Mixed-location cerebral hemorrhage/ microbleeds

Underlying microangiopathy and recurrence risk

Marco Pasi, MD, Andreas Charidimou, MD, PhD, Gregoire Boulouis, MD, Eitan Auriel, MD, Alison Ayres, BA, Kristin M. Schwab, BA, Joshua N. Goldstein, MD, PhD, Jonathan Rosand, MD, MSc, Anand Viswanathan, MD, PhD, Leonardo Pantoni, MD, PhD, Steven M. Greenberg, MD, PhD, and M. Edip Gurol, MD, MSc

Neurology® 2018;90:e119-126. doi:10.1212/WNL.0000000000004797

Correspondence

Dr. Edip Gurol
edip@mail.harvard.edu

Abstract

Objective

To assess the predominant type of cerebral small vessel disease (SVD) and recurrence risk in patients who present with a combination of lobar and deep intracerebral hemorrhage (ICH)/microbleed locations (mixed ICH).

Methods

Of 391 consecutive patients with primary ICH enrolled in a prospective registry, 75 (19%) had mixed ICH. Their demographics, clinical/laboratory features, and SVD neuroimaging markers were compared to those of 191 patients with probable cerebral amyloid angiopathy (CAA-ICH) and 125 with hypertensive strictly deep microbleeds and ICH (HTN-ICH). ICH recurrence and case fatality were also analyzed.

Results

Patients with mixed ICH showed a higher burden of vascular risk factors reflected by a higher rate of left ventricular hypertrophy, higher creatinine values, and more lacunes and severe basal ganglia (BG) enlarged perivascular spaces (EPVS) than patients with CAA-ICH (all $p < 0.05$). In multivariable models mixed ICH diagnosis was associated with higher creatinine levels (odds ratio [OR] 2.5, 95% confidence interval [CI] 1.2–5.0, $p = 0.010$), more lacunes (OR 3.4, 95% CI 1.7–6.8), and more severe BG EPVS (OR 5.8, 95% CI 1.7–19.7) than patients with CAA-ICH. Conversely, when patients with mixed ICH were compared to patients with HTN-ICH, they were independently associated with older age (OR 1.03, 95% CI 1.02–1.1), more lacunes (OR 2.4, 95% CI 1.1–5.3), and higher microbleed count (OR 1.6, 95% CI 1.3–2.0). Among 90-day survivors, adjusted case fatality rates were similar for all 3 categories. Annual risk of ICH recurrence was 5.1% for mixed ICH, higher than for HTN-ICH but lower than for CAA-ICH (1.6% and 10.4%, respectively).

Conclusions

Mixed ICH, commonly seen on MRI obtained during etiologic workup, appears to be driven mostly by vascular risk factors similar to HTN-ICH but demonstrates more severe parenchymal damage and higher ICH recurrence risk.

RELATED ARTICLE

Editorial

Mixed emotions: What to do with patients who have lobar and deep hemorrhages on MRI?

Page 55

From the Hemorrhagic Stroke Research Program (M.P., A.C., G.B., E.A., 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, France; and Division of Neurocritical Care and Emergency Neurology (J.N.G., J.R.), Massachusetts General Hospital, Harvard Medical School, Boston.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

BG = basal ganglia; CAA = cerebral amyloid angiopathy; CI = confidence interval; CSO = centrum semiovale; cSS = cortical superficial siderosis; EPVS = enlarged perivascular space; HTN = hypertension; ICH = intracerebral hemorrhage; LVH = left ventricular hypertrophy; OR = odds ratio; SVD = small vessel disease; WMH = white matter hyperintensity.

Cerebral amyloid angiopathy (CAA) and hypertensive small vessel disease (HTN-SVD) are considered to be the main causes of primary intracerebral hemorrhage (ICH).¹ CAA affects primarily the cortical/leptomeningeal vessels, whereas HTN-SVD affects mainly the deep perforating arterioles.^{1–4} Patients with multiple strictly lobar bleeds, including cerebral microbleeds and cortical superficial siderosis (cSS), on MRI are likely to have CAA, whereas patients with strictly deep hemorrhages are likely to have HTN-SVD.^{5–8}

Understanding the underlying SVD type is clinically important because CAA and HTN-SVD are associated with different risks of ICH recurrence. Patients with ICH/microbleeds in both lobar and deep hemispheric brain regions (mixed ICH) are commonly encountered in clinical practice. Previous work suggests that HTN-SVD may cause lobar microbleeds.^{9–13} The pathologic process underlying mixed ICH may be a severe vasculopathy, similar to HTN-SVD, caused by risk factors such as hypertension and diabetes mellitus or more of a combination of both CAA and HTN-SVD, but this issue is unresolved at that time.¹⁴

The principal aim of this study is to evaluate the potential mechanisms and ICH recurrence risk in patients with mixed ICH. We had 3 research questions. Do patients with mixed ICH share similar clinical and radiologic phenotypes, regardless of the location of the symptomatic bleed, that differ significantly from those in patients with CAA and HTN-ICH? What is the principal mechanism underlying mixed ICH, a predominant severe HTN-SVD driven by vascular risk factors or an overlap between HTN-SVD and CAA? Finally, is the risk of recurrent ICH different in mixed ICH and in CAA and HTN-ICH?

Methods

Study population

We have analyzed prospectively collected data from consecutive patients admitted to the Massachusetts General Hospital between 2003 and 2012 with spontaneous symptomatic ICH who underwent MRI and were enrolled in an ongoing cohort study as extensively described in previous publications.^{15–19} All patients had CT angiography/magnetic resonance angiography to rule out vascular malformation or other ICH etiologies.

We defined as having mixed ICH those patients with lobar ICH and ≥ 1 deep microbleeds, deep ICH and ≥ 1 lobar microbleeds, and deep and lobar ICHs with or without microbleeds in any location (figure 1). Patients with lobar ICH involving the

cerebral cortex and underlying white matter with strictly lobar microbleed or cSS were coded as having CAA-ICH per modified Boston criteria.^{5,14,17–19} The CAA-ICH diagnosis included definite, pathologically proven CAA based on full autopsy; probable CAA with supporting pathology, i.e., lobar ICH with or without lobar microbleed and pathologic evidence of CAA; and probable CAA, based on the presence of lobar ICH and purely lobar microbleed or cSS (figure 1). For the purpose of this study, we decided to exclude patients with possible CAA because this category in Boston criteria does not have very good sensitivity and specificity to detect CAA.⁶ Patients with strictly deep hemorrhages in the basal ganglia (BG), thalamus, or brainstem (deep locations) with or without deep microbleeds

Figure 1 Gradient-recalled echo MRI sequences showing different combinations of hemorrhagic pathologies analyzed in this study

(A) Patient with mixed ICH with left posterior lobar hemorrhage and both lobar and deep cerebral microbleeds. (B) Patient with mixed ICH with right thalamic hemorrhage and both lobar and deep microbleeds. (C) Patient with mixed ICH with right lenticulocapsular and right parietal hemorrhages with 1 deep microbleed. (D) Patient with probable CAA with a right posterior lobar hemorrhage and several posterior lobar microbleeds without hemorrhagic lesion in deep locations. Arrows indicate ICH; thick arrows, microbleed. Vertical orientation shows lobar location; oblique orientation, deep location. CAA = cerebral amyloid angiopathy; ICH = intracerebral hemorrhage.

but no lobar microbleeds were diagnosed as having HTN-ICH.^{14,17–19} Even if not all the participants with strictly deep ICH have a clinical history of hypertension, we have decided to use the term HTN-ICH for simplicity and consistency and because no widely accepted replacement has been proposed so far. Patients with lower diagnostic certainty such as primary cerebellar bleeds and participants with other etiologies were excluded from our study (figure 2).

Baseline and follow-up clinical data collection

Baseline data collection was performed as described previously.^{15–19} Briefly, the following clinical variables were systematically recorded for each participant: age, sex, hypertension, diabetes mellitus, hypercholesterolemia, serum creatinine, history of ICH, and ischemic stroke. Presence of left ventricular hypertrophy (LVH) on transthoracic echocardiogram was recorded when available (118 patients with CAA-ICH, 80 with HTN-ICH, and 57 with mixed ICH).

Follow-up data were collected as extensively described previously.^{16,20} All patients were followed up from their date of enrollment until the occurrence of death, the last phone call (last in September 2015), or the last clinical documentation useful for the purpose of this study present on charts.

Standard protocol approvals, registrations, and patient consents

This study was performed with the approval of and in accordance with the guidelines of the institutional review board of Massachusetts General Hospital.

MRI data

Images were obtained with a 1.5T magnetic resonance scanner (GE Sigma; Chicago, IL) and included whole-brain T2 weighted, T1 weighted, a hemosiderin sequence such as T2*-weighted gradient-recalled echo (in 380 patients) or susceptibility-weighted imaging (in 11 patients, 10 with follow-up data), and fluid-attenuated inversion recovery as previously described.^{15–19}

Patients who underwent susceptibility-weighted imaging instead of T2*-weighted gradient-recalled echo were not different in any baseline demographic, clinical, or imaging data (data not shown).

White matter hyperintensity (WMH) volume was quantified as previously validated¹² with a computer-assisted algorithm that involves MRicron (<http://people.cas.sc.edu/rorden/mricron/index.html>), a freely available tool.

Presence and number of microbleed and macrobleeds were evaluated (by E.A.) according to current consensus criteria and as previously described.^{15–19,21} For the purpose of this study, we used total, lobar, and deep microbleed counts. Lacunes were defined according to current consensus criteria.²² In our analyses, we used the binary definition of presence/absence of any lacune. Enlarged perivascular spaces (EPVS) were rated (by A.C.) in the BG and centrum semiovale (CSO), and we prespecified a dichotomized classification of EPVS degree as high (score >20) or low (score ≤20).^{18,23,24} The presence or absence of cSS was evaluated in

Figure 2 Flow diagram of study enrollment

this study as previously described.^{5,25} Nineteen patients underwent surgical evacuation before having the MRI scan. All of the neuroimaging markers described above were reliably assessable. All MRI analyses were performed and recorded by investigators blinded to all clinical information.

Statistical analyses

To evaluate the homogeneity of the mixed ICH group, we compared in univariate models the clinical and neuroimaging characteristics between lobar and deep locations of symptomatic bleed within patients with mixed ICH. Clinical and neuroimaging characteristics of patients with mixed ICH vs patients with CAA and those with HTN-ICH were compared in univariate analyses with 2-independent-sample *t* test, Wilcoxon rank sum test, and Fisher exact test as appropriate.

To assess for the presence of independent associations with the diagnosis of mixed ICH vs CAA-ICH, a multivariable logistic regression analysis was performed with the following potential effectors that were either significant in univariate analyses or relevant on the basis of prior reports: demographic and vascular risk factors (age, hypertension, and diabetes mellitus), clinical variables (previous ICH and creatinine), and SVD imaging markers (total WMH volume, CSO and BG EPVS, presence of lacunes, total microbleed count, and cSS). The same covariates also were used to evaluate for the presence of independent associations with the diagnosis of mixed ICH vs HTN-ICH. The same models were repeated with LVH added.

In the follow-up cohort, the mean follow-up time was calculated and the incidence rates of ICH, and death were determined from the incidence per 100 person-years of follow-up in each diagnostic category. We used Cox regression analyses to calculate the crude hazard ratios for occurrence of ICH and death. Adjusted Cox regression models were performed for 2 different endpoints (ICH recurrence and death) to evaluate differences between mixed ICH and CAA-ICH and between mixed ICH and HTN-ICH. The following variables were entered as covariates: demographic, clinical, and neuroimaging (age, sex, hypertension, creatinine, WMH volume, total microbleed count, cSS) variables. For the Cox models, we tested the proportional hazard assumption using graphical checks and Schoenfeld residuals-based tests.

All analyses were performed with SPSS 22.0 (released 2012, IBM SPSS Statistics for Windows, version 22.0; IBM Corp, Armonk, NY). All tests of significance were 2 tailed.

Results

Our study sample was composed of 391 patients with primary ICH categorized as follows: 75 (19%) patients with mixed ICH (40 with primarily lobar ICH, 29 with primarily deep ICH, and 6 with the concomitant presence of hemorrhages in both locations), 191 (48%) with CAA-ICH, and 125 (31%) with HTN-ICH (figure 2).

We first compared the baseline characteristics between patients who had a primarily lobar and those with deep ICH within the mixed ICH cohort. None of the risk factors or imaging features were different in univariate analyses (table e-1, <http://links.lww.com/WNL/A20>) or multivariable regression models (data not shown). In the primarily lobar ICH group, we found 4 patients with cSS, while just 1 patient from each category in the groups with primarily deep ICH and ICH in both locations had cSS.

Mixed ICH group compared to CAA and HTN-ICH groups

We compared the baseline characteristics of the mixed ICH group with the other etiologic categories (table 1). Compared to patients with CAA-ICH, patients with mixed ICH were more likely to have hypertension, diabetes mellitus, LVH, and lacunes, higher creatinine levels, and high-degree BG EPVS and less likely to have high-degree CSO-EPVS or cSS (all $p < 0.05$). Patients with mixed ICH had more frequent history of ischemic stroke ($p = 0.056$), less frequent history of previous ICH ($p = 0.056$), and younger age ($p = 0.053$), although these results did not reach statistical significance. In a multivariable regression model, diagnosis of mixed ICH was associated with the presence of lacunes (odds ratio [OR] 3.4, 95% confidence interval [CI] 1.7–6.8, $p < 0.001$), BG EPVS (OR 5.8, 95% CI 1.7–19.7, $p = 0.005$), and higher creatinine values (OR 2.5, 95% CI 1.2–5.0, $p = 0.010$), while diagnosis of CAA-ICH was associated with lobar CSO EPVS (OR 0.36, 95% CI 0.2–0.7, $p = 0.006$) and cSS (OR 0.13, 95% CI 0.05–0.3, $p < 0.001$).

Compared to patients with HTN-ICH, patients with mixed ICH were older and had greater WMH volume, presence of lacunes, microbleed counts, and high-degree CSO EPVS (all $p < 0.05$). In a multivariable model, compared to HTN-ICH, mixed ICH diagnosis was associated with older age (OR 1.03, 95% CI 1.02–1.1, $p = 0.02$), presence of lacunes (OR 2.4, 95% CI 1.1–5.3, $p = 0.03$), and higher microbleed count (OR 1.6, 95% CI 1.3–2.0, $p < 0.001$). All models were repeated with LVH added, which did not alter the above reported associations.

Risk of recurrent ICH and death in follow-up

Three hundred three patients who survived the first 90 days after their index event were followed up longitudinally. Mean follow-up time from the index event was 4.1 ± 3.2 years.

Among 90-day survivors, the ICH event recurrence rates were 5.1%/y for mixed ICH, 10.4%/y for CAA-ICH, and 1.6%/y for HTN-ICH patients. Cox regression analysis showed a lower risk of incident ICH in patients with mixed ICH vs CAA-ICH and higher risk of hemorrhage recurrence in patients with mixed ICH vs HTN-ICH. The differences in ICH recurrence between mixed ICH and the other etiologic categories remained significant after adjustment for demographic, clinical, and neuroimaging characteristics (table 2 and figure 3).

Among 90-day survivors, 34 patients with mixed ICH, 81 with CAA-ICH, and 35 with HTN-ICH died during follow-up,

Table 1 Comparison of baseline demographics, clinical, and neuroimaging characteristics between patients with mixed ICH and those with both CAA and HTN-ICH

	Mixed ICH (n = 75)	CAA-ICH (n = 191)	HTN-ICH (n = 125)
Age, mean (SD), y	71.8 (12.6)	74.9 (9.3)	66.1 (13.6) ^a
Female sex, n (%)	32 (42.7)	96 (50.3)	52 (41.6)
HTN, n (%)	66 (88.0)	126 (66.0) ^b	103 (82.4)
Hypercholesterolemia, n (%)	30 (40.0)	86 (45.0)	50 (40.0)
Diabetes mellitus, n (%)	21 (28.0)	22 (11.5) ^a	33 (26.4)
Previous ICH, n (%)	6 (8.0)	33 (17.3)	9 (7.2)
Previous ischemic stroke, n (%)	13 (17.3)	17 (8.9)	14 (11.2)
LVH, n (%) ^c	25 (43.9)	25 (21.2) ^a	32 (40.0)
Creatinine, mean (SD), mg/dL	1.4 (0.8)	1.0 (0.4) ^b	1.3 (1.1)
WMH volume, mL, median (IQR)	23.5 (12.9–46.1)	21.9 (11.8–38.7)	11.8 (3.5–30.2) ^b
Total microbleed count, median (IQR), n	4 (1–13)	1 (0–6)	0 (0–0) ^b
Lobar microbleed count, median (IQR), n	2 (0–5)	1 (0–5)	None
Deep microbleed count, median (range), n	1 (0–18)	None	0 (0–14) ^b
Lacunes ≥1, n (%)	45 (60.0)	56 (29.3) ^b	40 (32.0) ^b
CSO EPVS high degree (score <20), n (%)	21 (28.0)	92 (48.2) ^a	19 (15.2) ^a
BG EPVS high degree (score <20), n (%)	13 (17.3)	6 (3.1) ^b	15 (12.0)
Presence of cSS, n (%)	6 (8.0)	90 (47.1) ^b	3 (2.4)

Abbreviations: BG = basal ganglia; CAA = cerebral amyloid angiopathy; CSO = centrum semiovale; cSS = cortical superficial siderosis; EPVS = enlarged perivascular spaces; HTN = hypertension; ICH = intracerebral hemorrhage; IQR = interquartile range; LVH = left ventricular hypertrophy; WMH = white matter hyperintensities.

The *p* values reported in the CAA column refer to comparison between patients with mixed ICH and CAA-ICH. The *p* values reported in the HTN-ICH column refer to comparison between patients with mixed ICH and HTN-ICH.

^a *p* < 0.05.

^b *p* < 0.001; all others not significant.

^c LVH data available for 118 patients with CAA-ICH, 80 with HTN-ICH, and 57 with mixed ICH.

with an annual case fatality rate of 13.0%, 12.2%, and 11.8%, respectively.

Crude and adjusted case fatality hazard ratios between patients with mixed ICH and those with CAA-ICH were not significantly different. Case fatality for patients with HTN-ICH was lower than for patients with mixed ICH (*p* = 0.014), but after adjustment for demographic, clinical, and neuroimaging variables, this association was no more significant (table 2 and figure 3).

Discussion

Our study evaluated the clinical and detailed imaging profiles of patients who had ICH and microbleed in both lobar and deep cerebral locations. Nineteen percent of patients with primary ICH who received MRI as part of their etiologic workup in our large consecutive series were found to have mixed ICH. This high proportion indicates the importance of understanding the causes and consequences of the underlying SVD in this particular population. First, we found that vascular risk factors and clinical and detailed neuroimaging profiles were similar between

patients with mixed ICH who had a primarily lobar location and those with deep symptomatic bleed, suggesting that mixed ICH is a relatively homogeneous entity. In the larger group comparisons, patients with mixed ICH seemed to have a more pronounced classic vascular risk factor burden (more lacunes, higher creatinine) than patients with CAA-ICH but a vascular risk factor profile similar to those with HTN-ICH. In multivariable analyses, mixed ICHs were associated with higher values of creatinine, presence of lacunes, and degree of BG EPVS compared to CAA-ICH. Compared to patients with HTN-ICH, those with mixed ICH were older with more lacunes and microbleeds. Finally, in 90-day survivors, patients with mixed ICH had a lower cerebral hemorrhage recurrence rate compared to patients with CAA-ICH and a higher recurrence rate compared to those with HTN-ICH patients, as well as an overall similar case fatality rate compared with the other 2 etiologic categories.

Our data showed that patients with mixed ICH presented a clinical phenotype that shared more similarities with patients with HTN-ICH than those with CAA-ICH. Hypertension and

Table 2 Incidences rates and hazard ratios for the occurrence of ICH and death in patients with mixed ICH, CAA-ICH, and HTN-ICH

Event rate	Patients who survived the first 3 mo, n		
	Mixed ICH (n = 59)	CAA-ICH (n = 150)	HTN-ICH (n = 94)
Occurrence of ICH			
Observed person-years	195	498	500
Occurrence, n (%)	10 (16.9)	52 (34.7)	7 (7.4)
Incidence of ICH per 100 person-y (95% CI)	5.1 (2.5–9.4)	10.4 (7.8–13.7)	1.6 (0.6–3.2)
Crude hazard ratio (95% CI)	Reference	2.1 (1.0–4.1) ^a	0.4 (0.1–0.9) ^b
Adjusted hazard ratio (95% CI)	Reference	2.0 (1.0–3.9) ^c	0.2 (0.08–0.8) ^d
Occurrence of death			
Observed person-years	261	663	442
Occurrence, n (%)	34 (57.6)	81 (54.0)	35 (37.2)
Incidence of death per 100 person-y (95% CI)	13.1 (9.0–18.2)	12.2 (9.7–15.2)	11.8 (4.9–9.7)
Crude hazard ratio (95% CI)	Reference	0.9 (0.6–1.5)	0.6 (0.3–0.9) ^e
Adjusted hazard ratio (95% CI)	Reference	1.1 (0.7–1.9)	0.8 (0.5–1.5)

Abbreviations: CAA = cerebral amyloid angiopathy; CI = confidence interval; HTN = hypertensive; ICH = intracerebral hemorrhage.

^a $p = 0.036$.

^b $p = 0.037$.

^c $p = 0.047$.

^d $p = 0.016$.

^e $p = 0.014$.

diabetes mellitus were much more frequent in patients with mixed ICH compared to patients with CAA-ICH, and this could suggest that the classic vascular risk factor burden could be a major player in the development of a severe arteriopathy of brain vessels in both lobar and deep locations. The presence of a microangiopathy similar to HTN-SVD in patients with mixed ICH is suggested by a greater presence of severe BG EPVS and lacunes and lower presence of CSO EPVS and cSS compared to patients with CAA-ICH. Emerging data show that CSO-EPVS is associated with CAA, whereas BG-EPVS with HTN-SVD and cSS is now considered a relatively specific marker of CAA.^{18,25} Overall, our results suggest that the presence of severe hypertension and diabetes mellitus could play a role in promoting the concomitant presence of hemorrhages in lobar and deep locations. In some patients, severe hypertension could be responsible for macrobleeds/microbleeds in lobar locations that are generally thought to be associated with CAA. This issue might also explain the relative inaccuracy of the possible category in Boston criteria: the pathologic validation study showed that only 16 of 26 patients who presented with a single lobar ICH had CAA on detailed pathologic evaluation at autopsy.^{6–26} Data from both studies of older adults enrolled in population-based studies and hypertensive stroke cohorts also suggest that lobar microbleeds can be due to HTN-SVD.^{9–13} In this perspective, Fazekas and collaborators⁹ reported patients with lobar microbleeds without the pathologic finding of amyloid angiopathy but hypertensive arteriosclerosis. Further pathologic studies are needed to confirm

that hypertension and other systemic risk factors can result in lobar hemorrhages and deep cerebral bleeds.

Our results challenge the previous assumption that the majority of patients with ICH/microbleed in mixed (lobar and deep) locations would have both CAA and HTN-SVD as underlying pathologies. However, our data cannot exclude the concomitant presence of different degrees of CAA in patients with mixed ICH. A recent observation that patients with negative amyloid imaging who had hypertensive subcortical vascular cognitive impairment (n = 92) showed both lobar and deep microbleed also suggests that lobar microbleed can be related to HTN-SVD rather than severe CAA.²⁷ Amyloid PET imaging can shed light on the presence/absence of severe vascular amyloid in patients with mixed ICH.^{28,29}

Our study has important clinical implications. Nineteen percent of our large primary ICH cohort (total n = 391) evaluated with MRI showed ICH/microbleed in both lobar and deep locations, so this is a rather prevalent condition. These patients are likely to have a vasculopathy more similar to HTN-SVD than CAA, which should allow clinicians to better identify secondary prevention measures, especially when such patients need antithrombotics or statins for concomitant ischemic risks.^{30,31} The longitudinal results we report could be useful for clinicians, especially in those situations that require balancing the hemorrhagic and ischemic risk. Future registries and trials are needed to address the interaction of antiplatelets

Figure 3 Survival curves of the 3 groups for occurrence of ICH and death in follow-up

(A) Percentages of patients free of recurrent ICH among the 3 diagnostic categories. (B) Mortality among the 3 diagnostic categories. CAA = cerebral amyloid angiopathy; HTN = hypertension; ICH = intracerebral hemorrhage.

and anticoagulants with risk of ICH in patients with mixed-location ICH.

In our study, only 21 patients had a pathologic confirmation of CAA, potentially leading to a relative diagnostic uncertainty. However, we have tried to overcome this drawback by applying strict selection criteria for each diagnostic category. We did not include patients with possible CAA in the CAA-ICH group and included only patients with purely deep bleeds in the HTN-ICH group. The pathologic validation studies showed perfect accuracy of the probable category of Boston criteria to detect CAA.^{5,6,26} Another possible limitation is the lack of data on LVH in 35% of our cohort, which might explain the absence of significant associations with the diagnosis of mixed ICH despite the fact that it was more common in these patients compared to patients with CAA-ICH. We also note the fact that many patients with ICH do

not undergo MRI because of factors such as being too sick, early death, and contraindications, creating a potential for selection bias. This is a well-known problem in ICH research, but the current study had the highest numbers of patients with ICH with MRIs, mitigating the problems originating from the lack of MRI to the extent possible. Despite the high number of consecutive patients with ICH with MRIs, we acknowledge that the relatively smaller mixed ICH cohort may have affected the estimates of our multivariable models. Another strength of our work is the systematic evaluation with MRI scans by trained raters using validated scales for a comprehensive range of imaging markers of SVD.

Our study showed that patients with mixed ICH could be considered a relatively homogeneous group who share a significant presence of classic vascular risk factors and a similar clinical/radiologic profile regardless of the location of the

symptomatic bleed. As a group, they seem to be more similar to patients with HTN-ICH than those with CAA-ICH, and this is probably driven by vascular risk factors. Compared to patients with CAA-ICH, patients with mixed ICH showed a more consistent presence of hypertension, diabetes mellitus, and evidence for hypertensive end-organ damage, suggesting a severe vascular risk factor–driven microangiopathy as the major underlying SVD. In patients with mixed ICH, hemorrhage recurrence is relatively common, an important factor to consider in clinical management. Further work will need to elucidate the genetic and pathologic correlates of mixed ICH and the value of molecular neuroimaging approaches that might characterize this condition in living individuals.

Author contributions

M. Pasi: project concept and design, imaging analysis, data analysis, write-up. A. Charidimou and G. Boulouis: project design, imaging analysis, critical revisions. E. Auriel: imaging analysis, critical revisions. A. Ayres and K. M. Schwab: data collection and management. Joshua N. Goldstein, Jonathan Rosand, Anand Viswanathan, and L. Pantoni: data collection, critical revisions. S. M. Greenberg: funding, data collection, critical revisions. M.E. Gurol: funding, project concept and design, data collection, imaging analysis, data analysis, write-up.

Study funding

Funded by NIH National Institute of Neurological Disorders and Stroke grants K23-NS083711 (Dr. Gurol) and R01-NS NS070834 (Dr. Greenberg).

Disclosure

M. Pasi, A. Charidimou, G. Boulouis, E. Auriel, A. Ayres, K. Schwab, J. Goldstein, J. Rosand, A. Viswanathan, and L. Pantoni report no disclosures relevant to the manuscript. S. Greenberg reports funding from NIH NS070834. M. Gurol reports funding from NIH NS083711. Go to Neurology.org/N for full disclosures.

Received May 10, 2017. Accepted in final form September 10, 2017.

References

1. Qureshi AI, Tuhim S, Broderick JP, et al. Spontaneous intracerebral hemorrhage. *N Engl J Med* 2001;344:1450–1460.
2. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* 2010;9:689–701.
3. Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. *Ann Neurol* 2011;70:871–880.
4. Takebayashi S, Kaneko M. Electron microscopic studies of ruptured arteries in hypertensive intracerebral hemorrhage. *Stroke* 1983;14:28–36.
5. Linn J, Halpin A, Demaerel P, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology* 2010;74:1346–1350.
6. Knudsen KA, Rosand J, Karluk D, et al. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. *Neurology* 2001;56:537–539.
7. van Rooden S, van der Grond J, van den Boom R, et al. Descriptive analysis of the Boston criteria applied to a Dutch-type cerebral amyloid angiopathy population. *Stroke* 2009;40:3022–3027.
8. Fisher CM. Pathological observations in hypertensive cerebral hemorrhage. *J Neuropathol Exp Neurol* 1971;30:536–550.
9. Fazekas F, Kleinert R, Roob G, et al. Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. *Am J Neuroradiol* 1999;20:637–642.
10. Kim YJ, Kim HJ, Park JH, et al. Synergistic effects of longitudinal amyloid and vascular changes on lobar microbleeds. *Neurology* 2016;87:1575–1582.
11. Vernooij MW, van der Lugt A, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. *Neurology* 2008;70:1208–1214.
12. Romero JR, Preis SR, Beiser A, et al. Risk factors, stroke prevention treatments, and prevalence of cerebral microbleeds in the Framingham Heart Study. *Stroke* 2014;45:1492–1494.
13. Yakushiji Y, Yokota C, Yamada N, et al. Clinical characteristics by topographical distribution of brain microbleeds, with a particular emphasis on diffuse microbleeds. *J Stroke Cerebrovasc Dis* 2011;20:214–221.
14. Smith EE, Nandigam KR, Chen YW, et al. MRI markers of small vessel disease in lobar and deep hemispheric intracerebral hemorrhage. *Stroke* 2010;41:1933–1938.
15. Gurol ME, Irizarry MC, Smith EE, et al. Plasma beta-amyloid and white matter lesions in AD, MCI, and cerebral amyloid angiopathy. *Neurology* 2006;66:23–29.
16. van Etten ES, Auriel E, Haley KE, et al. Incidence of symptomatic hemorrhage in patients with lobar microbleeds. *Stroke* 2014;45:2280–2285.
17. Charidimou A, Boulouis G, Haley K, et al. White matter hyperintensity patterns in cerebral amyloid angiopathy and hypertensive arteriopathy. *Neurology* 2016;86:505–511.
18. Charidimou A, Boulouis G, Pasi M, et al. MRI-visible perivascular spaces in cerebral amyloid angiopathy and hypertensive arteriopathy. *Neurology* 2017;21:1157–1164.
19. Pasi M, Boulouis G, Fotiadis P, et al. Distribution of lacunes in cerebral amyloid angiopathy and hypertensive small vessel disease. *Neurology* 2017;88:2162–2168.
20. Rosand J, Eckman MH, Knudsen KA, et al. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. *Arch Intern Med* 2004;164:880–884.
21. Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol* 2009;8:165–174.
22. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013;12:822–838.
23. Martinez-Ramirez S, Pontes-Neto OM, Dumas AP, et al. Topography of dilated perivascular spaces in subjects from a memory clinic cohort. *Neurology* 2013;80:1551–1556.
24. Charidimou A, Meegahage R, Fox Z, et al. Enlarged perivascular spaces as a marker of underlying arteriopathy in intracerebral haemorrhage: a multicentre MRI cohort study. *J Neurol Neurosurg Psychiatry* 2013;84:624–629.
25. Charidimou A, Jaunmuktane Z, Baron JC, et al. Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. *Brain* 2015;138:2126–2139.
26. Smith EE, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. *Curr Atheroscler Rep* 2003;5:260–266.
27. Park JH, Seo SW, Kim C, et al. Pathogenesis of cerebral microbleeds: in vivo imaging of amyloid and subcortical ischemic small vessel disease in 226 individuals with cognitive impairment. *Ann Neurol* 2013;73:584–593.
28. Gurol ME. Molecular neuroimaging in vascular cognitive impairment. *Stroke* 2016;47:1146–1152.
29. Gurol ME, Becker JA, Fotiadis P, et al. Florbetapir-PET to diagnose cerebral amyloid angiopathy: a prospective study. *Neurology* 2016;87:2043–2049.
30. Thon JM, Gurol ME. Intracranial hemorrhage risk in the era of antithrombotic therapies for ischemic stroke. *Curr Treat Options Cardiovasc Med* 2016;18:29.
31. Lauer A, Greenberg SM, Gurol ME. Statins in intracerebral hemorrhage. *Curr Atheroscler Rep* 2015;17:46.

Mixed-location cerebral hemorrhage/microbleeds

Underlying microangiopathy and recurrence risk

Marco Pasi, MD, Andreas Charidimou, MD, PhD, Gregoire Boulouis, MD, Eitan Auriel, MD, Alison Ayres, BA, Kristin M. Schwab, BA, Joshua N. Goldstein, MD, PhD, Jonathan Rosand, MD, MSc, Anand Viswanathan, MD, PhD, Leonardo Pantoni, MD, PhD, Steven M. Greenberg, MD, PhD, and M. Edip Gurol, MD, MSc

Correspondence

Dr. Gurol
edip@mail.harvard.edu

Neurology® 2018;90:60. doi:10.1212/WNL.0000000000004797

Study question

What are the predominant cerebral small vessel risk factors and the intracerebral hemorrhage (ICH) recurrence risk in patients presenting with a combination of lobar and deep ICH/microbleed locations (mixed ICH)?

Summary answer

Mixed ICH is driven by vascular risk factors similar to those of hypertensive ICH (HTN-ICH), but mixed ICH carries greater ICH recurrence risks.

What is known and what this paper adds

The etiology of mixed ICH was formulated as a combination of hypertensive small vessel disease (HTN-SVD) and cerebral amyloid angiopathy (CAA), but the matter remains unresolved. This study provides evidence that the etiology of mixed ICH is more likely to be HTN-SVD.

Participants and setting

Of the participants, 75 had mixed ICH, 191 had CAA-ICH, and 125 had HTN-ICH. All presented at the Massachusetts General Hospital between 2003 and 2012.

Design, size, and duration

Prospectively collected demographic, clinical, and MRI data from consecutive patients were analyzed. All patients were followed up from the date of enrollment until death, the date of the last useful medical chart entry, or September 2015. Multivariable logistic regression analyses were used to calculate odds ratios (ORs) for variables that were associated with specific ICH diagnoses. Cox regression analyses were also used to examine ICH recurrence risks.

Main results and the role of chance

Compared to CAA-ICH, mixed ICH was associated with the presence of lacunes (OR 3.4, 95% confidence interval [CI] 1.7–6.8, $p < 0.001$), enlarged perivascular space in the basal ganglia (OR 5.8, 95% CI 1.7–19.7, $p = 0.005$), and higher serum creatinine levels (OR 2.5, 95% CI 1.2–5.0, $p = 0.010$). Compared to HTN-ICH, mixed ICH was associated with the presence of lacunes (OR 2.4, 95% CI 1.1–5.3, $p = 0.03$) and more microbleeds (OR 1.6, 95% CI 1.3–2.0, $p < 0.001$). Mixed ICH exhibited greater differences from CAA-ICH than from HTN-ICH. The

Examples of mixed ICH (A–C) and probable CAA (D)

ICH recurrence risk for mixed ICH (5.1 per 100 person-years) was intermediate between those for CAA-ICH (10.4 per 100 person-years) and HTN-ICH (1.6 per 100 person-years).

Bias, confounding, and other reasons for caution

Most patients with CAA-ICH did not have pathologic confirmation, but the gold standard, previously validated clinical-radiologic Boston criteria, was used for this diagnosis. Many patients with ICH do not undergo MRI, which may have caused selection bias.

Generalizability to other populations

The cases with mixed ICH were relatively homogeneous in their vascular risk factors, clinical characteristics, and MRI profiles, which suggests that the results of this study should be generalizable.

Study funding/potential competing interests

This study was supported by NIH grants. The authors report no competing interests. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.