Interrelationship of superficial siderosis and microbleeds in cerebral amyloid angiopathy

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ABSTRACT

Objective: We sought to explore the mechanisms leading to cerebral amyloid angiopathy (CAA)-related cortical superficial siderosis (cSS) by examining its neuroimaging and genetic association with cerebral microbleeds (CMBs).

Methods: MRI scans of 84 subjects with probable or definite CAA participating in a longitudinal research study were graded for cSS presence and severity (focal, restricted to ≤ 3 sulci vs disseminated, ≥ 4 sulci), and CMB count. *APOE* ϵ variants were directly genotyped. We performed cross-sectional analysis comparing CMB counts and *APOE* $\epsilon 2$ and $\epsilon 4$ allele frequency between subjects with no, focal, or disseminated cSS.

Results: cSS was present in 48% ($n = 40$) of the population. *APOE* $\epsilon 2$ was overrepresented among participants with focal (odds ratio [OR] 7.0, 95% confidence interval [CI] 1.7–29.3, $p = 0.008$) and disseminated (OR 11.5, 95% CI 2.8–46.2, $p = 0.001$) cSS relative to individuals without cSS. CMB counts decreased with increasing severity of cSS (median: 41, 38, and 15 for no cSS, focal cSS, and disseminated cSS, respectively, $p = 0.09$). The highest CMB count tertile was associated with *APOE* $\epsilon 4$ (OR 3.0, 95% CI 1.4–6.6, $p = 0.006$) relative to the lowest tertile.

Conclusions: Among individuals with advanced CAA, cSS tends to occur in individuals with relatively lower CMB counts and with a distinct pattern of *APOE* genotypes. These results suggest that CAA-related cSS and CMBs may arise from distinct vasculopathic mechanisms.

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GLOSSARY

CAA = cerebral amyloid angiopathy; **CI** = confidence interval; **CMB** = cerebral microbleed; **cSS** = cortical superficial siderosis; **GRE** = gradient echo; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **OR** = odds ratio.

Cerebral amyloid angiopathy (CAA), representing deposition of β -amyloid in the walls of cerebral small vessels, is an important cause of both symptomatic intracerebral hemorrhages (ICHs) and small, typically asymptomatic cerebral microbleeds (CMBs). Neuropathologic analysis has shown substantially greater thickening of amyloid-laden vessel walls in CAA brains with many CMBs relative to those with ICH and few CMBs,¹ suggesting that these 2 types of hemorrhagic lesions may arise from different vessel pathologies in advanced CAA.

Recent attention has focused on a third type of CAA-related hemorrhagic lesion: linear hemosiderin deposits along the subpial space and underlying cortical convexities, defined as cortical superficial siderosis (cSS).^{2,3} cSS is frequently visualized on MRIs of individuals with CAA at prevalence rates ranging from 40% to 70% in comparison to 0.7% in the general population,^{2,4–6} making it a promising neuroimaging marker for the disease.⁴ cSS may also have important clinical implications as a trigger for CAA-related transient focal neurologic episodes⁷ and a potential indicator of increased risk of future ICH.^{8,9}

We sought to explore the mechanisms leading to CAA-related cSS by examining its neuroimaging association with CMBs and genetic association with *APOE*. The genetic analysis focused on the *APOE* $\epsilon 4$ and $\epsilon 2$ alleles, which have been shown to promote different types of

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pathologic changes in CAA.^{10–12} We hypothesized that CAA-related cSS and CMBs represent distinct forms of bleeding with different genetic correlates.

METHODS Study design. This is a retrospective, cross-sectional analysis of prospectively acquired data from an ongoing single-center longitudinal cohort on the natural history of CAA at Massachusetts General Hospital since 1995.

Standard protocol approvals, registrations, and patient consents. The Institutional Review Board approved the study and informed consent was obtained from all participants or their surrogates.

Study participants and data collection. As part of the longitudinal study, participants are recruited to return for research MRI scans. Participants were eligible for the current analysis if they had an interpretable T2*-weighted gradient echo (GRE) sequence performed as part of their study MRI and met Boston criteria for probable or definite CAA.¹³ Of the 111 total participants within the cohort, 14 were excluded because of inadequate or motion-degraded MRIs and 13 for not meeting criteria for probable or definite CAA. The remaining 84 participants included in our analysis either had pathologic confirmation of CAA (full postmortem examination [*n* = 6] or tissue biopsy [*n* = 14]) or were 55 years or older with at least 2 or more strictly lobar intraparenchymal hemorrhagic lesions (macrohemorrhages or CMBs) with no other identified cause (*n* = 64).¹³ Demographic information and vascular risk factors were prospectively recorded at the time of study enrollment.¹⁴ Variables of interest were age at MRI, sex, history of hypertension, prior ICH, family history of ICH (data available in 55 participants), and antithrombotic use. *APOE* genotypes were determined¹⁵ in participants who consented for genetic testing (*n* = 79, 94%). Genotyping personnel were unaware of the clinical and neuroimaging data.

Study participants underwent structural MRI at 1.5T field strength using Siemens Avanto system (Siemens Healthcare, Erlangen, Germany). All participants had sagittal T1-weighted,

axial T2-weighted, axial T2*-weighted GRE (1 × 1 mm in-plane resolution, 5-mm slice thickness; repetition time/echo time: 763/24 milliseconds), and axial fluid-attenuated inversion recovery scans. T2*-weighted GRE images were systematically assessed for the presence and number of CMBs and cSS by one rater (A.S.). CMBs were identified and counted per published criteria.¹⁶ cSS was defined as linear gyriiform areas of low signal along the superficial layers of the cerebral cortex (without corresponding hyperintense signal on T1-weighted or fluid-attenuated inversion recovery image) that were noncontiguous with ICH.⁵ cSS severity was classified as focal (involving ≤3 sulci) or disseminated (≥4 sulci) per published definitions.⁴ In a sample of 20 MRIs, an additional cSS reading was performed by a second rater (J.O.-F.) to assess interrater agreement, which was 90% (Cohen κ = 0.79) for cSS presence and 85% (Cohen κ = 0.74) for cSS severity. All MRI analyses were performed without knowledge of participant characteristics and genetic data.

Statistical analysis. Discrete variables are presented as count (%) and continuous variables as mean (SD) or median (interquartile range [IQR]), as appropriate. Categorical variables were analyzed using Pearson χ^2 or Fisher exact test, and continuous variables using the 2-sample *t* test (for normal distributions) and Kruskal–Wallis test (for nonnormal distributions). *APOE* allele frequencies were calculated by determining the proportion of a given allele among all *APOE* alleles within the particular subgroup of interest. Separate multinomial logistic regression models were used to assess the relationship between *APOE* alleles (coded as the number of alleles per participant [0, 1, or 2]) and cSS severity (coded as: 0 = no cSS; 1 = focal cSS; and 2 = disseminated cSS), as well as CMB count categorized according to tertiles (≤12, 13–50, and ≥51 CMBs). These models were predetermined to adjust for age and sex. A predetermined secondary subgroup analysis was performed in individuals without prior symptomatic ICH to address the possibility that cSS might arise as a result of ICH rupturing into the subarachnoid space rather than as an independent event.

RESULTS We analyzed the interrelationship among cSS severity, CMB count, and *APOE* genotype in

Table 1 Characteristics of participants with and without cSS

Characteristic	Entire sample (n = 84)	No cSS (n = 44)	Any cSS (n = 40)	p Value
Age, y, mean ± SD	70.9 ± 8.4	69.2 ± 8.6	72.8 ± 7.9	0.05
Male, n (%)	60 (71)	27 (61)	33 (83)	0.03
Hypertension, n (%)	47 (56)	20 (46)	27 (68)	0.04
Antithrombotic, n (%)	16 (25)	10 (23)	11 (28)	>0.2
Prior lobar ICH, n (%)	53 (63)	26 (59)	27 (68)	>0.2
Family history of ICH, n (%) ^a	4 (9)	2 (8)	3 (10)	>0.2
APOE genotypes, n (%)^b				
ε2/ε2	1 (1)	0 (0)	1 (3)	>0.2
ε2/ε3	15 (19)	5 (12)	10 (27)	0.11
ε2/ε4	8 (10)	0 (0)	8 (21)	0.002
ε3/ε3	26 (33)	14 (34)	12 (32)	>0.2
ε3/ε4	12 (15)	8 (20)	4 (11)	>0.2
ε4/ε4	17 (22)	14 (34)	3 (8)	0.006

Abbreviations: cSS = cortical superficial siderosis; ICH = intracerebral hemorrhage.

^aInformation available in 55 participants (30 with cSS, 25 without).

^bInformation available in 79 participants (41 with cSS, 38 without).

Table 2 APOE allele frequencies according to severity of cSS and CMB count

APOE AF (n = 79, 158 alleles)	cSS severity			p Value	CMB count			p Value
	No cSS (n = 41)	Focal cSS (n = 18)	Disseminated cSS (n = 20)		1st tertile (n = 26)	2nd tertile (n = 27)	3rd tertile (n = 26)	
APOE ε2 AF	0.06	0.22	0.30	0.002	0.13	0.22	0.12	>0.2
APOE ε4 AF	0.44	0.22	0.25	0.03	0.19	0.31	0.52	0.002

Abbreviations: AF = allele frequency; CMB = cerebral microbleed; cSS = cortical superficial siderosis.

84 subjects with CAA. cSS was common (present in 40 of 84 subjects, 48%) and often disseminated (21/40, 53%). In comparison to participants without cSS, those with cSS were more frequently male and hypertensive, and tended to be older (difference in mean age 3.6 years, $p = 0.049$) (table 1). Distinguishing between focal and disseminated cSS did not reveal any additional noteworthy trends relative to participants without cSS. The *APOE* ε2 allele was overrepresented among CAA subjects with cSS relative to those without (table 2). *APOE* ε2 was associated with both focal and disseminated cSS and remained so after adjustment for age and sex. A similar relationship between focal/disseminated cSS and *APOE* ε2 was seen in subgroup analysis of participants without ICH, whereas *APOE* ε4 was inversely associated with disseminated cSS in this subgroup (odds ratio [OR] 0.1, 95% confidence interval [CI] 0.0–0.6, $p = 0.008$).

CMB count was high across all subjects in this research cohort (median CMB count 29, IQR 7–84), but decreased with increasing severity of cSS (table 3). A more pronounced inverse relationship was seen in subgroup analysis of participants without ICH (table 3). In participants with strictly unilateral cSS (n = 37), the CMB count did not differ between the affected hemisphere (median 13, IQR 3–38) and the contralateral hemisphere (median 16, IQR 5–35), suggesting no major spatial association between these 2 hemorrhage types. Similarly, in 20 participants with both unilateral cSS and ICH, cSS occurred at a similar frequency in the hemisphere ipsilateral to ICH (n = 9, 45%) vs the contralateral hemisphere (n = 11, 55%). Participants

with prior ICH had lower CMB count (median 21, IQR 4–57) than participants without ICH (median 49, IQR 16–194, $p = 0.004$). Among subjects with available genetic testing, CMB count was associated with *APOE* ε4 (table 4), an association that remained independent after adjusting for age and sex, and in subgroup analysis of participants without ICH (OR for highest CMB tertile relative to the lowest: 18.0, 95% CI 1.8–178, $p = 0.01$).

DISCUSSION The primary findings in our study were that CAA-related cSS is associated with lower CMB counts and overrepresentation of the *APOE* ε2 allele. These results suggest that cSS may arise from vasculopathic mechanisms that are fundamentally different from those causing CAA-related microbleeding.

We find a high prevalence of cSS in CAA as previously reported.^{4,5} The observed cSS prevalence rate of 48% is similar to a recent analysis of cSS in persons with CAA defined by Boston criteria, which also found an approximately 40% prevalence of cSS, mostly (approximately 60%) disseminated.⁵ Data shown in the prior study also suggested a lower prevalence of CMB among individuals with cSS than those without.⁵ Indeed, some patients with CAA demonstrate cSS in the absence of multiple CMBs, resulting in increased sensitivity for CAA when counting cSS as an independent hemorrhagic lesion per the modified Boston criteria.⁴

The tendency for cSS to associate with *APOE* ε2 and CMBs with *APOE* ε4 offers potential clues to

Table 3 Relationship between severity of cSS and CMB burden

	No cSS	Focal (≤3 sulci) cSS	Disseminated (≥4 sulci) cSS	p Value
Entire sample (n = 79^a)				
CMB count, median (IQR)	41 (7–125)	38 (10–84)	15 (4.5–31)	0.09
Subgroup without ICH (n = 31^b)				
CMB count, median (IQR)	104.5 (40–332)	53 (39–162)	13 (5–44)	0.004

Abbreviations: CMB = cerebral microbleed; cSS = cortical superficial siderosis; ICH = intracerebral hemorrhage; IQR = interquartile range.

^a41 absent, 18 focal and 20 disseminated.

^b18 absent, 4 focal and 9 disseminated.

Table 4 Multinomial logistic regression of relationships among *APOE* genotype, severity of cSS, and CMB count

	Focal cSS			Disseminated cSS			CMB count (2nd tertile)			CMB count (3rd tertile)		
	OR ^a	95% CI	p Value	OR ^a	95% CI	p Value	OR ^b	95% CI	p Value	OR ^b	95% CI	p Value
<i>APOE</i> ϵ 2												
Unadjusted	5.3	1.5-19.1	0.01 ^c	9.0	2.5-31.5	0.001 ^c	2.0	0.7-5.9	>0.2	0.8	0.2-2.8	>0.2
Adjusted for age and sex	7.0	1.7-29.3	0.008 ^c	11.5	2.8-46.2	0.001 ^c	2.0	0.7-6.0	>0.2	0.8	0.3-2.8	>0.2
<i>APOE</i> ϵ 4												
Unadjusted	0.5	0.2-1.1	0.07	0.5	0.3-1.1	0.10	1.6	0.7-3.5	>0.2 ^d	3.0	1.4-6.4	0.006 ^d
Adjusted for age and sex	0.5	0.2-1.1	0.10 ^d	0.6	0.3-1.2	0.16 ^d	1.8	0.8-3.9	0.15 ^d	3.0	1.4-6.6	0.006 ^d

Abbreviations: CI = confidence interval; CMB = cerebral microbleed; cSS = cortical superficial siderosis; OR = odds ratio.

^aMultinomial logistic regression: OR per each additional allele in comparison to participants without cSS.

^bMultinomial logistic regression: OR per each additional allele in comparison to participants within the lowest tertile.

^cGlobal likelihood ratio test (assessing whether predictor has an effect on any of the categories of outcome) $p < 0.01$.

^dGlobal likelihood ratio test (assessing whether predictor has an effect on any of the categories of outcome) $p = 0.01$ -0.05.

their pathogenesises. *APOE* ϵ 2 is linked to vascular breakdown of amyloid-laden vessels and ICH^{11,12,15,17-19} as well as to histologic type 2 CAA tending to spare cortical capillaries.²⁰ *APOE* ϵ 4, conversely, appears associated with increasing vascular amyloid burden¹⁰ and histologic type 1 CAA that prominently affects cortical capillaries.²⁰ The current findings thus raise the possibility that the *APOE* ϵ 2-associated vasculopathic changes that give rise to ICH are also fundamental to

cSS. This link is particularly intriguing in light of reports that cSS may predict future ICH.^{8,9} Increasing burdens of vascular (particularly capillary) amyloid associated with *APOE* ϵ 4 may instead favor CMB in preference to cSS (figure). In our sample, it was predominantly participants without ICH, with very high degrees of CMB burden, who drove the inverse relationship between increasing severity of cSS and CMB counts, suggesting a possible distinct CAA

Figure Representative cases of cerebral microbleed and cortical superficial siderosis predominant cerebral amyloid angiopathy phenotypes

Axial T2*-weighted gradient echo images in 2 participants, with the first (A-C) showing a high degree of lobar cerebral microbleed burden without cortical superficial siderosis, and the second (D-F) with disseminated cortical superficial siderosis and minimal cerebral microbleed burden.

phenotype characterized by extreme levels of CMB formation that is devoid of other CAA-related hemorrhages. Although these associations with *APOE* genotype provide biological plausibility for the inverse association between severity of cSS and CMB count within our CAA cohort, we concede that our results are limited by small sample size (40 cases with cSS). Furthermore, these mechanistic links need to be treated cautiously, because *APOE* genotype does not fully determine type of CAA-related hemorrhage, and indeed cSS, CMB, and ICH often coexist, as exemplified by the relatively high CMB count even in participants with disseminated cSS. Our results differ from a recent analysis of patients from a dementia clinic, which found positive associations among cSS, CMB, and *APOE* $\epsilon 4$.²¹ The discrepancy may partly reflect the different populations being studied, because analysis of a dementia cohort²¹ that includes both CAA and non-CAA subjects might produce overlaps of these markers within the CAA subgroup that would not appear in an analysis like ours solely of subjects diagnosed with advanced CAA.

Our results were limited by small sample size and unavailability of *APOE* genotype in all individuals. The “unmodified” Boston criteria may also exclude some individuals with CAA lacking ICH and CMB, thus potentially biasing away from cSS-predominant CAA. Patients with CAA who are considered for research studies tend to be those with particularly salient MRI findings, as indicated by the very high median CMB count, potentially limiting the generalizability of our findings to the full spectrum of CAA in the population. A final limitation is that although MRI ratings were blinded to clinical and genetic data, the ratings of CMBs and cSS on T2*-weighted images could not be blinded to each other. It is reassuring in this regard that our measured prevalence of cSS and the tendency for an inverse relationship between cSS and CMB were similar to that of an independent dataset.⁵

Results from this well-defined cohort of CAA suggest that cSS is a distinct manifestation of CAA that results from *APOE* $\epsilon 2$ -related vasculopathic changes and may thus share some mechanistic features with symptomatic ICH. Accordingly, cSS may prove to be an important neuroimaging marker for future trials aimed at blocking the pathogenic steps that generate CAA-related ICH. These findings will require replication in larger CAA cohorts and in future pathologic studies.

AUTHOR CONTRIBUTIONS

Study concept: Ashkan Shoamanesh. Study design: Ashkan Shoamanesh, Anand Viswanathan, and Steven M. Greenberg. Statistical analysis: Ashkan Shoamanesh, Guido J. Falcone, and Jamarly Oliveira-Filho. Drafting of the manuscript: Ashkan Shoamanesh and Steven M. Greenberg. Revising the manuscript for content: Sergi Martinez-Ramirez, Guido J. Falcone, Jamarly Oliveira-Filho, Yael Reijmer, Joshua N. Goldstein, Jonathan Rosand, M. Edip

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DISCLOSURE

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