MRI Markers of Small Vessel Disease in Lobar and Deep Hemispheric Intracerebral Hemorrhage

Eric E. Smith, MD, MPH; Kaveer R.N. Nandigam, MD; Yu-Wei Chen, MD; Jed Jeng, BS; David Salat, PhD; Amy Halpin, BA; Matthew Frosch, MD, PhD; Lauren Wendell, MS; Louis Fazen, BA; Jonathan Rosand, MD, MS; Anand Viswanathan, MD, PhD; Steven M. Greenberg, MD, PhD

Background and Purpose—MRI evidence of small vessel disease is common in intracerebral hemorrhage (ICH). We hypothesized that ICH caused by cerebral amyloid angiopathy (CAA) or hypertensive vasculopathy would have different distributions of MRI T2 white matter hyperintensity (WMH) and microbleeds.

Methods—Data were analyzed from 133 consecutive patients with primary supratentorial ICH and adequate MRI sequences. CAA was diagnosed using the Boston criteria. WMH segmentation was performed using a validated semiautomated method. WMH and microbleeds were compared according to site of symptomatic hematoma origin (lobar versus deep) or by pattern of hemorrhages, including both hematomas and microbleeds, on MRI gradient recalled echo sequence (grouped as lobar only–probable CAA, lobar only–possible CAA, deep hemispheric only, or mixed lobar and deep hematomas).

Results—Patients with lobar and deep hemispheric hematoma had similar median normalized WMH volumes (19.5 cm³ versus 19.9 cm³, \(P=0.74\)) and prevalence of ≥1 microbleed (54% versus 52%, \(P=0.99\)). The supratentorial WMH distribution was similar according to hemorrhage location category; however, the prevalence of brain stem T2 hyperintensity was lower in lobar hematoma versus deep hematoma (54% versus 70%, \(P=0.004\)). Mixed ICH was common (23%). Patients with mixed ICH had large normalized WMH volumes and a posterior distribution of cortical hemorrhages similar to that seen in CAA.

Conclusions—WMH distribution is largely similar between CAA-related and non-CAA-related ICH. Mixed lobar and deep hematomas are seen on MRI gradient recalled echo sequence in up to one fourth of patients; in these patients, both hypertension and CAA may be contributing to the burden of WMH. (Stroke. 2010;41:1933-1938.)

Key Words: cerebral amyloid angiopathy ■ intracerebral hemorrhage ■ leukoaraiosis ■ MRI ■ white matter disease

Hypertension and cerebral amyloid angiopathy (CAA) account for most primary intracerebral hemorrhage. CAA affects the vessels of the cortex and leptomeninges without significant involvement of the penetrating arteries.¹ By contrast, hypertension causes arteriosclerosis in both cortical and subcortical arteries. Patients with multiple strictly lobar hematomas, including cerebral microbleeds (MB) on MRI gradient recalled echo (GRE) sequence, but no hemorrhages in deep hemispheric brain locations are highly likely to have CAA according to the Boston criteria.² Some patients with solitary lobar hematoma may have hypertension as the cause, however. When patients present with acute or chronic hemorrhages in both lobar and deep hemispheric brain regions, it is unclear whether they have severe hypertensive vasculopathy or a combination of hypertensive vasculopathy and CAA.

MRI white matter hyperintensity (WMH) is another manifestation of cerebral small vessel disease. The relationship between WMH distribution and underlying arterial pathology is unclear. Our previous study of WMH in CAA, Alzheimer disease, and mild cognitive impairment found little difference in distribution.³ WMH anterior to the temporal horn of the lateral ventricles may be relatively specific for cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), however.⁴,⁵

Few studies have compared the severity and distribution of WMH and microbleeds in CAA and hypertension. Because hypertensive arteriosclerosis and CAA have different vascular distributions, we hypothesized that WMH distribution would also differ. We examined a consecutive series of patients with intracerebral hemorrhage (ICH) to determine whether there might be a more posterior distribution of WMH.
in lobar ICH caused by CAA than deep ICH caused by hypertension, reflecting the known posterior distribution of CAA pathology,\textsuperscript{1,6,7} and more brain stem WMH in deep ICH, reflecting the paucity of CAA in this vascular territory.\textsuperscript{1}

**Methods**

**Study Population**

Study subjects were recruited from an ongoing single-center prospective longitudinal cohort study of ICH outcome.\textsuperscript{8} Eligible subjects were consecutive patients aged \( \geq 55 \) years who presented to Massachusetts General Hospital between January 1, 1999, and December 31, 2002, with supratentorial primary ICH and had MRI within 90 days. Patients with ICH caused by vascular malformations or other secondary causes were excluded; ICH associated with anticoagulant use was included. There were 320 consecutive admissions for supratentorial ICH during the study period; 4 patients with multiple simultaneous symptomatic lobar and deep hemispheric ICH were excluded. MRI was performed within 90 days in 141 of the 316 eligible patients with adequate fluid-attenuated inversion recovery sequence in 122 (69 lobar, 53 deep hemispheric) and susceptibility gradient echo sequence in 113 (67 lobar, 46 deep hemispheric). Patients with deep hemispheric ICH, warfarin-related ICH, larger hemorrhages, or those who died of ICH were less likely to get MRI (\( P < 0.05 \), data not shown).

Baseline clinical information was obtained as described.\textsuperscript{8} The APOE genotype was measured\textsuperscript{8} in the 101/141 (72.1\%) who consented to provision of blood for genetic research.

**Imaging Acquisition and Analysis**

MR images were acquired on 1.5-Tesla Signa scanners (GE Medical Systems, Milwaukee, Wis). Segmentation of white matter T2 hyperintensity, normalized to average subject head size, was performed using the fluid-attenuated inversion recovery sequence as previously described.\textsuperscript{9,10} We created a region of interest encompassing the brain stem to test an a priori hypothesis that brain stem T2 hyperintensity would be less frequently present in lobar ICH. WMH on CT was graded according to the van Swieten scale.\textsuperscript{11} Cerebral MBs were identified and labeled on the MRI GRE sequence by consensus of 2 experienced raters as previously described.\textsuperscript{9}

Based on MRI and CT data, the hemorrhage locations were categorized as lobar origin or deep hemispheric origin (basal ganglia or thalamus). Patients with lobar ICH were classified as definite, probable, or possible CAA using the previously validated Boston criteria.\textsuperscript{12} Patients with probable CAA had \( \geq 2 \) strictly lobar hemorrhages. Patients with possible CAA had a single lobar hemorrhage. We additionally defined a category of mixed ICH based on MRI evidence of hemorrhage, either symptomatic hematoma or MB, in both lobar and nonlobar locations. Cerebellar MBs were not considered when assigning the mixed ICH category because of pathological evidence that either CAA or hypertensive vasculopathy can cause cerebellar hemorrhage.\textsuperscript{13} All imaging data were analyzed by raters blinded to clinical and genetic information.

To compare WMH and cerebellar MB distribution across subjects, sequences from each subject were anatomically coregistered to sequence data from a single study subject visually selected as having overall brain and ventricular volumes close to the average values for the study population. After spatial coregistration of the WMH segmentations, maps were created to display the voxelwise frequency of WMH across the whole brain in the different study groups. Similarly, labels of the MBs and hematoma origins were anatomically coregistered to produce maps of hemorrhage locations in each group of interest. To test the hypothesis that the distribution of lobar hemorrhages along the anterior–posterior plane would differ among groups, we determined the position coordinate along the anterior–posterior plane in coregistered space for each hemorrhage and compared them across groups. Freesurfer software (www.surfer.nmr.mgh.harvard.edu) was used for these image analyses.\textsuperscript{13}

**Statistical Analysis**

Univariate comparisons were by Fisher exact test, \( t \) test, Wilcoxon rank-sum test, Pearson correlation coefficient or Spearman correlation coefficient as appropriate. WMH was log-transformed to a normal distribution for univariate and multivariable analyses as in other studies.\textsuperscript{9} Logistic or linear regression models, as appropriate, were used to determine the medical and genetic risk factors that were independently associated with the presence of cerebral MB and log-transformed WMH. First, all the variables associated with the outcome in univariate analysis (\( P < 0.15 \)) were entered into the model and then backward elimination was used to remove nonsignificant variables (\( P > 0.05 \)). To test hypotheses about hemorrhage location in the anterior–posterior plane, we used linear models to estimate mean hemorrhage location across groups using a compound symmetry structure for estimation of the covariance matrix. SAS Version 9.1.3 (SAS Institute, Cary, NC) was used for the statistical analyses.

**Results**

**Extent of MRI WMH and MBs in Lobar and Deep Hemispheric ICH**

Baseline characteristics of the study cohort with adequate MRI data, grouped according to symptomatic ICH location, are shown in Table 1. Median normalized WMH volume was similar in lobar and deep hemispheric ICH (Table 1; 19.5 cm\(^3\) versus 19.9 cm\(^3\), \( P = 0.74 \)). Characteristics independently associated with increased normalized WMH (nWMH) in the whole study cohort, according to a multivariable linear regression model, were increased age (adjusted \( P = 0.03 \)) and hypertension (adjusted \( P = 0.007 \)).
Patients with deep hemispheric ICH were more likely than patients with lobar ICH to have brain stem T2 hyperintensity (Table 1; 70% versus 44%, \( P = 0.004 \)). Deep hemispheric ICH location was independently associated with the presence of brain stem T2 hyperintensity (adjusted OR 2.79, 95% CI 1.25 to 6.24, \( P = 0.01 \)) in a multivariable model controlling for age and hypertension.

Like with total nWMH volume, there was no difference between lobar ICH and deep ICH in the proportion with \( \geq 1 \) MB (54% versus 52%, \( P = 0.99 \)). Lobar ICH was more commonly associated with \( \geq 1 \) lobar MB (seen in 49% of lobar ICH and 30% of deep ICH, \( P = 0.05 \)), and deep ICH was more commonly associated with deep MB (seen in 18% of lobar ICH and 39% of deep ICH, \( P = 0.02 \)). The median number of MB was also similar in each group (\( P = 0.53 \); Table 1). Hypertension was the only clinical characteristic associated with the presence of \( \geq 1 \) MB (48 of 79 hypertensive patients had \( \geq 1 \) MB, whereas 12 of 34 nonhypertensives had \( \geq 1 \) MB; \( P = 0.01 \)).

### Distribution of MRI WMH and MBs According to Likelihood of Underlying CAA or Hypertensive Arteriosclerosis

Next, we divided the study cohort according to categories derived from the published Boston criteria for CAA (Table 2).\(^2\) We additionally defined a category of mixed ICH consisting of either patients with lobar ICH and deep hemispheric MB (\( n = 12 \)) or deep hemispheric ICH and lobar MB (\( n = 14 \)). Patients with mixed ICH had a similarly high prevalence of hypertension as patients with deep hemispheric ICH, had more MBs than deep hemispheric ICH, and tended to have high nWMH volumes, suggesting severe small vessel disease (Table 2).

Because CAA and hypertension are different arterial pathologies, we explored whether the risk factors for WMH and MB were different in possible or probable CAA compared with the group with deep hemispheric ICH using interaction terms in fully adjusted models. Patients with mixed ICH were excluded because these patients might have both CAA and hypertensive vasculopathy. There was evidence that hypertension (\( P = 0.03 \)) and age (\( P = 0.07 \)) were differently related to nWMH volume. Hypertension was associated with increased nWMH in CAA-related ICH (hypothesis 0% CI 52% to 457%, \( P = 0.003 \), adjusted for other characteristics) but not in deep ICH (\( P = 0.55 \)). Age was correlated with nWMH volume in CAA-related ICH (nWMH volume was 6.0% greater for each additional year of age, 95% CI 1.5% to 10.7%, \( P = 0.005 \)) but not in deep ICH (\( P = 0.76 \)). Risk factors for the presence of MB were similar in CAA-related ICH and deep ICH (\( P > 0.20 \) for comparisons). We also compared the risk factors for nWMH and MB in patients with mixed ICH versus all other ICH types, using similar analyses, and failed to find differences.

The voxelwise frequency of WMH, grouped according to Boston criteria, is shown in Figure 1. The distribution of WMH appeared similar in each group despite some differences in overall extent (Table 2). This was confirmed by voxelwise statistical tests that failed to show major clusters of voxels where the WMH frequency was different between groups (data not shown).
To determine the comparability of MRI and CT measures of WMH, we compared total WMH and distribution (anterior versus posterior grade) among groups using a commonly used CT visual rating scale in the 110 with available CT. Similar to the MRI findings, we did not find significant group differences in either total CT WMH grade ($P > 0.20$ for comparisons) or the within-subject difference between posterior and anterior grade ($P > 0.20$ for comparisons, data not shown). We did confirm a previous finding that CT WMH was of higher grade in the posterior than anterior region in patients with probable or possible CAA, however ($P = 0.01$ by Wilcoxon signed-rank test). This posterior predominance of CT WMH was not detected in the groups with mixed ICH ($P = 0.99$) or deep ICH only ($P = 0.27$).

Inspection of the cumulative distribution of hematomas and MBs showed a posterior predominance of the lobar hemorrhages in mixed ICH as well as CAA-associated ICH (Figure 2). Mean hemorrhage location in the anterior-posterior plane was similar between the groups ($P = 0.99$). A single patient with mixed ICH and history of hypertension died and had autopsy; severe CAA and non-CAA-associated arteriosclerosis were seen (Figure 3).

**Discussion**

We show that the WMH volume and frequency of MB are similar in deep hemispheric ICH and lobar ICH. Contrary to our study hypothesis, we did not find major differences in supratentorial WMH distribution (Figure 1). The prevalence of brain stem T2 hyperintensity was lower in lobar ICH compared with deep ICH, however, probably because CAA does not affect the arteries that penetrate into the brain stem. The absence of brain stem T2 hyperintensity was not very specific for CAA-related hemorrhage because a substantial number of subjects with CAA had brain stem T2 hyperintensity, reflecting the high population prevalence of hypertension in the elderly.

The periventricular-predominant distribution of WMH in these vascular pathologies with remarkably dissimilar topographical distributions is striking. We have previously reported a similar distribution of WMH in patients with CAA, mild cognitive impairment, or Alzheimer disease. The relatively conserved spatial distribution of WMH across various neurological diseases and syndromes could be related to the spatial distribution of blood flow or spatial variation in the vulnerability of the white matter to ischemia. The periventricular zone is the most distal perfusion zone of the white matter and experiences the lowest resting blood flow. Therefore, blood flow in this region could be readily compromised regardless of the distribution of vascular pathology. The observation that white matter lesions in CAA are most frequently periventricular, whereas vascular amyloid deposition is mostly restricted to the pial or cortical course of the arteries, suggests to us that white matter injury in CAA occurs by impairment of blood flow, possibly caused by altered vascular reactivity.
In our study, we found that lobar hematoma was more closely associated with lobar MB than deep MB and that deep hemispheric hematoma was more closely associated with deep MB than lobar MB as previously observed. However, we also found a relatively high prevalence of mixed ICH (26 of 113 [23%]). Mixed ICH may result from either hypertensive vasculopathy of both the deep and cortical arteries or from a combination of hypertensive vasculopathy and CAA in the same patient, which would not be unexpected given the relatively high prevalence of hypertension and CAA in the elderly. A previous autopsy series found that 7 of 40 patients with deep ICH also had pathological evidence of CAA. There was some evidence from our data to support either possibility. The prevalence of hypertension and brain stem WMH in the group with mixed ICH was similar to the group with deep hemispheric ICH and higher than the group with probable or possible CAA (Table 2). On the other hand, a cumulative map of the lobar hemorrhages in the group with mixed ICH showed a posterior distribution of hemorrhages, consistent with the distribution of hemorrhages seen in probable or possible CAA (Figure 2). A posterior distribution of hemorrhages in CAA, favoring the occipital, parietal, and posterior temporal lobes, has previously been observed and likely reflects the distribution of vascular amyloid deposition. This evidence is not conclusive, however, because some studies of hypertensives and patients with ischemic stroke also suggest a relatively posterior distribution of lobar microbleeds, although a contribution from coexistent CAA cannot be ruled out.

In contrast to the posterior predominance of hemorrhages and microbleeds, we did not observe a major posterior predominance of MRI WMH in CAA based on visual inspection of the WMH frequency maps (Figure 1). Despite this, we did confirm a previous finding that posterior CT WMH was greater than anterior CT WMH in patients with CAA but could not demonstrate this posterior predominance in the groups with deep hemispheric ICH or mixed ICH, suggesting that it may be feature of CAA. This discrepancy between MRI and CT measures may reflect differences between the type and severity of white matter injuries detected by these 2 modalities.

WMH volumes were highest in the groups with probable CAA or mixed ICH, likely reflecting more severe small vessel disease. Age and hypertension were risk factors for WMH in the overall study cohort, whereas hypertension was a risk factor for the presence of MB. Hypertension was associated with WMH in probable or possible CAA but not in deep hemispheric ICH and was associated with MB in both groups, suggesting that hypertension may add to vascular pathology even in the presence of CAA. The finding of higher WMH volumes in patients with mixed ICH also supports an additive effect of both pathologies. The most likely reason we could not detect a relationship between WMH and hypertension in deep ICH is that few patients with deep hemispheric ICH were nonhypertensive, and some may have had unrecognized hypertension before ICH. There was a trend toward a stronger relationship between age and WMH in the group with CAA ($P=0.07$).

There are several limitations to this study. MRI was only performed in a subset of patients with less severe hemorrhagic stroke severity. The sample size is small and the findings reported here should be confirmed in subsequent larger studies. This is a hospital-based study; therefore, pre-ICH characteristics were by necessity assessed in retrospect.

These findings have implications for the pathophysiology, diagnosis, and management of cerebral small vessel disease. We found that a similar pattern of WMH distribution was present in CAA and hypertensive hemorrhage, supporting the concept that anatomic location is a more important determinant of white matter vulnerability to WMH than the specific small vessel pathology. WMH volume was greater in patients with CAA who additionally had hypertension. Because WMHs have previously been associated with cognitive impairment in patients with lobar ICH, this finding raises the possibility that strict control of hypertension might reduce disability from CAA. Many patients with consecutive ICH with MRI had evidence of mixed lobar and deep hemorrhages on the MRI GRE sequence. These patients would not be diagnosed with CAA based on the Boston criteria, which require that all hemorrhages be lobar in origin, but our data suggest that some of these patients may have CAA. Therefore, although the Boston criteria for CAA are highly specific...
and are useful for research by allowing selection of a population that is very likely to have CAA, it must be recognized that the true overall burden of CAA-related disease could be underestimated by the Boston criteria. Newer approaches to the diagnosis of CAA, including molecular imaging of β-amyloid, may improve our ability to define the true prevalence of this condition.

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Disclosures

None.

References

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