Distribution of lacunes in cerebral amyloid angiopathy and hypertensive small vessel disease

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ABSTRACT

Objective: To evaluate whether the burden of deep and lobar lacunes differs between patients with intracerebral hemorrhage (ICH) with definite/probable cerebral amyloid angiopathy (CAA) per the Boston criteria and hypertensive small vessel disease (HTN-SVD; ICH in basal ganglia, thalami, brainstem).

Methods: We defined lobar and deep lacunes similar to the topographic distribution used for ICH and cerebral microbleeds (CMBs). We then compared their distribution between patients with CAA-ICH and those with strictly deep CMB and ICH (HTN-ICH). The independent associations of lacune location with the diagnosis of CAA-ICH and HTN-ICH were evaluated with multivariable models. The relationship between lobar lacunes and white matter hyperintensity (WMH) volume was evaluated by means of partial correlation analyses adjusted for age and a validated visual scale.

Results: In our final cohort of 316 patients with ICH, lacunes were frequent (24.7%), with similar rates in 191 patients with CAA and 125 with HTN-ICH (23% vs 27.2%, $p = 0.4$). Lobar lacunes were more commonly present in CAA (20.4% vs 5.7%, $p < 0.001$), while deep lacunes were more frequent in HTN-ICH (15.2% vs 2.1%, $p < 0.001$). After correction for demographics and clinical and neuroimaging markers of SVD, lobar lacunes were associated with CAA ($p = 0.003$) and deep lacunes with HTN-ICH ($p < 0.001$). Lobar lacunes in 80% of the cases were at least in contact with WMH, and after adjustment for age, they were highly correlated to WMH volume ($r = 0.42$, $p < 0.001$).

Conclusions: Lobar lacunes are associated with CAA, whereas deep lacunes are more frequent in HTN-SVD. Lobar lacunes seem to have a close relationship with WMH, suggesting a possible common origin. *Neurology*® 2017;88:2162-2168

GLOSSARY

BG = basal ganglia; **CAA** = cerebral amyloid angiopathy; **CI** = confidence interval; **CMB** = cerebral microbleed; **CSO** = centrum semiovale; **cSS** = cortical superficial siderosis; **EPVS** = enlarged perivascular spaces; **HTN** = hypertensive; **ICH** = intracerebral hemorrhage; **MGH** = Massachusetts General Hospital; **OR** = odds ratio; **SVD** = small vessel disease; **WM** = white matter; **WMH** = white matter hyperintensities; **WMHP** = white matter hyperintensity pattern.

Lacunar infarcts (lacunes in this text, figure 1), defined as 3- to 15-mm CSF-filled cavities in the basal ganglia (BG) or white matter (WM), are frequently observed in patients with small vessel disease (SVD) and often accompanied by other markers such as WM hyperintensities (WMH), enlarged perivascular spaces (EPVS), and cerebral microbleeds (CMBs).¹⁻³ Although attributed mainly to SVD, the mechanisms of lacune formation are unknown.⁴ Lacunes have been described mostly in deep brain areas such as the BG, thalamus, internal capsule, and pons,³ but they have been reported also in lobar WM such as centrum semiovale (CSO) by Fisher^{5,6} and others,³ also associated with intracerebral hemorrhage (ICH). The characteristics of lacunes in cerebral amyloid angiopathy (CAA) and hypertensive SVD (HTN-SVD)^{3,7} and their association with other SVD markers such as CMBs⁸ and EPVS^{9,10} are not well known. In cerebral

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From the Hemorrhagic Stroke Research Program (M.P., G.B., P.F., E.A., A.C., K.H., A.A., K.M.S., A.V., S.M.G., M.E.G.), Department of Neurology, Massachusetts General Hospital Stroke Research Center, Harvard Medical School, Boston; NEUROFARBA Department (M.P., L.P.), Neuroscience Section, University of Florence, Italy; Université Paris-Descartes (G.B.), INSERM UMR 894, Department of Neuroradiology, Centre Hospitalier Sainte-Anne, Paris, France; and Division of Neurocritical Care and Emergency Neurology (J.N.G., J.R.), Massachusetts General Hospital, Harvard Medical School, Boston.

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Figure 1 Lobar and deep lacunes on brain MRI in patients with CAA and HTN-ICH

(A and B) Patient with CAA-ICH with one lobar lacune (arrow). (C and D) Patient with HTN-ICH with one deep lacune (arrow). (A and C) Fluid-attenuated MRI sequences. (B) T1-weighted MRI sequence. (D) T2-weighted MRI sequence. CAA = cerebral amyloid angiopathy; HTN = hypertensive; ICH = intracerebral hemorrhage.

autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy and age-related SVD, a spatial relationship between lacunes and WMH was shown.^{11–13} Recently, different patterns of WMH (white matter hyperintensity pattern [WMHP], multiple spots) have been shown to discriminate CAA from HTN-SVD.¹⁴ Therefore, it is plausible that lacunes follow different spatial distributions in CAA and HTN-SVD, reflecting the anatomic involvement of affected vessels.

In this study, we aimed to determine whether the topographic distribution of lacunes (lobar vs deep) differs between patients with CAA and those with HTN-SVD. We also mapped the lacunes to provide a visual representation of their locations in patients with different SVD types. As a secondary question, we investigated whether lobar lacunes have a spatial relationship with WMH and CMBs.

METHODS We prospectively analyzed data from consecutive patients admitted at the Massachusetts General Hospital (MGH) with spontaneous symptomatic ICH from January 2003 through February 2012 who underwent MRI as extensively described in previous publications.^{14–16} CT angiography or magnetic resonance angiography was performed in all patients, and vascular malformation or other ICH etiologies were ruled out. Details of patient enrollment are given in figure 2. Patients who were admitted to MGH during the same time frame for primary ICH but did not get an MRI during their clinical workup ($n = 560$) were not included because MRI is mandatory to detect microbleeds and to determine the etiology of SVD. Compared to patients who had MRI, patients without MRI had similar age and sex distributions, but they showed higher rate of hypertension and deeply located ICH ($p < 0.05$).

Patients with lobar ICH involving the cerebral cortex and underlying WM with strictly lobar CMBs or cortical superficial siderosis (cSS) were coded as CAA-ICH per the modified Boston criteria.¹⁷ The CAA-ICH diagnosis included definite, pathologically proven CAA found on full autopsy; probable CAA with supporting pathology, i.e., lobar ICH with or without lobar CMBs and pathologic evidence of CAA; and probable CAA, based on the presence of lobar ICH and purely lobar CMBs or cSS. To improve CAA diagnostic accuracy, we decided to exclude patients with single lobar ICH, no CMB, and without cSS (possible CAA according to the modified Boston criteria). Patients with HTN-ICH were defined as patients with ICH in the BG, thalamus, or brainstem (deep locations) with or without deep CMB but no lobar CMB. Patients with lower diagnostic certainty such as a combination of mixed-location macrobleed/microbleed and primary cerebellar ICH and patients with other possible etiologies were excluded from our study (figure 2).

Baseline data collection was performed as previously described.^{14,15} Briefly, the following clinical variables were systematically recorded for each participant: age, sex, presence of hypertension, atrial fibrillation, diabetes mellitus, hypercholesterolemia, history of ICH and ischemic stroke, and values of creatinine. Presence of left ventricular hypertrophy was also recorded for patients who had a transthoracic echocardiogram (available for 118 patients with CAA-ICH and 80 with HTN-ICH).

Standard protocol approvals, registrations, and patient consents. This study was performed with approval and in accordance with the guidelines of the MGH institutional review board, which allows us to collect data on all participants with ICH treated at MGH.

MRI data. Images were obtained with a 1.5T magnetic resonance scanner (GE Sigma, Chicago, IL) and included whole-brain T2-weighted, T1-weighted, and T2*-weighted gradient-recalled echo (echo time 750/50 milliseconds, 5-mm slice thickness, 1-mm interslice gap) and fluid-attenuated inversion recovery (repetition time/echo time 10,000/140 milliseconds, inversion time 2,200 milliseconds, 1 excitation, 5-mm slice thickness, 1-mm interslice gap). WMH volume was quantified semiautomatically as previously validated¹⁵ with a computer-assisted process that involves MRIcron software (<http://www.mccauslandcenter.sc.edu/micro/mricron/>). The presence and number of CMBs, macrobleeds, and cSS were evaluated on axial-sequences previously described.^{8,14,16} For the purpose of this study, we used total, lobar, and deep CMB count and lobar and deep CMB presence. EPVS were rated on axial T2-weighted MRIs in the BG and CSO, and we prespecified a dichotomized classification of EPVS degree as high (score > 20) or low (score ≤ 20) in line with previous studies.^{14,18}

Figure 2 Flowchart of patient enrollment and final study sample

Mixed ICH includes patients with the presence of concomitant lobar and deep bleeds. CAA = cerebral amyloid angiopathy; HTN-ICH = hypertensive intracerebral hemorrhage; MGH = Massachusetts General Hospital.

The degree of cortical atrophy was scored on a 4-point rating scale based on the size of the gyri and sulci from 0 (no cortical atrophy) to 3 (severe cortical atrophy) at 5 regions (frontal, parietal, temporal and occipital lobes, and insular region) with the use of reference scans. The sum of these 5 regions (0–15) was calculated.¹⁹ Cortical atrophy was consistently measured on the hemisphere not affected by ICH. As recently published, we have evaluated the presence of WMHP divided as follow: multiple subcortical spots and peri-BG pattern.¹⁴

We have defined lacunes in accordance with the Standards for Reporting Vascular Changes on Neuroimaging criteria: “round or ovoid, subcortical, fluid-filled (similar signal as CSF) cavity, of between 3 mm and about 15 mm in diameter.”¹ The lesions to be defined as lacunes had to be hypointense in T1-weighted images. We reviewed fluid-attenuated inversion recovery and T2-weighted images to ensure that those structures identified as lacunes on T1 had CSF-like signal (figure 1). Blood-sensitive sequences were also reviewed to exclude an incorrect classification of CMB as lacunes. We classified supratentorial lacunes topographically (figure 1): lobar (when located in CSO, frontal, parietal, insular/subinsular, temporal, and occipital lobes) or deep (when located in thalamus, BG, internal and external capsule). Presence of any lacune and total lacune counts refer to presence and number of lacunes in any of the above-mentioned locations and infratentorial areas. A comparison of 60 scans between 2 trained raters (trained by reviewing a range of test cases based on the definitions) was performed to assess the interrater agreement for the presence of lobar and deep lacunes.

In the present study, 12 lacunes were excluded from analyses for the following reasons: they were associated with past acute focal neurologic events (n = 10), and 2 lacunes were also present

on MRI diffusion-weighted sequence as small acute hyperintense lesions at the time of ICH.

To determine the spatial relationship between lobar lacunes and WMH, we used a previously validated visual rating scale.¹¹ Lacunes were rated for their location with regard to WMH with the following categories: no contact (grade 0), contact without overlap (grade Ia), partial overlap (grade Ib), and complete overlap (grade II) with a preexisting WMH.

To create a composite image of the spatial distribution of lacunes, the primary rater labeled each lesion using MRIcron. T1-weighted scans were coregistered to an intermediate target volume (one of the T1-weighted volumes that lacked any apparent structural defects) using affine registration (FLIRT, FSL). The target was then registered to an anatomic atlas (Montreal Neurological Institute 305 volume). Manually marked lesions were subsequently resampled into the atlas space with the use of the T1 coregistrations, and 3D Slicer was used to generate the composite figures. For displaying the position of lesions within the brain tissue, the brain was subdivided into fifteen 10-mm axial slabs, with each lesion overlaid onto the middle slice of the slab.

Statistical analyses. In univariate analyses, we compared baseline demographics, clinical, and neuroimaging variables between the CAA-ICH and HTN-ICH groups. Lobar vs deep lacune presence/absence was compared in univariate analyses between patients with CAA and patients with HTN-ICH.

A multivariable logistic regression model with a dichotomous dependent variable (CAA-ICH vs HTN-ICH) was built to look for independent associations between the SVD type and lacune location after adjustment for relevant covariates: lobar lacune count, deep lacune count, demographics, vascular risk factors (age, sex, hypertension), and neuroimaging markers of SVD severity (WMH volume and total CMB count).

To confirm the spatial relationship between WMH and lobar lacunes, we evaluated the correlation between WMH volume and lobar lacune count, performing partial correlation analyses adjusted for age. Correlation analyses between deep lacunes and WMH were explicitly not performed because deep lacunes are situated mostly within the deep gray matter and such comparisons would be unbalanced by definition. The imaging variables entered in the models were log transformed to obtain a normal distribution when needed.

To assess the association between presence of lobar lacunes and both WMH multiple spots pattern and lobar CMB presence, we used the Fisher exact test.

Agreement statistics on categorical variables (no lacune or lobar vs deep lacune) were performed with the Cohen κ interrater agreement test.

All analyses were performed with JMP Pro 12 software (SAS Institute Inc, Cary, NC).

RESULTS From an initial cohort of 524 consecutive patients with primary ICH and available MRI, we excluded patients with other causes of ICH (1.5%) (e.g., inflammatory CAA), cerebellar location of primary ICH (6.4%), mixed ICH (14%), and possible CAA (17.3%) (figure 2). Our final sample included 316 patients with primary ICH divided as follows: 191 patients with probable/definite CAA-ICH and 125 patients with HTN-ICH.

We compared baseline characteristics between patients with CAA-ICH and those with HTN-ICH in univariate analyses (table). Almost one-fourth of all

Table	Comparison of demographic, clinical, and neuroimaging characteristics between CAA and HTN-ICH		
	CAA-ICH (n = 191)	HTN-ICH (n = 125)	p Value
Age, mean (SD), y	74.9 (9.3)	66.1 (13.6)	<0.001
Female, n (%)	96 (50.3)	52 (41.6)	
Hypertension, n (%)	126 (66.0)	103 (82.4)	0.001
Hypercholesterolemia, n (%)	86 (45.0)	50 (40.0)	
Diabetes mellitus, n (%)	22 (11.5)	33 (26.4)	0.001
Atrial fibrillation, n (%)	32 (16.7)	17 (13.6)	
Previous ICH, n (%)	33 (17.3)	9 (7.2)	0.007
Previous ischemic stroke, n (%)	17 (8.9)	14 (11.2)	
LVH, n (%) ^a	25 (21.2)	32 (40.0)	0.006
Creatinine, mean (SD), mg/dL	1.0 (0.4)	1.3 (1.1)	0.011
WMH volume, median (IQR), mL	21.9 (11.8–38.7)	11.8 (3.5–30.2)	<0.001
WMH multiple spots, n (%)	65 (34.0)	23 (18.4)	0.002
WMH peri-BG, n (%)	14 (7.3)	21 (16.8)	0.010
Total CMB count, median (IQR), n	1 (0–6)	0 (0–0)	<0.001
Lobar CMB count, median (IQR), n	1 (0–5)	None	
Deep CMB count (range), n	None	0 (0–14)	
Cortical atrophy score, median (IQR)	7 (3–9)	5 (2–9)	0.042
CSO EPVS high degree (>20), n (%)	92 (48.2)	19 (15.2)	<0.001
BG EPVS high degree (>20), n (%)	6 (3.1)	15 (12)	0.004

Abbreviations: BG = basal ganglia; CAA = cerebral amyloid angiopathy; CMB = microbleed; CSO = centrum semiovale; EPVS = enlarged perivascular spaces; HTN = hypertensive; ICH = intracerebral hemorrhage; IQR = interquartile range; LVH = left ventricular hypertrophy; WMH = white matter hyperintensity.

^aLVH available for 118 patients with CAA-ICH and 80 patients with HTN-ICH.

patients had at least one lacune in any location (24.7%), with similar rates between patients with CAA-ICH and HTN-ICH (23% vs 27.2%, respectively, $p = 0.4$). Presence of lobar lacunes was more common in CAA-ICH (20.4% vs 5.7% in HTN-ICH, $p < 0.001$), while deep lacunes were more frequent in patients with HTN-ICH (15.2% vs 2.1%, $p < 0.001$). The interrater agreement for detecting the presence of both lobar lacunes and deep lacunes was excellent ($\kappa = 0.83$, 95% confidence interval [CI] 0.68–1; $\kappa = 0.81$, 95% CI 0.56–1, respectively). Figure 3 displays a visual representation of the topographic distribution of lacunes in patients with CAA-ICH and HTN-ICH.

In the multivariable logistic regression analysis, lobar lacunes were independently associated with the diagnosis of CAA-ICH (odds ratio [OR] 3.5, 95% CI 1.6–9.1, $p = 0.003$). Conversely, deep lacunes were independently associated with the diagnosis of HTN-ICH (OR 6.9, 95% CI 2.4–20, $p < 0.001$).

We used a simple tool proposed by Duering et al.¹¹ to assess the relationship between lobar lacunes and WMH. We found that 80% of lobar

lacunes were at least in contact with WMH (contact without overlap 18%, partial overlap 30%, complete overlap 32%). To confirm this spatial relationship between lobar lacunes and WMH, we performed partial correlation analyses adjusting for age. Lobar lacune count was correlated with WMH volume ($r = 0.42$, $p < 0.001$).

There was no association between the presence of lobar lacunes and WMH multiple spots pattern ($p = 0.29$). The presence of lobar lacunes was nevertheless associated with lobar CMB ($p = 0.003$). This result was also significant after adjustment for age (OR 2.5, 95% CI 1.2–4.9, $p = 0.006$). Including the patients with symptomatic lacunes in the analyses did not change any of the associations reported here.

DISCUSSION The overarching question of the present project was whether a different topographic distribution of lacunes, similar to CMB topography, could be found between patients with CAA-ICH and those with HTN-ICH. We found that patients with CAA-ICH showed lacunes predominantly in lobar regions, similar to CMBs. Conversely, patients with HTN-ICH had lacunes mainly in deep cerebral areas. Moreover, the association between the topographic location of lacunes and diagnostic categories was independent of important risk factors such as age and hypertension but also other MRI markers of SVD severity. Our results suggest that the topographic distribution of lacunes (lobar vs deep) can help distinguish the type of underlying SVD (CAA vs HTN-SVD) in patients with primary ICH.

Understanding the type of SVD in older adults with or without a history of symptomatic stroke is important because the most common SVDs pose different risks of incident ICH and dementia.^{20,21} Such differentiation particularly helps in situations of concomitant ischemic risk that require antithrombotic management. The results of the current report add a commonly available marker to the gamut of MRI findings that can help distinguish CAA from HTN-SVD. It is interesting to note that deep lacunes were very uncommon in CAA-ICH (2.1% vs 15.2% in HTN-ICH). As with other MRI markers (EPVS, WMHP), the association between lacune location and SVD type should next be validated with pathologic correlation studies. For now, lacunar location may serve as an easily diagnosed marker with a prevalence and diagnostic relevance similar to those of EPVS and WMHPs.

The majority of lacunes located in lobar areas (80%) were in contact with WMH, suggesting a strong relationship. To corroborate these results, we also evaluated the relationship between lobar lacunes and WMH. After adjustment for age, we found a high positive correlation between these 2 neuroimaging

Figure 3 Three-dimensional maps: distribution of lacunes in patients with HTN-ICH and CAA

The topographic distribution of lacunes in patients with HTN-ICH (red) and CAA-ICH (blue) is shown. To better distinguish the anatomic distribution of lacunes in both diagnostic categories, we highlighted lacunes in patients with HTN-ICH in panel (A) and lacunes in patients with CAA-ICH in panel (B). CAA = cerebral amyloid angiopathy; HTN-ICH = hypertensive intracerebral hemorrhage.

markers of SVD. We did not find a significant association between presence of lobar lacunes and presence of WMH multiple spots pattern; therefore, these radiologic findings can be complementary in diagnosing CAA. The significant independent association found between lobar lacunes and the lobar microbleeds, the most specific imaging marker of CAA in this well-characterized cohort, suggests that CAA can be the cause of these lacunes. For these analyses, we explicitly excluded deep lacunes because they are often located in deep gray nuclei, compared to lobar lacunes, which are present only in WM. Their correlation with WMH thus would have been unbalanced for definition in respect to lobar lacunes.

Our results are in line with previous findings showing a spatial relationship between lacunes and WMH, despite some differences in study design and included cohorts.¹¹ A common pathophysiologic mechanism between lacunes and WMH was proposed, supported by the finding of incident lacunes aligned along perforating arteries. Vessel wall alterations of the long perforators thus could lead to both WMH and lacunes.¹² Further studies should use the combination of pathologic data and ex vivo/in vivo

MRI to address this question and to evaluate the relationship between cortical microinfarcts and lacunes. Both of these SVD-related cerebral lesions have a profound association with cognitive status, supporting the importance of understanding their mechanisms in elderly patients.^{22,23}

In the present study, several limitations have to be taken into account. Our study had a cross-sectional design; thus, we were not able to evaluate and restrict our analyses to incident lacunes, a suggested way to avoid mistaking a lacune with EPVS.¹³ Hypothetically, CSO EPVS adjacent to or surrounding WMH could show a diameter >3 mm in very few cases. Only the combination of ex vivo MRI and histopathology could specifically address this important question. However, the cutoff of 3 mm and the systematic evaluation of the scans for lacunes by one trained rater have helped to overcome this issue to the extent possible. Moreover, after review of 60 scans with a second trained rater, the interrater agreement was excellent for presence and location of any lacune.

The method for measuring atrophy is probably reasonable for the clinical MRI data that have been used in this study, but we acknowledge that compared to automated measures, it can be considered

less accurate. It can also be noted that atrophy was not one of the main variables of interest for this study.

We used an MRI-based cohort for this study to optimize the accuracy to detect SVD related to CAA and HTN because the presence of strictly lobar ICH/CMBs showed 100% accuracy for CAA in a radiologic/pathologic validation study, and gradient-recalled echo/susceptibility-weighted MRI sequences are the only ones that show CMBs.²⁴ By the same token, we did not include patients with any combination of lobar and deep ICH/CMBs in this study because the distinction of the predominant SVD type is unclear in these patients. We also did not include primary cerebellar ICH because the SVD pathology underlying cerebellar ICH is also unclear; it might be either CAA or HTN-SVD.

We also note that similar to previous studies based on clinical MRI cohorts, this study did not include patients who had only head CTs. Patients with lobar ICH are more likely to receive an MRI during their clinical workup, mostly to confirm the diagnosis of probable CAA per the Boston criteria. Although a higher number of MRIs for lobar ICH might create some selection bias in SVD research, our study has one of the largest numbers of patients with detailed quantifications of a large range of relevant MRI markers. To increase diagnostic certainty, we excluded from the CAA-ICH group patients with possible CAA (only one lobar ICH without the presence of CMBs/cSS) and excluded from the analyses patients with the presence of concomitant lobar and deep bleeds. Other possible strengths were the high number of consecutive patients with ICH, which enabled robust multivariate models, and the systematic evaluation of MRI scans by trained raters using volumetric methods and validated scales for a comprehensive range of imaging markers of SVD.

Our study provides an important MRI marker that can help us understand the etiology of SVD in the management of patients with hemorrhage-prone cerebral microangiopathies. We also found a profound spatial relationship between lobar lacunes and WMH that could suggest a common origin. In case of uncertainty of the underlying primary SVD, the presence and distribution of lacunes that follow the distinct topographic involvement of small vessels affected primarily by CAA and HTN-SVD can help clarify the correct underlying SVD. The association between CAA and lobar lacunes and the relationship between HTN-SVD and deep lacunes can help guide the clinician to distinguish these 2 types of SVD with very different ICH risks.

AUTHOR CONTRIBUTIONS

M. Pasi contributed to project concept and design, imaging analysis, data analysis, write-up. G. Boulouis contributed to project design, imaging analysis, critical revisions. P. Fotiadis and E. Auriel contributed to

imaging analysis, critical revisions. A. Charidimou contributed to project design, imaging analysis, critical revisions. K. Haley, A. Ayres, and K.M. Schwab contributed to data collection and management. J.N. Goldstein, J. Rosand, A. Viswanathan, and L. Pantoni contributed to data collection, critical revisions. S.M. Greenberg contributed to funding, data collection, critical revisions. M.E. Gurol contributed to funding, project concept and design, data collection, imaging analysis, data analysis, write-up.

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DISCLOSURE

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