White matter hyperintensity volume is increased in small vessel stroke subtypes

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ABSTRACT

Objective: White matter hyperintensity (WMH) may be a marker of an underlying cerebral microangiopathy. Therefore, we hypothesized that WMH would be most severe in patients with lacunar stroke and intracerebral hemorrhage (ICH), 2 types of stroke in which cerebral small vessel (SV) changes are pathophysiologically relevant.

Methods: We determined WMH volume (WMHV) in cohorts of prospectively ascertained patients with acute ischemic stroke (AIS) (Massachusetts General Hospital [MGH], $n = 628$, and the Ischemic Stroke Genetics Study [ISGS], $n = 263$) and ICH (MGH, $n = 122$).

Results: Median WMHV was 7.5 cm^3 (interquartile range $3.4\text{--}14.7 \text{ cm}^3$) in the MGH AIS cohort (mean age 65 ± 15 years). MGH patients with larger WMHV were more likely to have lacunar stroke compared with cardioembolic (odds ratio [OR] = 1.87 per SD normally transformed WMHV), large artery (OR = 2.25), undetermined (OR = 1.87), or other (OR = 1.85) stroke subtypes ($p < 0.03$). These associations were replicated in the ISGS cohort ($p = 0.03$). In a separate analysis, greater WMHV was seen in ICH compared with lacunar stroke (OR = 1.2, $p < 0.02$) and in ICH compared with all ischemic stroke subtypes combined (OR = 1.34, $p < 0.007$).

Conclusions: Greater WMH burden was associated with SV stroke compared with other ischemic stroke subtypes and, even more strongly, with ICH. These data, from 2 independent samples, support the model that increasing WMHV is a marker of more severe cerebral SV disease and provide further evidence for links between the biology of WMH and SV stroke. *Neurology*® 2010;75:1670-1677

GLOSSARY

AF = atrial fibrillation; **AIS** = acute ischemic stroke; **CAD** = coronary artery disease; **CI** = confidence interval; **DM** = diabetes mellitus; **DWI** = diffusion-weighted imaging; **FLAIR** = fluid-attenuated inversion recovery; **HTN** = hypertension; **ICA** = intracranial area; **ICC** = intraclass correlation coefficient; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **ISGS** = Ischemic Stroke Genetics Study; **MGH** = Massachusetts General Hospital; **OR** = odds ratio; **SV** = small vessel; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment; **WMH** = white matter hyperintensity; **WMHV** = white matter hyperintensity volume.

White matter hyperintensity (WMH), also known as *leukoaraiosis*, has been proposed as a radiographic marker of cerebral small vessel (SV) disease.¹ Up to 70% of subjects older than 65 years have MRI evidence of WMH²; however, the burden of WMH varies substantially across populations and disease states.³⁻⁵ The extent of WMH can be assessed semiquantitatively by using ordinal visual rating scales^{6,7} or by volumetric analysis,^{8,9} including reliable measurements in patients with stroke.¹⁰ WMH burden independently predicts severity of cerebrovascular disease as reflected in the greater risk of ischemic and hemorrhagic stroke,^{8,11} stroke recurrence,^{12,13} and infarct growth¹⁴ as well as worse outcomes in acute ischemic stroke (AIS).^{15,16}

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Increased WMH burden has been previously linked to SV stroke subtype,^{17–20} including the recent findings of lacunar infarct evolution²¹; however, diffuse abnormality of the small cerebral vasculature that is WMH and SV stroke are not synonymous.^{1,22} We hypothesized that WMH would be most severe in patients with symptomatic SV stroke such as lacunar infarcts and primary intracerebral hemorrhage (ICH), a finding consistent with the model that symptomatic SV stroke and increased WMH volume (WMHV) are markers of more severe cerebral SV disease. Thus, we sought to determine whether WMH severity, assessed by volumetric MRI analysis, is associated with stroke subtypes in large, prospective, hospital-based cohorts of patients with ischemic and hemorrhagic stroke.

METHODS Population. Two independent, prospectively ascertained cohorts of patients with AIS and ICH from different institutions were analyzed retrospectively. Patients were evaluated by a neurologist in the emergency department (ED), at which point the NIH Stroke Scale score was determined and all laboratory values were measured. Clinical information was abstracted prospectively by patient or proxy interview and was supplemented through medical chart review.

Ischemic stroke was defined as either an appropriate clinical stroke syndrome associated with radiographically proven infarct or a fixed neurologic deficit persisting for ≥ 24 hours, consistent with a vascular pattern of involvement and without radiographic evidence of a demyelinating disease, or other nonvascular structural disease. All AIS patients were considered for enrollment, but only those who had diffusion-weighted MRI (DWI) confirmation of acute cerebral infarction were included in this analysis. Patients with symptoms of TIA or ischemic strokes related to specific vascular disorders (vasculitis, subacute bacterial endocarditis, fibromuscular dysplasia, vasospasm due to subarachnoid hemorrhage or cocaine abuse) were excluded.

For patients with primary ICH, the diagnosis was confirmed with CT scanning in all individuals. Those with secondary causes of ICH such as vascular malformations or trauma were excluded. Both AIS and ICH subjects without MRI within 2 weeks of their index event were excluded from this study.

All patients were assessed, and Trial of Org 10172 in Acute Stroke Treatment (TOAST) stroke subtypes²³ were assigned by study neurologists at the respective study sites independently and blinded to any quantification of severity of leukoariosis, i.e., TOAST subtype was determined by investigators at the time of the patient's admission and well before the WMH measurements were completed. Investigators used all available information, including clinical stroke syndrome, neuroimaging characteristics of the ischemic lesion, including its size and location, and the results of available testing for possible underlying etiology of the stroke, in assigning a TOAST category. Furthermore, in the case of conflicting etiologies, either the most likely subtype was assigned or patients were classified as "undetermined," in accordance with the original TOAST classification.

All acute ischemic and hemorrhagic strokes were considered for analysis regardless of location (supratentorial or infratentorial) or radiographic stroke characteristics.

Massachusetts General Hospital AIS cohort. Study subjects were drawn from an ongoing longitudinal cohort study of patients with ischemic stroke.²⁴ All consecutive subjects aged ≥ 18 years admitted to the Massachusetts General Hospital (MGH) Stroke Unit from January 2003 to May 2008 were considered for enrollment, including those admitted directly through the MGH ED or transferred to the ED from a referring hospital. Time of stroke onset was defined as the time at which a subject or proxy reported acute onset of a neurologic deficit. When time of onset could not be established or when individuals awoke with a deficit, the time a subject was last known to be normal was considered the time of onset.

Ischemic Stroke Genetics Study cohort. The Ischemic Stroke Genetics Study (ISGS) is a prospective, 5-center, case-control study of patients with ischemic stroke who consented to blood donation for genetic studies.²⁵ All patients who presented to the center-specific ED with rapidly developing signs of focal or global disturbance of neurologic function with symptoms lasting 24 hours or longer and with no apparent cause other than vascular origin were considered for enrollment. Index strokes were centrally reviewed and classified according to TOAST criteria. There were 263 subjects with first-ever ischemic stroke who had volumetric WMH assessment completed.

Massachusetts General Hospital ICH cohort. Study subjects were drawn from an ongoing longitudinal cohort study of primary ICH.²⁶ Patients were excluded if they had cerebral hemorrhage associated with trauma, excessive anticoagulation (international normalized ratio > 3.0), vasculitis, cerebral tumor, coagulopathy, or vascular malformation. All consecutive primary ICH subjects aged ≥ 18 years, including those admitted directly through the MGH ED or transferred to the ED from a referring hospital, were admitted to the MGH Stroke Unit from January 2003 to May 2008, of whom 443 consented to this study and were included in the analysis.

Neuroimaging analysis. MRI was acquired on 1.5-T Signa scanners (GE Medical Systems, Milwaukee, WI). Only those patients who demonstrated DWI evidence of AIS were included in further neuroimaging analysis. Scans were converted from DICOM to Analyze format by using MRIcro software (University of Nottingham School of Psychology, Nottingham, UK; www.mricro.com) for computer-assisted determination of WMHV.^{12,27} For each subject, we analyzed the MRI closest to the time of onset of clinical symptoms. A region-of-interest map of supratentorial WMHs was created by signal intensity thresholding followed by manual editing. Axial T2 fluid-attenuated inversion recovery (FLAIR) sequences were used to create the WMH maps. T2 FLAIR and the corresponding DWI sequences were aligned to exclude acute ischemia, edema, and chronic territorial infarcts. To further avoid confounding by the presence of focal white matter damage caused by the index stroke, we measured only total WMHV from the hemisphere unaffected by the stroke, a validated approach with high interhemispheric correlation in WMH severity (intraclass correlation coefficient [ICC] = 0.97).^{10,12} In the case of brainstem or other infratentorial infarcts, the total WMHV was calculated as a sum of the bilateral hemispheric WMH, unless a large chronic territorial infarction precluded this. Areas of signal change from previous infarctions were not considered WMH, and the corresponding brain regions were masked. To correct WMHV for head size, we used the sagittal midline cross-

sectional intracranial area (ICA) as a surrogate measure of the intracranial volume. Normalized WMHV was the measured WMHV multiplied by the ratio of the individual ICA to mean ICA, according to a previously validated method.^{28,29} We have previously shown a high interrater reliability for ICA and WMHV measurements, with ICCs of 0.92 and 0.98.¹⁰ All MRI measurements were performed centrally by readers blinded to clinical data, including outcome and TOAST subtype assignment.

Standard protocol approvals, registrations, and patient consents. All participating subjects or their healthcare proxy provided informed consent to be enrolled as part of the ongoing prospective hospital-based cohort studies at the participating institutions, all aspects of which were approved by the respective institutional review boards.

Statistical analysis. All statistical analyses were performed by using STATA 10.0. Continuous numerical variables are expressed as mean $\pm$ SD, with the exception of WMHV, which is expressed as median $\pm$ interquartile range (IQR). Original WMHV measurements (in cubic centimeters) were transformed for analysis by using the Box-Cox method.

To explore differences in clinical characteristics between the background cohorts and the subset of subjects with MRIs, χ^2 , Kruskal-Wallis, or Wilcoxon-Mann-Whitney tests were used, as appropriate. Age, sex, race (white vs nonwhite), WMHV, history of or being treated for hypertension (HTN), diabetes mellitus (DM), atrial fibrillation (AF), coronary artery disease (CAD), and alcohol and tobacco use (>3 oz/d and >1 pack/d) were evaluated in univariate analyses of stroke subtypes.

Independent predictors of stroke subtype in the MGH AIS cohort were identified by using multinomial regression analysis ($\lambda = 0.11$), including all the univariate predictors with $p < 0.3$ in a Wald test for independent variables, and the findings were replicated in the ISGS AIS cohort by using multivariable logistic

regression analysis with SV stroke subtype as dependent variable and the same independent variables as in the discovery cohort. These findings were then extended to the ICH cohort by using additional multivariable logistic regression analyses, including age, sex, race, HTN, WMHV, DM, AF, and CAD (all $p < 0.2$ in univariate analyses), to differentiate predictors of stroke subtype between the patients with AIS and ICH. The level of significance was set at 2-sided $p < 0.05$ for all statistical analyses.

RESULTS Of the 849 patients presenting to MGH with AIS during the study period who consented for this study, 628 had MRI evidence of acute cerebral infarct on DWI and images suitable for volumetric analysis (median WMHV was 7.5 cm³, IQR 3.4–14.7). Among these, 252 (40%) had cardioembolic, 144 (23%) undetermined, 112 (18%) large artery, 69 (11%) SV, and 51 (8%) other stroke subtype. Comparison of the 221 individuals without analyzable MRI who were excluded from this study revealed that patients with MRI were less likely to have AF on presentation or a history of prior stroke (table 1).

In univariate analysis of MGH AIS cohort, individuals with SV stroke subtype had larger WMHV (SV 11.1 cm³, IQR 6.7–25.8; undetermined 7.63 cm³, IQR 3.8–17.9; cardioembolic 7.37 cm³, IQR 3.1–13.3; large artery 7.35 cm³, IQR 3.7–16.3; other 3.85 cm³, IQR 2.1–7.64; $p < 0.001$). Other clinical characteristics that differed significantly across stroke subtypes included age, HTN, DM, AF, smoking, and moderate to heavy alcohol consumption (table 2). Subjects classified as having “other” TOAST stroke subtype were considerably younger; however, excluding this category from the univariate analysis did not change the relationship of age across the stroke subtypes ($p = 0.0001$).

In multivariable analysis, an increase in WMHV equal to 16 cm³ (1 SD normally transformed WMH) was associated with an increase in the risk of the stroke being of SV ischemic stroke subtype instead of cardioembolic (odds ratio [OR] = 1.87, 95% confidence interval [CI] 1.22–2.12, $p < 0.001$), large artery (OR = 2.25, 95% CI 1.35–2.54, $p < 0.001$), undetermined (OR = 1.87, 95% CI 1.19–2.18, $p < 0.002$), or other (OR = 1.85, 95% CI 1.04–2.45, $p < 0.03$) subtype (figure e-1 on the *Neurology*[®] Web site at www.neurology.org).

The mean age of the replication ISGS cohort ($n = 263$) was 67.2 ± 13.8 years (median WMHV 5.3 cm³ [IQR 2.5–11.1] (table 3). TOAST classification was as follows: cardioembolic (27.2%), large artery (21.5%), SV (10.7%), undetermined (35.6%), and other etiology (4.9%). Compared with MGH AIS subjects, the ISGS cohort was more ethnically diverse (23.3% nonwhite) and had fewer patients with AF (6.9%) ($p = 0.001$). In multivariable logistic regression analysis of baseline predictors of isch-

Table 1 Clinical characteristics of the Massachusetts General Hospital ischemic stroke cohort ($n = 849$)

	Brain MRI not available	Brain MRI available	p Value ^a
Total no. of subjects	221	628	
Age, mean $\pm$ SD, y	66.4 $\pm$ 16	65.3 $\pm$ 15	
Male, %	53.9	56.6	
Race, % white	95.4	95.0	
WMH volume, median (IQR), cm ³	—	7.5 (3.4–14.7)	
HTN, %	57.9	64.5	
DM, %	24.9	19.3	
AF, %	24.9	15.1	0.001
CAD, %	20.8	20.8	
Prior stroke, %	20.4	14.4	0.038
Admission NIHSS score, mean $\pm$ SD	5.8 $\pm$ 6	5.6 $\pm$ 7	
mRS score at 90 d, mean $\pm$ SD	2.0 $\pm$ 2	1.8 $\pm$ 2	
Tobacco, >1 pack/d	63.5	56.2	
Alcohol, >3 oz/d	74.4	72.2	

Abbreviations: AF = atrial fibrillation; CAD = coronary artery disease; DM = diabetes mellitus; HTN = hypertension; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; WMH = white matter hyperintensity.

^a Significance was tested via rank-sum test or Student t test (continuous variables) or Fisher exact test (categorical). p values >0.15 are not shown.

Table 2 Stroke subtypes within the Massachusetts General Hospital ischemic stroke cohort (n = 628)

	Cardioembolic	Large artery	Small vessel	Other	Undetermined	p Value ^a
Total no. of subjects	252	112	69	51	144	
Age, mean ± SD, y	66.1 ± 16.6	67.2 ± 11.8	65.3 ± 11.8	48.4 ± 14.1	68.26 ± 14.5	<0.001
Sex, % male	57.5	62.5	63.77	49.2	48.61	0.09
Race, % white	95.2	96.4	90.5	95.7	96.3	
HTN, %	64.9	73.2	75.4	31.4	63.9	0.001
WMH volume, median (IQR), cm ³	7.37 (3.1–13.0)	7.35 (3.73–16.3)	11.1 (6.7–25.8)	3.85 (2.13–7.64)	7.63 (3.8–17.9)	<0.001
DM, %	16.7	25.9	31.9	7.8	17.4	0.004
AF, %	29.8	6.25	0	0	9.0	<0.001
CAD, %	25.0	20.5	24.6	9.8	16.0	0.054
Alcohol, >3 oz/d	49.5	58.2	59.3	55.3	67.8	0.033
Tobacco, >1 pack/d	36.6	62.5	33.9	52.6	48.7	<0.001

Abbreviations: AF = atrial fibrillation; CAD = coronary artery disease; DM = diabetes mellitus; HTN = hypertension; IQR = interquartile range; WMH = white matter hyperintensity.

^a Significance was tested via Kruskal-Wallis (continuous variables) or Fisher exact row-column method test (categorical). p values >0.15 are not shown.

emic stroke subtypes within the ISGS cohort, WMHV remained an independent predictor of SV stroke subtype (OR = 1.5, 95% CI 1.01–2.12, *p* = 0.03) (figure e-2).

The mean age of the 122 patients with primary ICH who underwent brain MRI within 2 weeks of their index event was 72.5 ± 12 years (median WMHV 17.8 cm³, IQR 7.3–38.3). Of these, 50% were women and 85.3% were white. HTN was present in 74.2%, DM in 20.2%, AF in 19.5%, and CAD in 9.9%. ICH subjects without MRI (n =

321) were more likely to have a history of prior stroke (*p* < 0.04) and had higher rates of CAD (*p* = 0.003) (data not shown). The frequency of MRI use was lower in ICH compared with AIS (74% in AIS vs 22% in ICH), regardless of AIS subtype.

Patients with ICH had larger WMHV than patients with AIS (*p* < 0.001). In addition, they were older and had higher rates of hypertension as well as lower rates of CAD at baseline (table 4). In multivariable logistic regression analysis, the association of increased WMHV with ICH was independent of other factors (OR = 1.34, 95% CI 1.25–1.72, *p* = 0.007). When the multivariable comparison was restricted to ICH and SV subtype alone, the association of higher WMHV with ICH persisted (OR = 1.2, 95% CI 1.05–1.52, *p* = 0.023; figure 1).

All final multivariable models in this study were adjusted for age, thus making the comparison of WMH volume across the cohorts possible, despite their differences in baseline characteristics.

DISCUSSION Our results demonstrate that among patients with acute stroke, WMH burden is highest in those with SV stroke subtype. This finding was evident in 2 independent ischemic stroke cohorts. Furthermore, comparison between subjects with acute ICH and AIS revealed that WMHV in subjects with acute ICH exceed those of any ischemic stroke subtype. These data support the model that increasing WMHV is a marker of more severe cerebral SV disease and provide further evidence for links between the biology of WMH and SV ischemic and hemorrhagic stroke.

Our study supports prior reports of association between higher WMH grade, as assessed by CT or

Table 3 Stroke subtypes within the Ischemic Stroke Genetics Study cohort

	Non-small vessel	Small vessel	p Value ^a
Total no. of subjects	235	28	
Age, mean ± SD, y	67.2 ± 13.9	67.7 ± 16.8	
Sex, % male	61.8	67.86	
Race, % white	89.7	78.5	
HTN, %	63.5	60.7	
WMH volume, median (IQR), cm ³	4.5 (1.7–10.7)	8.0 (4.7–16.4)	0.008
DM, %	22.13	28.6	
AF, %	7.7	3.5	
CAD, %	26.7	21.4	
Alcohol, >3 oz/d	9.0	21.4	0.05
Tobacco, >1 pack/d	16.3	25.0	

Abbreviations: AF = atrial fibrillation; CAD = coronary artery disease; DM = diabetes mellitus; HTN = hypertension; IQR = interquartile range; WMH = white matter hyperintensity.

^a Significance was tested via rank-sum test or Student *t* test (continuous variables) or Fisher exact test (categorical). p values >0.05 are not shown.

Table 4 Comparison of subjects with ischemic stroke and intracerebral hemorrhage

	All ischemic stroke subtypes	ICH	p Value ^a
Total no. of subjects	889	122	
Age, mean $\pm$ SD, y	65.6 $\pm$ 15.2	72.5 $\pm$ 11.6	0.001
Sex, % male	58.16	50.0	0.09
Race, % white	79.9	82.3	0.01
HTN, %	64.1	74.2	0.001
WMH volume, median (IQR), cm ³	6.73 (2.84–13.8)	17.8 (7.24–38.6)	0.001
DM, %	20.4	20.2	
AF, %	12.7	19.5	0.057
CAD, %	22.4	9.9	0.002

Abbreviations: AF = atrial fibrillation; CAD = coronary artery disease; DM = diabetes mellitus; HTN = hypertension; ICH = intracerebral hemorrhage; IQR = interquartile range; WMH = white matter hyperintensity.

^a Significance was tested via rank-sum test or Student *t* test (continuous variables) or Fisher exact test (categorical). *p* values >0.15 are not shown.

MRI, and higher risk of lacunar infarcts.^{18,30} Lacunar infarcts and ICH were significant determinants of CT-detected leukoaraiosis in patients with ischemic and hemorrhagic strokes.¹⁹ Grading WMH on MRI by using another semiquantitative method, the Fazekas scale, patients with lacunar infarcts were found to have more severe WMH compared with other subtypes at baseline, had more WMH progression, and predicted formation of new lacunes in the LADIS study.³¹ The only report of association between the WMHV and large artery stroke subtype in 594 Korean subjects, whose WMH was measured by using

another semiquantitative grading scale, was thought to be particular to the selected population and has not been replicated to date.³²

The severity of WMH burden in patients with ICH is greater than that of subjects with SV ischemic stroke subtype. Previous reports indicated that WMH burden is highest in patients with ICH and lacunar stroke; however, limitations of the neuroimaging methods precluded further analysis.^{19,33} Here, we extend those findings by using quantitative methods in a larger population to show that WMHV is in fact higher in ICH than in all other ischemic stroke types, even lacunar stroke. This possibly speaks to the severity of SV disease in primary ICH, which results from the microangiopathic damage due to either amyloid protein deposition or lipohyalinosis due to common vascular risk factors, such as advancing age^{8,34} or HTN.⁵ Given the established high heritability of WMH, it is possible that interaction between these and novel genetic risk factors that are not yet discovered may provide important biologic clues to this link.^{5,35,36}

In our study, severity of WMH was assessed by using semiautomated volumetric analysis, a method that has been shown to be reliable in prior studies but requires considerable operator-mediated input to maintain its accuracy.^{10,27} We calculated WMHV from the hemisphere unaffected by stroke and excluded the areas of hyperintensity from previous infarctions to avoid confounding; however, in patients with lacunar infarcts, total WMHV might inadver-

Figure 1 Box plot graphic representation of white matter hyperintensity volume distribution by acute ischemic stroke subtype (combined MGH and ISGS cohorts) and intracerebral hemorrhage

AIS = acute ischemic stroke; ICH = intracerebral hemorrhage; ISGS = Ischemic Stroke Genetics Study; MGH = Massachusetts General Hospital; WMH = white matter hyperintensity.

tently incorporate prior lacunar infarcts. This is a technical limitation of current neuroimaging modalities available for differentiation of chronicity and pathophysiologic origin of WMH, and as such, a potential limitation of the study. It is unlikely, however, to account for the relationship between larger WMHV and ICH.

An inherent limitation of our study is that the number of SV strokes in both the MGH and ISGS cohorts is relatively small compared with the previous epidemiologic reports.³⁷ In part, this is a finding related to the geographic and referral patterns of the study centers. Furthermore, the decision to have a patient undergo MRI was made by the clinical teams caring for each patient at the time of stroke, thus conceivably limiting our study population (table 1). Another factor that may have influenced the apparent composition of our cohorts was our use of TOAST to classify stroke subtype. Although TOAST is the most widely accepted tool to categorize stroke subtype, its only moderate interexaminer reliability, potential for overestimation of the “undetermined” category, and possible misinterpretation of stroke causality based on the presumed role of risk factors have prompted the development of more advanced stroke subtype classification systems in the recent years.^{38,39} Thus, in our retrospective study design, a misclassification bias cannot be entirely ruled out.

Unmeasured confounding too could affect the results of association between stroke subtype and severity of WMH. Some of this potential confounding might be related to limitations of hospital-based studies, which lack previous data on underlying chronic conditions (such as severity of HTN) and their potential effects on the associations between the study variables. Furthermore, we have previously demonstrated that increased plasma homocysteine level is independently related to WMHV in patients with AIS.⁴ In the present study, homocysteine level was not associated with any particular stroke subtype in the MGH AIS cohort ($p < 0.13$); moreover, the relationship between SV stroke and WMHV is probably less subject to unmeasured confounding given the replication of our results in an independent cohort.

We also acknowledge that there might be a small proportion of patients with SV strokes not visible on DWI, and therefore, these patients might not have been included in our analyses. Although every attempt was made to reevaluate all but the small number of patients with a clinical picture of stroke, who would have been otherwise considered “DWI negative” on admission, with a repeated MRI before their discharge, some of these would still have been

missed. This and other limitations related to use of MRI in patients with an acute cerebrovascular event, such as the disproportionate number of AIS as compared with ICH subjects who underwent MRI after their index event, are related to the complexities of clinical care and technical limitations of existing neuroimaging modalities that we still encounter as part of hospital-based research.

Because only a relatively small proportion of ICH subjects underwent MRI (in addition to CT scanning) and those patients had less severe hemorrhages, the results of our study may reflect “healthier” ICH subjects. Finally, few data exist on specific effects of race and ethnicity on severity of WMH⁴⁰; however, this issue could not be addressed in our study population, which is predominantly of European descent. Further studies of the common pathophysiology underlying cerebral SV disease, including WMH, may yield novel diagnostic and therapeutic approaches to the prevention of SV disease.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Alessandro Biffi.

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