White Matter Perivascular Spaces Are Related to Cortical Superficial Siderosis in Cerebral Amyloid Angiopathy

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Background and Purpose—We set out to investigate whether MRI-visible centrum semiovale perivascular spaces (CSO-PVS), a potential biomarker of impaired interstitial fluid drainage in sporadic cerebral amyloid angiopathy, is associated with cortical superficial siderosis (cSS), reflecting recurrent hemorrhage from severe leptomeningeal and superficial cortical vascular amyloid.

Methods—Retrospective multicenter cohort study of possible/probable cerebral amyloid angiopathy according to the Boston criteria. PVS were rated in basal ganglia and CSO (CSO-PVS) on axial T2-weighted sequences, using a validated 4-point visual rating scale and were classified as high (score >2) or low degree (score ≤2) for prespecified analyses. Independent risk factors for high CSO-PVS degree were investigated in logistic regression.

Results—The final cohort consisted of 138 cerebral amyloid angiopathy patients (mean age, 71.8 years; 95% confidence interval, 70.2–73.4 years; 52.2% men). High CSO-PVS degree was present in 61.2% of cases. The prevalence of any cSS, and disseminated cSS (involving >3 sulci), was higher in patients with high versus low CSO-PVS degree (for any cSS 45.9% versus 13.5%; P<0.00005; for disseminated cSS 31.8% versus 0%; P<0.00005). In multivariable logistic regression analysis, cSS presence (odds ratio, 4.78; 95% confidence interval, 1.64–13.87; P=0.004) was an independent predictor of high CSO-PVS degree. We found no associations between basal ganglia PVS and cSS.

Conclusions—High degree of CSO-PVS is highly prevalent in sporadic cerebral amyloid angiopathy and is related to cSS. Our findings suggest that severe leptomeningeal and cortical vascular amyloid (causing cSS) is related to impaired interstitial fluid drainage from cerebral white matter, although determining the causal direction of this relationship requires prospective studies. (Stroke. 2014;45:2930-2935.)

Key Words: cerebral amyloid angiopathy ➤ cerebral hemorrhage ➤ cerebral small vessel diseases ➤ magnetic resonance imaging ➤ siderosis

Sporadic cerebral amyloid angiopathy (CAA) is a common small vessel disease that results from progressive amyloid-β deposition within the walls of small cortical and leptomeningeal arteries.1,2 CAA is most often recognized in life by symptomatic, lobar intracerebral hemorrhage (ICH) and cognitive impairment in elderly patients.1–3 CAA is also associated with characteristic MRI markers including strictly lobar cerebral microbleeds (CMBs) and white matter hyperintensities (WMHs).1–4 These imaging markers might be suggestive of CAA even in asymptomatic elderly individuals.

Accumulating evidence suggests that cortical superficial siderosis (cSS)5–8 and MRI-visible centrum semiovale (ie, cerebral hemisphere white matter) perivascular spaces (CSO-PVS) are new imaging markers of CAA, which may reflect distinct but related aspects of pathophysiology. However, the precise relationship between CSO-PVS and other imaging manifestations of CAA, including cSS and lobar CMBs, has not been explored.

We hypothesized that progressive amyloid-β deposition in small leptomeningeal or superficial cortical vessels (leading to fragility, repeated hemorrhage into the subarachnoid space and cSS) blocks perivascular drainage pathways from white matter to the cortical surface, resulting in CSO-PVS. To test this hypothesis and to gain insights into potential mechanisms, we investigated the relationship between MRI-visible CSO-PVS and cSS in patients with possible or probable CAA according to the Boston criteria.

Methods

Study Population and Data Collection

Consecutive CAA patients (according to the original Boston criteria; ie, not including cSS as a criterion) from an ongoing multicenter
cohort study at 4 stroke centers over defined time periods as previously described were evaluated. The centers were University College London Hospitals NHS Foundation Trust (London; 03/2003–09/2011), Addenbrooke’s Hospital (Cambridge; 07/2002–03/2010), Cliniques Universitaires Saint Luc (Brussels; 12/2003–04/2010), and CHU Mont-Godinne UCL (Brussels; 08/2005–03/2009). At participating centers, MRI is a routine investigation for cases of suspected CAA, unless there are contraindications. Essential inclusion criteria for the multicenter CAA cohort and the analysis (1) CAA, defined according to the Boston criteria, including lobar CMs, but not CS and (2) available MRI sequences of adequate quality including T2-weighted, T2*-weighted gradient-recalled echo (T2*-GRE), and fluid attenuation inversion recovery sequences. The selection process of this multicenter cohort has been described previously in brief, from a total of 358 patients with suspected CAA/spontaneous ICH screened, 144 were initially excluded because of MRI was not performed or was not available/interpretable. After reviewing available MRI and clinical data, 56 patients not fulfilling the Boston criteria for CAA were further excluded, leaving a total of 158 CAA patients potentially eligible for the current analysis: 59 patients from University College London Hospitals, 49 from Addenbrooke’s Hospital, 36 from Cliniques Universitaires Saint Luc, and 14 patients from CHU Mont-Godinne UCL. Patients with no T2 MR (n=14), T2 MR of insufficient quality (n=1), and irretrievable sequences (n=5) were further excluded from this analysis. Demographic and clinical information was obtained from prospectives and by medical records review using standardized data collection forms, as previously described. Hypertension was defined as a history of antihypertensive treatment or documented elevated blood pressure (systolic >150 or diastolic >95 mmHg) before admission, diabetes mellitus as ongoing use of a hypoglycemic agent, and smoking as history of tobacco use before admission. The study received ethical approval by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee, the Commission d’Ethique Biomedicale Hospitalo Facultaire of the Faculte de Medicine (Université Catholique de Louvain), and the Comite d’etique medicale du CHU Dinant-Godinne (Université Catholique de Louvain). Neuroimaging Data and Analysis The MRI protocols were similar in each hospital. Imaging was performed at field strength of 1.5T for all patients and included T2-weighted (slice thickness, 4–6 mm; slice gap, 2–6 mm; echo time, 89–90/92 ms; relaxation time, 4408/6040/5610/6630/4520 ms), fluid attenuation inversion recovery, T2*-GRE (slice thickness, 5 mm; slice gap, 1.5/5.6; 5 mm; repetition time, 500–1000 ms; echo time, 40/26/15/50–70 ms), and diffusion-weighted imaging sequences. MR images were reviewed by a single trained rater blinded to clinical data. PVS were assessed and rated on axial T2-weighted MR images, according to Standards for Reporting Vascular changes on nEuroimaging (STRIVE), by a trained observer using a validated 4-point visual rating scale (0=no PVS; 1=1–10 PVS; 2=11–20 PVS, 3=21–40 PVS, and 4=40 PVS) in the basal ganglia (BG) and CSO. The numbers refer to PVS on one side of the brain: after reviewing all relevant slices for the anatomic area being assessed, the slice and side with the highest number of PVS were recorded. The assessment of PVS may be influenced by the presence of confluent WMH; in such cases, estimation was made of the closest PVS rating category, using the appearance of noninvolved white matter, according to the rating scale used. In cases of large lobar ICH, centrum semiouale PVS were assessed contralateral to the index ICH lesion; an estimation of the closest category ipsilateral to the lesion was made, and the highest severity was recorded. Intrarater reliability testing of the PVS scale using a data set of ICH scans showed an intrarater Cohen’s κ of 0.91 for BG-PVS and 0.82 for CSO-PVS. The κ was defined as a linear residues of chronic blood products in the superficial layers of the cerebral cortex showing a characteristic gyriiform pattern of low signal on T2*-GRE images, without corresponding hyperintense signal on T1-weighted or fluid attenuation inversion recovery images. The distribution of CS was classified as focal (restricted to ≤3 sulci) or disseminated (≥4 sulci). The inter-rater agreement for the presence or absence of PVS in our group has been previously and was 89.6% (Cohen κ=0.79). T2-weighted MR images were assessed for PVS blinded to CS status on T2*-GRE and vice versa; both markers were rated blind to the study hypothesis. WMH (leukoaraiosis) were assessed with a 4-step simplified Fazekas rating scale, from 0 to 3 (0=no lesions; 1=focal lesions; 2=early confluent; and 3=confluent). Lobar CMs were evaluated on T2*-GRE images according to the Microbleeds Anatomical Rating Scale, as previously described Statistically Analysis We prespecified a dichotomized classification of PVS degree as high (score ≥2) or low (score ≤2). This definition is in line with the most severe category of CSO-PVS used in a previous study (and found to relate to vascular risk factors) and seems to be sensitive for CAA diagnosis. We compared demographic, clinical, and imaging characteristics of CAA patients with high versus low CSO-PVS degree using appropriate univariable tests: χ2 test or Fisher exact test for categorical variables and Student t-test for age. Multivariable logistic regression analysis was used to explore the relation between high CSO-PVS degree and CS adjusted for other variables based on the results of univariable analysis, plus other biologically plausible confounders related to PVS or CS severity, including age, sex, hypertension, WMH, CMB number, and previous history of symptomatic ICH (see Results section of this article). We further adjusted our multivariable model for possible or probable CAA diagnostic category. We repeated these analyses only within the probable CAA Boston diagnostic category. Because CMB number distribution in our cohort was not normally distributed, as a sensitivity analysis, we repeated our multivariable logistic regression analyses by including multiple (≥2) CMBs or CMB categories (0, 2–4, 5–10, and >10 CMBs) into the models, which remained consistent. Multicollinearity was assessed by computing variance inflation factors for all predictors and removing all variables with variance inflation factors >5. None of our included predictors in multivariable models had a variance inflation factors >5. Significance level was set at 0.05 for all analyses. Statistical analyses were performed using STATA (Version 11.2, StataCorp.). Results The final cohort consisted of 138 patients; 32 patients with possible CAA, 97 with probable CAA, and 9 patients with supportive pathology based on the Boston criteria (Table 1). Of these, 120 (87%) patients presented with symptomatic lobar ICH at baseline, 9 with transient focal neurological episodes, 3 with cognitive decline, 1 with acute convexity subarachnoid hemorrhage, and 5 with ischemic stroke. All patients had some degree of MRI-visible CSO-PVS; high CSO-PVS degree was present in 61.2% (n=85) of cases. Fifteen (10.9%) individuals had 1 to 10 CSO-PVS, 38 (27.5%) had 11 to 20 CSO-PVS, 50 (36.2%) had 21 to 40 CSO-PVS, and 35 (25.4%) patients had ≥40 CSO-PVS. There was no correlation between BG-PVS and CSO-PVS severity (data not shown). CS was detected in 46 (33.3%; 95% confidence interval [CI], 25.5%–41.9%) CAA patients; 19 (13.8%; 95% CI, 8.5%–20.7%) patients had focal, and 27 (19.7%; 95% CI, 13.3%–27.2%) had disseminated CS. Patients with CS more often had ≥5 CMs than patients without sidosclerosis (47.8% versus 30%; P=0.040) and a higher (but not statistically significant at the 5% level) prevalence of small acute ischemic
lesions on diffusion-weighted imaging sequences (22% versus 11.3%; P=0.117).

Comparisons of characteristics between patients with high degree and low degree of CSO-PVS are summarized in Table 1. Representative examples of cSS and CSO-PVS are shown in the Figure. The prevalence of any cSS was higher in patients with high CSO-PVS degree (45.9% versus 13.5%; P<0.00005). Disseminated cSS was present in 31.8% of participants with high CSO-PVS degree but none of those with low CSO-PVS degree (P<0.00005). High degree of CSO-PVS was associated with lower prevalence of moderate-to-severe leukoaraiosis and lower prevalence of hypertension (Table 1). cSS extent (ie, no cSS, to focal and disseminated) was associated with CSO-PVS degree in ordinal logistic regression analysis (odds ratio, 3.22; 95% CI, 1.99–5.21; P<0.00005). We found no association between BG-PVS and cSS.

In multivariable logistic regression models, high degree of PVS in the CSO was independently associated with the presence of cSS (odds ratio, 4.78; 95% CI, 1.64–13.87; P=0.004) after adjusting for age, sex, hypertension, CMB number, WMH, previous history of symptomatic ICH, and probable versus possible CAA. All results were of similar effect size in sensitivity analyses including only patients with probable CAA (Table 2). Both models remained consistent when multiple (≥2) CMBs or CMB categories (0, 2–4, 5–10, and >10 CMBs) were included instead of CMB number.

**Discussion**

In this multicenter study we have shown that high degree of MRI-visible CSO-PVS is highly prevalent in patients with CAA and is related to the presence and severity of cSS, a characteristic neuroimaging marker of CAA.8,10 This association further adds to the accumulating evidence that CSO-PVS (but not BG-PVS) might be another potential MRI marker of CAA with implications for improving the sensitivity of in vivo diagnosis.15,19,21 We found neither an association between BG-PVS and any CAA-specific imaging markers (including cSS and lobar CMBs) nor any correlation between severe CSO-PVS and BG-PVS, supporting the hypothesis that MRI-visible CSO-PVS compared to BG-PVS are due to different pathophysiological processes.15,19,21 The structure of perivascular spaces in the BG, however, differs from those in the cerebral cortex, in that they are surrounded by two periarterial membranes, perhaps making them less vulnerable to vascular amyloid accumulation.23 Our findings also have implications for understanding CAA pathophysiology, and suggest that severe leptomeningeal and cortical vascular amyloid (causing cSS) might be related to impaired interstitial fluid drainage from cerebral white matter (causing severe CSO-PVS).

The link between CSO-PVS and CAA may indeed reflect interstitial fluid drainage impairment within the perivascular...

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**Table 1. Characteristics and Comparison of CAA Patients With and Without Severe CSO-PVS**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All CAA (n=138)</th>
<th>High Degree of CSO-PVS (n=85)</th>
<th>Low Degree of CSO-PVS (n=53)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (95% CI), y</td>
<td>71.8 (70.2–73.4)</td>
<td>72.6 (71–74.3)</td>
<td>70.5 (67.2–73.7)</td>
<td>0.189</td>
</tr>
<tr>
<td>Sex, men (%)</td>
<td>72 (52.2)</td>
<td>43 (50.6)</td>
<td>29 (54.7)</td>
<td>0.637</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>80 (63)</td>
<td>39 (50.7)</td>
<td>41 (82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>On antithrombotics (%)</td>
<td>36 (27.5)</td>
<td>24 (29.6)</td>
<td>12 (24)</td>
<td>0.483</td>
</tr>
<tr>
<td>History of prior symptomatic ICH (%)</td>
<td>44 (32.8)</td>
<td>22 (26.8)</td>
<td>22 (42.3)</td>
<td>0.063</td>
</tr>
<tr>
<td>Acute ischemic lesions (%)</td>
<td>18 (14.9)</td>
<td>14 (18)</td>
<td>4 (9.3)</td>
<td>0.287</td>
</tr>
<tr>
<td>Lobar CMB presence (%)</td>
<td>91 (66.9)</td>
<td>58 (68.2)</td>
<td>33 (64.7)</td>
<td>0.672</td>
</tr>
<tr>
<td>Lobar CMB count, median (IQR range)</td>
<td>2 (0–8)</td>
<td>2 (0–9)</td>
<td>2 (0–6)</td>
<td>0.479</td>
</tr>
<tr>
<td>Presence ≥5 lobar CMBs (%)</td>
<td>49 (36)</td>
<td>35 (41.2)</td>
<td>14 (27.5)</td>
<td>0.107</td>
</tr>
<tr>
<td>cSS presence (%)</td>
<td>46 (33.6)</td>
<td>39 (45.9)</td>
<td>7 (13.5)</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>Focal cSS (%)</td>
<td>19 (13.9)</td>
<td>12 (14.1)</td>
<td>7 (13.5)</td>
<td>0.914</td>
</tr>
<tr>
<td>Disseminated cSS (%)</td>
<td>27 (19.7)</td>
<td>27 (31.8)</td>
<td>0 (0)</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>Moderate-to-severe white matter</td>
<td>23 (16.9)</td>
<td>10 (11.8)</td>
<td>13 (25.5)</td>
<td>0.039</td>
</tr>
</tbody>
</table>

P values refer to differences between CAA patients with vs without CSO-PVS, using \( \chi^2 \) tests and the Fisher exact test for categorical variables, and 2-sample \( t \) tests or Mann–Whitney \( U \) tests depending on the distribution of continuous variables. CAA indicates cerebral amyloid angiopathy; CI, confidence interval; CMB, cerebral microbleed; CSO-PVS, centrum semiovale perivascular spaces; cSS, cortical superficial siderosis; ICH, intracerebral hemorrhage; and IQR, interquartile range.
spaces caused by leptomeningeal and superficial cortical vascular amyloid-β, a major feature in sporadic CAA and Alzheimer disease. Perivascular spaces form important pathways (along the basement membranes of capillaries and arteries) for the drainage of interstitial fluid and solutes, including soluble amyloid-β, from the brain. One key hypothesis for the development of CAA is that as perivascular drainage pathways fail with age (particularly in association with the ApoE e4 allele), or are overloaded by reduced capacity of other elimination mechanisms, amyloid-β is increasingly trapped and deposited in the walls of small arteries. Amyloid-β deposition in small cortical and leptomeningeal arteries in CAA could disrupt drainage, leading to retrograde dilation of perivascular spaces in the underlying white matter of the centrum semiovale (either by blocking bulk flow or by diminishing the pulsatility of small vessels required for efficient interstitial fluid drainage), leading to CSO-PVS visible on MRI. Cumulative superficial amyloid deposition could then promote further amyloid deposition, creating a feed-forward loop, further reducing drainage efficiency. Of note, histopathologic studies have shown a gradient of amyloid deposition in small cortical and leptomeningeal arteries in CAA, with more severe deposition in leptomeningeal than in parenchymal vessels of the same brain section, and superficial cortical layers have more extensive vascular amyloid-β deposition than deeper layers. Repeated episodes of hemorrhage from these brittle, severely CAA-affected leptomeningeal or superficial cortical vessels into the subarachnoid space are probably an important cause of cSS. Indeed, in CAA, cSS has a characteristic predilection for the cerebral convexities, reflecting linear blood residues in the superficial layers of the cerebral cortex or in the subarachnoid space.

Our study has several strengths including the systematic evaluation of MRI scans by trained raters using validated scales for a range of imaging markers of small vessel disease and the testing of a prespecified hypothesis. The main limitation is the potential selection bias because of the requirement for MRI done as part of routine clinical care; hence, our results can only be extrapolated to patient populations in a similar clinical context with available MRI and need to be validated using larger independent cohorts. Also, although the MRI protocols were similar in each hospital, they varied across centers, introducing another potential source of bias. However, our findings are unlikely to be accounted by differences in MRI sequence parameters. Although we did our best to blind the MRI rating of cSS from CSO-PVS severity and vice versa, by rating both markers using larger independent cohorts. Also, although the MRI protocols were similar in each hospital, they varied across centers, introducing another potential source of bias. However, our findings are unlikely to be accounted by differences in MRI sequence parameters. Although we did our best to blind the MRI rating of cSS from CSO-PVS severity and vice versa, by rating both markers using large independent cohorts.

### Table 2. Univariate (Unadjusted) and Multivariable (Adjusted) Logistic Regression Analysis of Associations With High-Degree Centum Semiovale Perivascular Spaces, in the Whole Cohort of Patients With CAA and in Patients With Probable CAA

<table>
<thead>
<tr>
<th></th>
<th>Whole CAA cohort (n=138)</th>
<th>Probable CAA (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>PValue</td>
</tr>
<tr>
<td>cSS presence</td>
<td>5.45 (2.21–13.45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.03 (0.99–1.06)</td>
<td>0.189</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.23 (0.10–0.53)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex (men vs women)</td>
<td>0.85 (0.43–1.69)</td>
<td>0.637</td>
</tr>
<tr>
<td>CMB count</td>
<td>1.01 (0.98–1.04)</td>
<td>0.449</td>
</tr>
<tr>
<td>History of prior symptomatic ICH</td>
<td>0.50 (0.24–1.04)</td>
<td>0.065</td>
</tr>
<tr>
<td>WMH (moderate to severe)</td>
<td>1.10 (0.55–2.20)</td>
<td>0.709</td>
</tr>
<tr>
<td>Probable vs possible CAA</td>
<td>1.58 (0.71–3.51)</td>
<td>0.263</td>
</tr>
<tr>
<td>cSS presence</td>
<td>5.29 (2.05–13.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.04 (1.00–1.08)</td>
<td>0.073</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.24 (0.09–0.63)</td>
<td>0.004</td>
</tr>
<tr>
<td>Sex (men vs women)</td>
<td>0.78 (0.35–7.74)</td>
<td>0.543</td>
</tr>
<tr>
<td>CMB count</td>
<td>1.0 (0.98–1.04)</td>
<td>0.582</td>
</tr>
<tr>
<td>History of prior symptomatic ICH</td>
<td>0.63 (0.27–1.47)</td>
<td>0.288</td>
</tr>
<tr>
<td>WMH (moderate to severe)</td>
<td>0.90 (0.40–2.03)</td>
<td>0.799</td>
</tr>
</tbody>
</table>

Both models remained consistent when multiple (≥2) CMBs or CMB categories (0, 2–4, 5–10, and >10 CMBs) were included. CAA indicates cerebral amyloid angiopathy; CI, confidence interval; CMB, cerebral microbleed; cSS, cortical superficial siderosis; ICH, intracerebral hemorrhage; OR, odds ratio; and WMH, white matter hyperintensities.
lesions on diffusion-weighted imaging, because of our limited sample size and the relatively low prevalence of these lesions in CAA. However, severe CAA is associated with numerous cortical microinfarcts, which are difficult to resolve on 1.5T MRI, as used in this study. It may be of interest to study the relation of CSO-PVS and microinfarcts on high field strength in the future.32 The inverse association between high CSO-PVS degree and the presence of hypertension is also interesting and may reflect a protective effect related to aggressive treatment of hypertension in these patients. Finally, we did not have pathological confirmation of CAA and acknowledge that the Boston criteria for CAA diagnosis have imperfect specificity, especially for the possible CAA category, in which some cases may include other cerebral small vessel diseases (eg, hypertensive arteriopathy).9,33 Our study should be considered hypothesis generating. Larger prospective CAA cohorts are needed to clarify how exactly CSO-PVS are linked to cSS (ie, to determine the causal direction of this relationship) as well as other specific MRI markers and whether they might identify an imaging phenotype of CAA with more superficial disease. A key question for future work will be whether CSO-PVS are an early marker of a CAA-related disease process, which ultimately leads to severe cortical and leptomeningeal amyloid deposition, with important implications for future hemorrhage risk.31 Both cSS and PVS have been shown to be more prevalent in memory clinic patients (with Alzheimer disease or mild cognitive impairment) compared with healthy controls31,34–36; it would be interesting to investigate whether patients with cSS and CSO-PVS differ from those without these findings with regard to cognitive function. MRI-visible PVS are also common in the general population, especially with increased age20,22,36,37 and might be related with worse cognitive function14 and incident dementia.38

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Disclosures

None.

References

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