MRI-visible perivascular spaces in cerebral amyloid angiopathy and hypertensive arteriopathy

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ABSTRACT

Objective: To assess MRI-visible enlarged perivascular spaces (EPVS) burden and different topographical patterns (in the centrum semiovale [CSO] and basal ganglia [BG]) in 2 common microangiopathies: cerebral amyloid angiopathy (CAA) and hypertensive arteriopathy (HA).

Methods: Consecutive patients with spontaneous intracerebral hemorrhage (ICH) from a prospective MRI cohort were included. Small vessel disease MRI markers, including cerebral microbleeds (CMBs), cortical superficial siderosis (cSS), and white matter hyperintensities (WMH), were rated. CSO-EPVS/BG-EPVS were assessed on a validated 4-point visual rating scale (0 = no EPVS, 1 = <10, 2 = 11–20, 3 = 21–40, and 4 = >40 EPVS). We tested associations of predefined high-degree (score >2) CSO-EPVS and BG-EPVS with other MRI markers in multivariable logistic regression. We subsequently evaluated associations with CSO-EPVS predominance (i.e., CSO-EPVS > BG-EPVS) and BG-EPVS predominance pattern (i.e., BG-EPVS > CSO-EPVS) in adjusted multinomial logistic regression (reference group, BG-EPVS = CSO-EPVS).

Results: We included 315 patients with CAA-ICH and 137 with HA-ICH. High-degree CSO-EPVS prevalence was greater in CAA-related ICH vs HA-related ICH (43.8% vs 17.5%, $p < 0.001$). In multivariable logistic regression, high-degree CSO-EPVS was associated with lobar CMB (odds ratio [OR] 1.33, 95% confidence interval [CI] 1.10–1.61, $p = 0.003$) and cSS (OR 2.08, 95% CI 1.30–3.32, $p = 0.002$). Deep CMBs (OR 2.85, 95% CI 1.75–4.64, $p < 0.0001$) and higher WMH volume (OR 1.02, 95% CI 1.01–1.04, $p = 0.010$) were predictors of high-degree BG-EPVS. A CSO-EPVS-predominant pattern was more common in CAA-ICH than in HA-ICH (75.9% vs 39.4%, respectively, $p < 0.0001$). CSO-PVS predominance was associated with lobar CMB burden and cSS, while BG-EPVS predominance was associated with HA-ICH and WMH volumes.

Conclusions: Different patterns of MRI-visible EPVS provide insights into the dominant underlying microangiopathy type in patients with spontaneous ICH. *Neurology*® 2017;88:1157–1164

GLOSSARY

BG = basal ganglia; **CAA** = cerebral amyloid angiopathy; **CI** = confidence interval; **CMB** = cerebral microbleeds; **CSO** = centrum semiovale; **cSS** = cortical superficial siderosis; **EPVS** = enlarged perivascular spaces; **FLAIR** = fluid-attenuated inversion recovery; **GRE** = gradient-recalled echo; **HA** = hypertensive arteriopathy; **ICH** = intracerebral hemorrhage; **STRIVE** = Standards for Reporting Vascular Changes on Neuroimaging; **WMH** = white matter hyperintensities.

Sporadic cerebral amyloid angiopathy (CAA) and hypertensive arteriopathy (HA) are common cerebral small vessel diseases in older adults.^{1,2} CAA results from β -amyloid deposition within small cortical and leptomeningeal arteries and is a common cause of spontaneous lobar intracerebral hemorrhage (ICH).^{3,4} By contrast, HA (characterized pathologically by lipohyalinosis, arteriolosclerosis, or fibrinoid necrosis) predominantly affects small perforating end arteries of the deep gray nuclei and deep white matter and is a common cause of ICH in deep brain regions.^{1,2,5} CAA and HA have intrinsically different pathomechanisms and clinical relevance, including ICH recurrence risk.¹

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Both CAA and HA are associated with characteristic hemorrhagic and nonhemorrhagic imaging markers, including cerebral microbleeds (CMBs),⁶ cortical superficial siderosis (cSS),⁷ white matter hyperintensities (WMH),^{8,9} and more recently MRI-visible enlarged perivascular spaces (EPVS).^{10–12} The location of CMBs, similar to macrobleeds, is a consistent marker of the underlying small vessel pathology: multiple strictly lobar CMBs are associated with CAA, whereas deep CMB are more strongly related to HA.⁶ Recently, small patient cohorts suggested that the topography of EPVS is also characteristic: EPVS in the centrum semiovale (CSO; i.e., cerebral white matter) are associated with CAA,^{10,11,13} while EPVS in the basal ganglia (BG) are linked to HA-related ICH.^{10,11,13} However, these findings have not yet been externally validated in independent large cohorts.

In the present study, we explored the hypothesis that a high degree of CSO-EPVS is a marker of CAA compared to high-degree BG-EPVS being a marker of HA,¹¹ and we aimed to investigate associations with other established small vessel disease MRI markers. In addition, we tested the hypothesis that a predominant CSO-EPVS over BG-EPVS burden pattern will show strong associations with CAA-ICH and putative markers of the disease, but not HA-ICH, which will be related to BG-EPVS predominance.

METHODS Study population and data collection. For this cross-sectional analysis, we used prospectively collected data from an ongoing study of consecutive patients admitted at the Massachusetts General Hospital between 2003 and 2012 with spontaneous symptomatic ICH (presumed to be due to small vessel disease after adequate evaluation¹⁴) and available MRI of good quality (including T2-weighted, T2*-weighted gradient-recalled echo [T2*-GRE], and fluid-attenuated inversion recovery [FLAIR] sequences) as previously described in detail.^{15–17} On the basis of a review of neuroimaging and clinical data, patients were divided into those with strictly lobar hemorrhages (including both CMB and ICH) meeting Boston criteria for definite, probable, or possible CAA¹⁸ and those with strictly deep hemispheric or brainstem hemorrhages consistent with HA (i.e., non-CAA-related ICH). Lobar ICH was defined as selective involvement of the cerebral cortex and underlying white matter, whereas deep ICH was defined as selective involvement of the BG, thalamus, or brainstem. To limit the diagnostic uncertainty, we excluded cerebellar ICH ($n = 27$) and mixed ICH/CMBs cases ($n = 60$).¹⁷

Participant enrollment and clinical data collection were performed as described previously.^{16,17}

Standard protocol approvals, registrations, and patient consents. This study was performed with approval and in

accordance with the guidelines of the Massachusetts General Hospital institutional review boards.

Neuroimaging acquisition and analysis. Images were obtained with a 1.5T magnetic resonance scanner (Signa, GE Healthcare, Chicago, IL). Whole-brain axial T2*-GRE (repetition time/echo time 750/50 milliseconds, 5-mm slice thickness, 1-mm interslice gap) and FLAIR images (repetition time/echo time 10,000/140 milliseconds, inversion time 2,200 milliseconds, 1 excitation, 5-mm slice thickness, 1-mm interslice gap) were performed. All MRI analyses were performed and recorded by investigators blinded to all clinical data and according to the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) recommendations.¹⁴

Total WMH volumes were quantitatively measured on FLAIR MRI as previously described.^{17,19} CMB presence and number were evaluated on axial blood-sensitive MRIs according to current consensus criteria⁶ and categorized as lobar (i.e., cortical-subcortical) or deep (i.e., BG, thalami, brainstem). For purposes of statistical analyses, the number of lobar and deep CMBs was categorized with the use of cut points (0, 1, 2–4, or ≥ 5).²⁰ cSS was jointly assessed by 2 trained raters on axial T2*-GRE (intrater $\kappa = 0.87$),^{21,22} in line with recent consensus recommendations and criteria.^{7,21,22}

MRI-visible EPVS were assessed in line with STRIVE recommendations¹⁴; they were rated on axial T2-weighted MRIs, in the BG and CSO, with 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).^{13,23,24} The numbers refer to EPVS on one side of the brain: the side/slice with the highest number of EPVS after all relevant slices for each anatomic area were reviewed. In the presence of confluent WMH, an estimation was made of the closest EPVS rating category. In cases of large lobar or deep ICH, EPVS were assessed in the contralateral hemisphere, an estimation of the closest category ipsilateral to the lesion was made, and the highest severity was recorded. The assessment of EPVS was done by investigators blinded to CMB status, cSS ratings, WMH, and diagnostic category. In addition, CSO-EPVS and BG-EPVS were assessed independently of each other. The interrater reliability was excellent for both CSO-EPVS and BG-EPVS ($\kappa = 0.81$ and 0.85 respectively, based on a sample of 30 cases).

The degree of cortical atrophy was scored on T1-weighted, T2-weighted, and FLAIR sequences with the use of reference scans in a 4-point rating scale (0–3) based on the size of the gyri and sulci at 5 regions (frontal, parietal, temporal and occipital lobes, and insular region). The sum of these 5 regions (0–15) was calculated.²⁵ Cortical atrophy was measured on the non-ICH-affected hemisphere.

Statistics. We prespecified a dichotomized classification of EPVS degree as high (score >2) or low (score ≤ 2). This definition is in line with the EPVS burden used in previous studies (and found to relate to different vascular risk factors and imaging markers of small vessel disease)^{10,26} and might be characteristic of CSO-EPVS and CAA.¹³ We also defined a composite variable containing 3 categories by comparing degree of CSO-EPVS and BG-EPVS burden: higher degree of CSO-EPVS (i.e., CSO-EPVS $>$ BG-EPVS), equal degree in the 2 regions (i.e., CSO-EPVS = BG-EPVS), and higher degree of BG-EPVS (i.e., BG-EPVS $>$ CSO-EPVS). The composite categories were based on the EPVS scores in the 2 regions, which were assessed by investigators blinded to the predominance pattern.

Clinical and neuroimaging characteristics of patients with CAA-ICH vs HA-related ICH were compared in univariate analyses with the 2-sample t test, Wilcoxon rank-sum test, Pearson χ^2 test, and Fisher exact test as appropriate. We also performed

appropriate univariate tests to compare clinical and neuroimaging data between patients with high and those with low degree of CSO-EPVS and BG-EPVS. We explored independent, pathophysiologically relevant predictors of high CSO-EPVS and BG-EPVS degree in logistic regression analyses on the basis of our prespecified hypothesis and the results of univariable analyses (including variables with $p < 0.1$). Variables included age, total WMH volume, lobar CMB categories, deep CMB categories, high CSO-EPVS grade, high BG-EPVS grade, and cSS presence. Logistic regression models were run with a stepwise, forward-elimination method to generate a minimal adjusted model. Age was forced as a covariate in all models. As a sensitivity analysis, we also performed multivariable ordinal regression analysis to identify predictors of increasing EPVS severity in the 2 anatomic areas.

We subsequently evaluated associations with having a CSO-EPVS predominance pattern (i.e., CSO-EPVS > BG-EPVS) and BG-EPVS predominance pattern (i.e., BG-EPVS > CSO-EPVS) in adjusted multinomial logistic regression. The base outcome for these analyses was the absence of an EPVS predominance pattern (i.e., BG-EPVS = CSO-EPVS).

All tests of significance were 2 tailed. Significance level was set at 0.05 for all analyses. Stata software (version 13, 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 guidelines.²⁷

RESULTS Our final cohort included 315 patients with CAA-ICH (6 pathology-proven, 18 probable with supportive pathology, 170 probable, and 121 possible CAA according to the Boston criteria¹⁸) and 137 with HA-ICH. Demographic and imaging characteristics of the study population are presented in table 1. Patients with CAA were older (mean age 74 vs 67 years, $p < 0.001$) with a higher WMH burden on univariable analyses than patients with HA-ICH (table 1).

The prevalence of high-degree CSO-EPVS was higher in patients with CAA-related ICH compared to those with HA-related ICH (43.8% vs 17.5%,

$p < 0.001$). In contrast, the prevalence of high BG-EPVS degree was higher in patients with HA-ICH compared to those with CAA-ICH (11.7% vs 3.8%, $p = 0.001$). After adjustment for age and sex, patients with CAA-ICH had almost 4 times the risk of having high CSO-EPVS degree (adjusted odds ratio 3.7, 95% confidence interval [CI] 2.23–6.17, $p < 0.0001$).

Comparison of characteristics between patients with high and low EPVS degree in the 2 brain regions is shown in table 2. Representative examples are illustrated in the figure. The prevalence of lobar CMB and cSS was higher among patients with high vs low degree of CSO-EPVS (48.8% vs 27.9%, $p < 0.0001$ and 37.3% vs 18%, $p < 0.0001$, respectively). Deep CMBs were more common in patients with high degree of BG-EPVS. High BG-EPVS degree was also significantly associated with older age and higher total WMH volume in univariable analyses (table 2). There was no relationship between high degree of CSO-EPVS and high degree of BG-EPVS and between the degree of CSO-EPVS and BG-EPVS when the 4-point scales were tested for correlation (Spearman $\rho = -0.04$, $p = 0.409$; table 2). Only 8 patients had concomitant high degree of EPVS in both regions.

In multivariable models, lobar CMB and cSS presence were found to be independently related to high CSO-EPVS degree after adjustment for age, deep CMBs, and total WMH volume (table 3). Deep CMBs and total WMH volume were independently associated with high degree of BG-EPVS after adjustment for age and lobar CMB burden (table 3). Similar associations and effect sizes were found in sensitivity analyses of similar ordinal logistic regression looking for predictors of increased EPVS severity across the

Table 1 Comparison of demographic, clinical, and neuroimaging characteristics between patients with CAA-ICH and those with HA-related ICH

	CAA-ICH (n = 315)	HA-ICH (n = 137)	p Value
Age, mean (95% CI), y	73.9 (72.7–75.1)	67.2 (64.8–69.5)	<0.001
Sex, female, n (%)	158 (50.2)	59 (43.1)	0.147
Hypertension, n (%)	208 (66)	115 (83.9)	<0.0001
Hypercholesterolemia, n (%)	137 (43.5)	55 (40.2)	0.502
Lobar CMB count, median (IQR), n	1 (0–3)	0	<0.001
Deep CMB count, median (range), n	0	0 (0–14)	<0.001
Total WMH, median (IQR), mL	19.7 (10.6–37)	12 (6.1–29.3)	<0.001
cSS presence, n (%)	107 (34.1)	5 (3.7)	<0.001
High degree of CSO-EPVS (>20), n (%)	138 (43.8)	24 (17.5)	<0.001
High degree of BG-EPVS (>20), n (%)	12 (3.8)	16 (11.7)	0.001

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; HA = hypertensive arteriopathy; ICH = intracerebral hemorrhage; IQR = interquartile range; WMH = white matter hyperintensities.

Table 2 Comparison of characteristics between patients with high and those with low degree of MRI-visible perivascular spaces in the CSO and BG

	CSO-PVS degree >2 (n = 162)	CSO-PVS degree ≤2 (n = 290)	p Value
Age, mean (95% CI), y	73.1 (71.6–74.7)	71.1 (69.5–72.6)	0.086
Sex, female, n (%)	69 (42.6)	148 (51)	0.085
Hypertension, n (%)	115 (71)	208 (71.7)	0.868
Hypercholesterolemia, n (%)	74 (45.7)	118 (41)	0.333
High degree of BG-EPVS, n (%)	8 (4.9)	20 (6.9)	0.408
Total WMH, median (IQR), mL	19.1 (9.7–34.6)	15.9 (8.2–34.3)	0.237
Presence of lobar CMB, n (%)	79 (48.8)	81 (27.9)	<0.0001
Presence of deep MB, n (%)	6 (3.7)	29 (10)	0.016
cSS presence, n (%)	60 (37.3)	52 (18)	<0.0001
Cortical atrophy, median (IQR)	6 (3–9)	6 (2–9)	0.799
	BG-PVS degree >2 (n = 28)	BG-PVS degree ≤2 (n = 424)	p Value
Age, mean (95% CI), y	76.9 (73.4–80.3)	71.5 (70.3–72.7)	0.024
Sex, female, n (%)	18 (64.3)	199 (46.9)	0.075
Hypertension, n (%)	24 (85.7)	299 (70.5)	0.085
Hypercholesterolemia, n (%)	10 (35.7)	182 (42.9)	0.442
High degree of CSO-EPVS, n (%)	8 (28.6)	154 (36.3)	0.408
Total WMH, median (IQR), mL	31.4 (19.9–55)	16.1 (8.6–32.8)	0.001
Presence of lobar CMB, n (%)	10 (35.7)	150 (35.4)	0.971
Presence of deep MB, n (%)	8 (28.6)	27 (6.4)	<0.0001
cSS presence, n (%)	3 (11)	109 (25.8)	0.088
Cortical atrophy score, median (IQR)	9.5 (8–12)	6 (2–9)	0.0002

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; PVS = perivascular spaces; WMH = white matter hyperintensities.

whole EPVS degree spectrum (results not shown). The inclusion of hypertension history in the models did not modify these associations, and hypertension was not associated with EPVS patterns ($p > 0.2$ for all comparisons).

EPVS degree predominance patterns in the CSO vs BG. Approximately 24% of the patients had the same burden of CSO-PVS and BG-EPVS (18.4% in the CAA-ICH group and 37.2% in HA-ICH). A CSO-EPVS-predominant pattern (CSO-EPVS > BG-EPVS burden) was found in 64.8% of the whole group and was more common in CAA-ICH vs HA-ICH (75.9% vs 39.4%, respectively, $p < 0.0001$). In contrast, BG-EPVS predominance (BG-EPVS > CSO-EPVS burden) was seen in 11% of the cohort and was more common in patients with HA-ICH than in those with CAA-ICH (23.4% vs 5.7%, respectively, $p < 0.0001$) (figure, C). The sensitivity and specificity of the CSO-EPVS-predominant pattern for distinguishing CAA-ICH from HA-ICH were 93% (95% CI 89.2–95.8) and 37.2% (95% CI 27–48.3), respectively.

In multinomial logistic regression, after adjustments for age and sex, CAA-ICH diagnosis was associated with CSO-EPVS-predominant pattern while HA-ICH was associated with lower odds of CSO-EPVS predominance (reference group: BG-EPVS = CSO-EPVS for all comparisons) (table 4). The opposite was true for the BG-EPVS-predominance pattern (table 4). In multinomial logistic regression models adjusted for different small vessel disease MRI markers, CSO-EPVS predominance (reference group: BG-EPVS = CSO-EPVS for all comparisons) was associated with lobar CMBs burden and cSS presence and inversely associated with deep CMB burden (table 4). BG-EPVS predominance (reference group: BG-EPVS = CSO-EPVS for all comparisons) was associated only with increased WMH volumes (table 4).

DISCUSSION The main finding from this cross-sectional study of a large consecutive cohort of patients with spontaneous ICH is that the topography pattern of MRI-visible EPVS is characteristic of the presumed underlying arteriopathy. High degree of CSO-EPVS has a higher prevalence in CAA-ICH and is strongly associated with putative markers of the

Figure Different enlarged perivascular spaces (EPVS) burden in the centrum semiovale (CSO) and basal ganglia (BG)

C. EPVS predominance patterns in CAA-ICH vs HA-ICH

(A.a and B.a) Representative examples of high degree of CSO-EPVS in patients with cerebral amyloid angiopathy-intracerebral hemorrhage (CAA-ICH). Arrowheads point to individual EPVS. (A.b and B.b) Examples of mild BG-EPVS (A.b) and high-degree BG-EPVS in 2 patients with deep hypertensive arteriopathy (HA)-ICH. (C) Box plot of the distribution of the 3 EPVS predominance patterns in patients with CAA-ICH vs HA-ICH.

disease, including lobar CMBs and cSS. High degree of BG-EPVS is more common in HA-ICH and independently associated with higher WMH volume and deep CMBs, a marker of HA severity. Similar results were found according to the predominant EPVS topography (compared to the reference group of equal predominance, i.e., BG-EPVS = CSO-EPVS) on MRI in each given patient. Taken together, our findings provide strong evidence of EPVS burden and pattern being additional markers of different small vessel disease processes in patients with spontaneous ICH.

MRI-visible EPVS have recently been suggested as useful markers of small vessel disease in STRIVE recommendations,¹⁴ but the relationship between EPVS distribution and different underlying small vessel

pathologies is still under active investigation. On the basis of the almost inverse topography of CAA and HA in the brain and previous small studies in patients with ICH, we expected striking differences in the regional distribution of EPVS in the CSO and BG (similar to lobar vs deep CMBs) between these small vessel diseases.²⁸ Our data provide support for this hypothesis from a large, independent cohort.^{10,11} Perivascular spaces (also known as Virchow-Robin spaces) are interstitial fluid-filled cavities around small perforating arteries as they course from the brain surface into and through the brain parenchyma.²⁹ These perivascular channels function as the brain drainage system for interstitial fluid and solutes, including soluble β -amyloid.^{30,31} The mechanisms of perivascular space enlargement and their appearance on MRI

Table 3 Multivariable logistic regression analyses of associations with high degree of CSO-EPVS and BG-EPVS in different models

	OR (95% CI)	p Value
High CSO-EPVS degree		
Age, y	1.01 (0.99–1.03)	0.347
Lobar CMB categories	1.33 (1.10–1.61)	0.003
Deep CMB categories	0.65 (0.39–1.11)	0.114
cSS presence	2.08 (1.30–3.32)	0.002
Total WMH, mL	0.99 (0.98–1.00)	0.266
High BG-EPVS degree		
Age, y	1.03 (0.99–1.07)	0.110
Lobar CMB categories	1.06 (0.74–1.52)	0.735
Deep CMB categories	2.85 (1.75–4.64)	<0.0001
Total WMH, mL	1.02 (1.01–1.04)	0.010

Abbreviations: BG = basal ganglia; CI = confidence interval; CMB = cerebral microbleed; CSO = centrum semiovale; cSS = cortical superficial siderosis; EPVS = enlarged perivascular spaces; OR = odds ratio; WMH = white matter hyperintensities.

remain poorly understood. The link between CSO-EPVS and CAA may specifically reflect interstitial fluid drainage impairment within the perivascular spaces caused by cumulative leptomeningeal and superficial cortical vascular β -amyloid deposition, a central and probably early event in the pathophysiology of CAA.^{10,32,33} In a postmortem study of

Alzheimer disease, pathologically defined CSO-EPVS were directly associated with CAA.³⁴

Previous studies across different populations have highlighted strong indirect associations between BG-EPVS severity (more consistently than CSO-EPVS) and hypertension, WMH, and deep lacunes of presumed vascular origin, which are all important features of HA.^{23,26,35} By contrast, CSO-EPVS have not been shown to be associated with conventional vascular risk factors, but only with increasing age,^{11,23} and thus may relate to a different underlying microarteriopathy. This is supported by a recent study among patients at a memory clinic showing an association between CSO-EPVS and lobar CMB count and BG-EPVS and hypertension.¹⁰ Our results are in line with these previous studies. It should be emphasized that the independent associations of CSO-EPVS with CAA-specific imaging markers (including cSS and lobar CMBs) were not seen for BG-EPVS. Interestingly, there was no correlation between high burden of CSO-EPVS and BG-EPVS, supporting the concept that these are due to different pathophysiological processes.^{10,11,13} It is important to bear in mind, however, that CAA and HA often coexist in the aging brain. HA is a broad umbrella term that groups together a spectrum of sporadic nonamyloid small vessel disease pathologies often associated with advanced age and hypertension.² However, HA is not necessarily, or even often, related specifically to hypertension.² Similarly, patients with CAA, a more well-defined microangiopathy, are also often hypertensive (table 1). The role of hypertension in CAA pathophysiology and evolution is uncertain, and in our cohort, the EPVS distribution was independent of hypertension history.

One important aspect of our study was the use of an EPVS predominance pattern, either CSO-EPVS, BG-EPVS or CSO-EPVS=BG-EPVS. The 2 main nonhemorrhagic MRI markers of cerebral small vessel disease, namely severe regional EPVS and WMH patterns, are not very sensitive for the detection of CAA vs HA.^{11,17} The highest prevalence shown has been $\approx 30\%$ for severe CSO-EPVS (40% in our cohort) and multiple white matter spots pattern, both in patients with CAA.^{11,17} The CSO-EPVS–predominant pattern was found in 75.9% of the patients with CAA enrolled in our current study, with a high sensitivity but low specificity for the disease. The EPVS predominance is easy to assess, and it takes into account their preferential distribution even in patients who do not demonstrate severe EPVS. It is important to note again that for the EPVS predominance analysis in our study, the comparison being made is not with no EPVS but with ICH patients who had equal distribution of CSO-EPVS and BG-EPVS. A potential limitation is thus the lack of a control group (e.g., age-matched healthy patients

Table 4 Multinomial logistic regression of associations with dominant EPVS patterns: CSO-EPVS > BG-EPVS and BG-EPVS > CSO-EPVS

	OR (95% CI)	p Value
CSO-EPVS > BG-EPVS degree		
CAA-ICH diagnosis ^a	5.03 (2.98–8.48)	<0.0001
HA-ICH diagnosis ^a	0.20 (0.12–0.34)	<0.0001
Age, years	0.98 (0.97–1.00)	0.122
Lobar CMBs categories	1.31 (1.02–1.68)	0.033
Deep CMBs categories	0.49 (0.29–0.82)	0.007
cSS presence	2.78 (1.46–5.30)	0.002
Total WMH, mL	0.99 (0.98–1.01)	0.361
BG-EPVS > CSO-EPVS degree		
CAA-ICH diagnosis ^a	0.41 (0.20–0.84)	0.015
HA-ICH diagnosis ^a	2.45 (1.19–5.04)	0.015
Age, y	1.00 (0.97–1.03)	0.830
Lobar CMBs categories	0.96 (0.67–1.39)	0.830
Deep CMBs categories	1.36 (0.85–2.18)	0.203
Total WMH, mL	1.02 (1.01–1.58)	0.005

Abbreviations: BG = basal ganglia; CAA = cerebral amyloid angiopathy; CI = confidence interval; CMB = cerebral microbleed; CSO = centrum semiovale; cSS = cortical superficial siderosis; HA = hypertensive arteriopathy; ICH = intracerebral hemorrhage; EPVS = enlarged perivascular spaces; OR = odds ratio; WMH = white matter hyperintensities. The base outcome for all analyses is the BG-EPVS = CSO-EPVS pattern.

^a Adjusted for age and sex.

or patients with other small vessel diseases) to test these predominance patterns, which might limit the generalizability of the results.

Strengths of the current study include the systematic evaluation of MRI scans by trained raters using validated scales for a range of small vessel disease imaging markers, the volumetric assessment of total WMH volume, and the use of prespecified EPVS cutoffs and patterns. The large sample size of consecutive patients with ICH with pure lobar and deep hemorrhages in our cohort allowed us to build robust, adjusted models to test prespecified hypotheses and to detect previously unreported associations, e.g., between high burden of CSO-EPVS and other markers of CAA. A limitation is the potential selection bias due to the requirement for MRI to be performed as part of routine clinical care. For example, the exclusion of patients with severe ICH who do not undergo clinical MRI might account for the relatively low prevalence of high degree BG-EPVS in our cohort. We also acknowledge the potential limitations of the EPVS visual rating scale used, which, although validated,^{23,24} is not truly quantitative and may be affected by observer variability. However, the distinction between CSO-EPVS vs BG-EPVS and the predefined cutoff used was sensitive enough to capture the topographic differences and independent associations consistently in different models.

The current study further supports the notion that different topographical patterns of MRI-visible EPVS can provide insights into the dominant type of underlying arteriopathy and potential mechanisms.¹³ High degree of CSO-EPVS and a CSO-EPVS predominance pattern seems to be quite characteristic of CAA, a finding supported by its strong relation with established hemorrhagic markers of the disease, including lobar CMBs and cSS. High degree of BG-EPVS and a BG-EPVS predominance pattern correlate well with the underlying anatomic distribution and burden of HA in the small deep perforators and are related to the total WMH lesion volume, partly reflecting a more advanced stage in the disease process. Our results hence provide a simple strategy for using predominant CSO-EPVS and BG-EPVS patterns as additional and relatively sensitive markers of the dominant microvasculopathy type in older individuals with ICH. Future research should explore these markers in ICH cohorts with neuropathologic confirmation of the small vessel disease type and in older individuals presenting with microbleeds but no symptomatic ICH. Validation in studies including healthy elderly control groups would also be useful.

AUTHOR CONTRIBUTIONS

A. Charidimou: project concept, data collection imaging analysis, data analysis, statistical analysis, write-up. G. Boulouis: data collection, imaging analysis, critical revisions. M. Pasi, E. Auriel, E.S. van Etten, and

K. Haley: imaging analysis, critical revisions. A. Ayres, and K.M. Schwab: data collection and management. Sergi Martinez-Ramirez and Joshua N. Goldstein: critical revisions. J. Rosand and A. Viswanathan: data collection, critical revisions. S.M. Greenberg: funding, data collection, critical revisions. M.E. Gurol: project concept and design, data collection, data analysis, write-up, critical revisions.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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