential symptomatic lobar ICH during follow-up. The characteristics of our cohort per incident lobar ICH are summarized in table 1. No differences were found in demographic characteristics or vascular risk factors between the 2 groups. Patients who had a first-ever symptomatic ICH during follow-up had slightly higher WMH volumes and significantly higher prevalence of cSS (67% vs 30%; $p < 0.0001$) compared to patients with CAA free of ICH during follow-up (table 1). All other imaging markers of CAA and small vessel disease were comparable between the 2 patient groups.

In Kaplan-Meier analysis, the presence of cSS at baseline MRI was a predictor of faster time until CAA-related lobar ICH ($p = 0.0007$, by the log-rank test) (figure 2A). The risk of symptomatic lobar ICH at 5 years of follow-up was 19% (95% CI 11%–32%) for patients with cSS at baseline vs 6% (95% CI 3%–12%) for patients without cSS. In univariable Cox regression analysis, cSS presence was a predictor of incident symptomatic lobar ICH (HR 3.68, 95% CI 1.64–8.25; $p = 0.002$); the HRs were similar for focal and disseminated cSS (3.84, 95% CI 1.60–9.23

Figure 2 Time to incident first-ever symptomatic lobar intracerebral hemorrhage (ICH) during follow-up

(A) Kaplan-Meier estimates of progression to symptomatic lobar ICH in the presence of cortical superficial siderosis (cSS) in patients with probable cerebral amyloid angiopathy. Testing of significance is by the log-rank test. (B) Adjusted survival curves from the Cox regression model on the effect of cSS presence on future lobar ICH risk (adjusting for baseline clinical and imaging characteristics). CI = confidence interval; HR = hazard ratio.

and 3.41, 85% CI 1.20–9.65, respectively). None of the demographic, clinical, or imaging variables (including lobar CMB burden, severe Fazekas WMH, CSO/EPVS, or moderate to severe atrophy) showed an association with future lobar ICH in univariable analysis (all HR < 1 and $p > 0.5$). Only WMH volume on a continuous scale was associated with increased hazard of ICH during follow-up (HR 1.65, 95% CI 1.08–2.52; $p = 0.021$).

In prespecified multivariable Cox regression models adjusting for biologically significant risk factors (including age, CMB burden, and WMH), presence of cSS was the only independent predictor of increased symptomatic CAA-related lobar ICH risk during follow-up (table 2 and figure 2B for the adjusted Kaplan-Meier curves). These results remained consistent in sensitivity multivariable models using covariates as continuous variables (table 2) and if the single case of a deep ICH is included in the cohort (data not shown). The effect sizes were similar for focal and disseminated cSS included in comparable models (HR 4.10, 95% CI 1.66–10.16 and HR 3.88, 95% CI 1.28–11.75, respectively) (table 2). Further adjusting these models for blood-sensitive MRI sequence parameters (SWI vs T2*-GRE) did not change the effect sizes.

DISCUSSION In this large consecutive cohort of patients with probable CAA presenting with neurologic

symptoms but without ICH, we found that cSS on T2*-GRE/SWI MRI is associated with an increased risk of future first-ever symptomatic lobar ICH (figure 3). The prognostic value of cSS in this setting was strong and independent of age and other neuroimaging markers of CAA severity, including lobar CMB burden and WMH. Hence, cSS may help stratify future bleeding risk even in symptomatic patients with CAA coming to medical attention without ICH, with implications for prognosis and treatment decisions.

cSS is a common hemorrhagic marker of CAA in the appropriate clinical setting (after other causes are excluded).^{1,26,27} Characteristically cSS affects the cerebral convexities and its imaging manifestation reflects blood breakdown products, including hemosiderin, that line the outermost surface of the cortex or lie in the subarachnoid space. One study reported cSS in up to 61% of patients ($n = 38$; mean age 71 years) with histopathologically confirmed CAA and no cSS in patients with ICH without histopathologic evidence of CAA ($n = 22$; mean age 55 years).¹⁸ A subsequent imaging study found cSS in 40% of patients with probable CAA with lobar ICH and fewer than 5% of patients with a strictly deep pattern of ICH, typically denoting non-CAA “hypertensive” hemorrhages.¹⁹ In another longitudinal cohort of probable CAA cases (most with ICH) ($n = 84$), the prevalence of cSS was also found to be 48%.²⁸ While cSS prevalence is relatively low in memory clinic cohorts in general (being found in around 5% of cases),^{29,30} it is still common in those patients with strictly lobar CMBs suggesting underlying CAA (15%–20%).³¹ The prevalence of cSS in our cohort of patients without ICH with probable CAA is in line with these previous reports.

Much of the enduring interest in cSS is due to the possibility that this marker might reflect a more aggressive disease phenotype related to particularly high future ICH risk. A previous retrospective study including 51 patients with CAA-ICH with cSS observed new lobar ICHs in 18 patients (35%) during a median follow-up time period of 35.3 months.³ A multicenter cohort of probable or possible CAA ($n = 118$), mainly patients with lobar ICH at baseline, found that over a median follow-up time of 2 years, cSS was a strong independent predictor of recurrent ICH (HR 2.53, 95% CI 1.05–6.15).⁴ Our study extends these findings to patients without prior ICH seen in 2 common clinical settings: stroke services (where patients with CAA are often seen for TFNEs or other nonfocal neurologic symptoms) and memory clinics (where they are evaluated for cognitive symptoms or subjective cognitive complaints).¹¹ It has been previously shown that patients with CAA first seen for acute neurologic symptoms often have recurrent symptoms and are at high risk of

Table 2 Multivariable Cox regression analyses of cortical superficial siderosis (cSS) and other potential predictors of first-ever symptomatic lobar intracerebral hemorrhage during follow-up in patients with cerebral amyloid angiopathy

Variables	HR (95% CI)	p Value
Main model: cSS presence		
cSS (yes vs no)	4.04 (1.73–9.44)	0.001
Presence of >5 lobar CMBs	0.86 (0.34–1.96)	0.720
Age (>80 y)	1.07 (0.43–2.69)	0.881
Severe (Fazekas 5–6) WMH	0.81 (0.35–1.86)	0.612
Sensitivity analysis model: cSS		
cSS (yes vs no)	3.54 (1.55–8.12)	0.003
Log lobar CMBs	0.76 (0.55–1.06)	0.104
Age (for each year increase)	1.00 (0.99–1.01)	0.763
Log WMH	1.58 (1.00–2.48)	0.048
Main model based on cSS burden (focal and disseminated)		
Focal cSS (vs no cSS)	4.11 (1.66–10.16)	0.002
Disseminated cSS (vs no cSS)	3.88 (1.28–11.75)	0.016
Presence of >5 lobar CMBs	0.86 (0.34–1.96)	0.719
Age (>80 y)	1.07 (0.42–2.69)	0.890
Severe (Fazekas 5–6) WMH	0.81 (0.35–1.91)	0.636

Abbreviations: CI = confidence interval; CMB = cerebral microbleed; HR = hazard ratio; WMH = white matter hyperintensity.

Figure 3 Cortical superficial siderosis (cSS) and intracerebral hemorrhage (ICH)

Representative examples of patients with probable cerebral amyloid angiopathy with pre-existing cSS and subsequent first-ever ICH during follow-up. Arrowheads show focal cSS in A and C and the shaded area depicts disseminated cSS in B. Of note, overall in our cohort areas of cSS did not seem to predict the exact site of future lobar ICH.

developing subsequent ICH.^{10,13,14} Our findings show that this risk is largely driven by cSS at baseline and reinforce the notion of cSS as a central hemorrhagic signature of CAA, providing insights into future ICH risk across the spectrum of CAA presentations.^{1,32} Of note, we did not find an association between lobar CMB burden and incident ICH risk, in line with a previous report⁸ and a multicenter study looking at risk of recurrent ICH in CAA-ICH.⁴ While multiple strictly lobar CMBs are useful as diagnostic markers of CAA in the context of the Boston criteria, cSS presence might be the strongest risk factor for future ICH, over and above CMB burden, across the spectrum of CAA subtypes.

The pathophysiologic mechanisms underlying cSS and its association with future ICH risk in CAA are not yet clear.¹ Several lines of evidence support the prevailing hypothesis that cSS reflects repeated episodes of hemorrhage into the subarachnoid space from fragile superficial cortical or leptomeningeal CAA-laden vessels.¹ cSS may thus be a marker of increased and widespread leptomeningeal small-vessel fragility and high CAA disease activity, heralding a high risk for lobar ICH.^{18,33,34} However, systematic neuropathologic studies specifically focusing on CAA-related cSS are currently lacking. A number of recent studies raised the interesting possibility that the *APOE* $\epsilon 2$ allele is more common in patients with CAA with vs without cSS and might influence pathophysiologic pathways and small vessel disease networks causing cSS.^{28,35,36} *APOE* $\epsilon 2$ is hypothesized to promote CAA vasculopathic changes (vessel cracking, vessel-within-vessel appearance, and fibrinoid necrosis), which can lead to vessel rupture,³⁷ including cSS in multiple spatially separated foci.^{28,35}

Key strengths of our study include the large sample size, the systematic evaluation of MRI using validated scales for the full spectrum of small vessel disease imaging markers, and the use of cSS definitions and rating methods in line with recent consensus recommendations.¹ The current group of patients with probable CAA without ICH presents an opportunity to characterize and investigate unambiguously the role of primary in situ cSS as opposed to the possible secondary cSS that can occur as the result of lobar ICHs rupturing into the overlying subarachnoid space or ventricular system.¹ The large sample size of consecutive patients with CAA without ICH combined with the long follow-up in our cohort allowed us to build robust multivariable survival models. A limitation is the potential selection bias due to the requirement for MRI performed as part of routine clinical care and the use of T2*-GRE/SWI sequences, which might have different sensitivity for cSS detection.²⁷ Also, the lack of research quality T1-weighted isometric sequences precluded any volumetric analyses of cortical atrophy. Another potential bias might come from referral of advanced CAA cases that might be at highest risk of future ICH to our tertiary center, though we have made every effort to include consecutive patients across non-ICH presentations. Further larger cohorts will be needed to explore cSS and ICH risk stratified by presentation and patient referral patterns. An additional limitation is that it is impossible to score cSS without some unblinding to imaging findings, though raters were blinded to MRI markers on the non-T2*-weighted images and to all clinical and ICH recurrence data.

Taken together, our observations further support the notion that cSS is a central component of

hemorrhagic CAA brain injury and can identify new mechanisms and distinct CAA phenotypes.^{2,38,39} The increased risk of future CAA-related lobar ICH associated with cSS may have important clinical implications for patient care, particularly in evaluating the risk vs benefit of antithrombotic agents, and for use of any future disease-modifying treatments.⁴⁰

AUTHOR CONTRIBUTIONS

A. Charidimou: study concept and design, data collection, imaging analysis, statistical analysis, writeup. G. Boulouis: study concept and design, data collection, imaging analysis, critical revisions. L. Xiong: data collection, critical revisions. M. Jessel: data collection and management. D. Roongpiboonsopit: critical revisions. A. Ayres: data collection and management. K.M. Schwab: data collection and management. J. Rosand: critical revisions. E.M. Gurol: critical revisions. S.M. Greenberg: funding, project concept and design, critical revisions. A. Viswanathan: funding, project concept and design, writeup, critical revisions.

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