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Predicting Symptomatic Intracerebral Hemorrhage Versus Lacunar Disease in Patients With Longstanding Hypertension

Elisabeth B. Marsh, MD, **Rebecca F. Gottesman, MD, PhD**, **Argye E. Hillis, MD**, **Joyce Maygers, DNP, RN**, **Erin Lawrence, BSN**, and **Rafael H. Llinas, MD**

Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD (E.B.M., R.F.G., A.E.H., R.H.L.); and Departments of Neurology (E.B.M., R.F.G., E.L., R.H.L.) and Clinical Practice (J.M.), Johns Hopkins Bayview Medical Center, Baltimore, MD

Abstract

Background and Purpose—Hypertension results in a spectrum of subcortical cerebrovascular disease. It is unclear why some individuals develop ischemia and others develop hemorrhage. Risk factors may differ for each population. We identify factors that predispose an individual to subcortical symptomatic intracerebral hemorrhage (sICH) compared with ischemia.

Methods—Demographic and laboratory data were prospectively collected for hypertensive patients presenting with ischemic stroke or sICH during an 8.5-year period. Neuroimaging was retrospectively reviewed for acute (subcortical lacunes [<2.0 cm] versus subcortical sICH) and chronic (periventricular white matter disease and cerebral microbleeds) findings. We evaluated the impact of age, race, sex, serum creatinine, erythrocyte sedimentation rate, low-density lipoprotein, presence of periventricular white matter disease or cerebral microbleeds, and other factors on the risk of sICH versus acute lacune using multivariate logistic regression.

Results—Five hundred seventy-one patients had subcortical pathology. The presence of cerebral microbleeds (adjusted odds ratio [OR], 3.39; confidence interval [CI], 2.09–5.50) was a strong predictor of sICH, whereas severe periventricular white matter disease predicted ischemia (OR, 0.56 risk of sICH; CI, 0.32–0.98). This association was strengthened when the number of microbleeds was evaluated; subjects with >5 microbleeds had an increased risk of sICH (OR, 4.11; CI, 1.96–8.59). It remained significant when individuals with only cortical microbleeds were removed (OR, 1.77, CI, 1.13–2.76). An elevated erythrocyte sedimentation rate (OR, 1.19 per 10 mm/h increase; CI, 1.06–1.34) was significantly associated with sICH, whereas low-density lipoprotein was associated with ischemic infarct (OR, 0.93 risk of sICH per 10 mg/dL increase; CI, 0.86–0.99).

Reprints requests to Elisabeth B. Marsh, MD, Department of Neurology, Johns Hopkins University School of Medicine, 600 N Wolfe St, Phipps 446C, Baltimore, MD 21287. ebmarsh@jhmi.edu.

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Disclosures

None.

Conclusions—Subclinical pathology is the strongest predictor of the nature of subsequent symptomatic event. Low-density lipoprotein and erythrocyte sedimentation rate may also have a role in risk stratification.

Keywords

cerebral hemorrhage; hypertension; inflammation; stroke

Each year, >40 000 people in the United States experience a symptomatic intracerebral hemorrhage (sICH).[1,2] sICH leads to high rates of morbidity and mortality, with only 38% surviving through the first year.[3] Another estimated 15 per 100 000 people present annually with a lacunar infarct (lacune)[4] or small area of ischemia secondary to occlusion of a single, deep penetrating vessel. A lacune may be silent (subclinical) or may result in unilateral motor or sensory deficits. Hypertension is the primary risk factor for both sICH and lacunes, but other factors may predispose an individual to one or the other. Currently, prevention guidelines are not distinct, because we are unable to predict who is at highest risk for each outcome.[5] Prevention strategies could be individually tailored if risk factors for each outcome were more clearly defined. Blood pressure management is critical to prevent all cerebrovascular complications[5]; however, there may be a greater benefit to choosing a more aggressive target in an individual predisposed to sICH.[6] Conversely, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors are highly effective at reducing long-term ischemic stroke risk,[5] but may even increase the risk of sICH.[7]

The cerebrovascular complications of hypertension often begin silently with the accumulation of subclinical lacunes and subcortical cerebral microbleeds (small, homogeneous hemorrhages visible on susceptibility-weighted MRI).[8] The predisposition for hemorrhage versus lacunar infarction likely applies not only to clinically significant events but also to these asymptomatic microbleeds. Cortical microbleeds have been associated with an increased risk of sICH in patients with amyloid angiopathy,[9,10] but the association between subcortical microbleeds and hypertensive sICH is less clear.

Medical comorbidities, along with an individual's demographic profile and underlying genetic predisposition,[11,12] probably determine the propensity for hemorrhage. Based on previous data, we suspected that factors such as kidney disease[13] and chronic inflammation would be associated with sICH, whereas tobacco use, low-density lipoprotein (LDL), and diabetes mellitus would be associated with ischemia.[14] In a single-center inpatient population, we evaluated the risk profile for propensity of subcortical sICH compared with lacunar infarct and specifically assessed whether subclinical phenotype predicts symptomatic disease (eg, microbleeds predict sICH). This concept is crucial to the understanding of the spectrum of hypertensive disease, and the results provide insight into potential mechanisms underlying the increased predisposition of some individuals to hemorrhage compared with ischemia.

Methods

Study Population

This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board. A retrospective review of a prospectively collected database was performed. We followed 2260 patients presenting to the Johns Hopkins Bayview Medical Center with an ischemic stroke or sICH during an 8.5-year period. Inclusion criteria included the following: age ≥18 years, history of hypertension (defined by patient-reported history of hypertension, currently taking antihypertensive medications, or left ventricular hypertrophy on echocardiogram),[15] and acute subcortical lacune or sICH on neuroimaging (noncontrast head computed tomography or stroke protocol MRI) corresponding to presenting symptoms. The electronic medical record was reviewed for demographic information (age, race, sex); medical variables (admission systolic and diastolic blood pressure, reported history of hypertension, history of diabetes mellitus, history of chronic kidney disease, left ventricular hypertrophy by echocardiography, and history of alcohol or tobacco use); neuroimaging (presence of periventricular white matter disease [PVWMD] and cerebral microbleeds); and laboratory studies on admission (serum creatinine, glucose, hematocrit, platelet count, liver function tests [aspartate transaminase (AST) and alanine transaminase (ALT)], international normalized ratio [INR], high-density lipoprotein and LDL, and erythrocyte sedimentation rate [ESR]).

Neuroimaging

All patients with ischemic stroke and the majority of those with sICH underwent MRI as part of their standard workup. Imaging was performed on a 3-T scanner using a standard quadrature transmit/receive head coil and included diffusion-weighted imaging (for acute infarct), susceptibility-weighted MRI (for blood), and T1- and T2-weighted imaging (for pathology, aging of hemorrhage).[16] Sequences beyond the standard stroke protocol were not required. All head computed tomography and brain MRIs were reviewed by a board-certified vascular neurologist, blinded to clinical status, with 10% read by a second vascular neurologist. We have previously reported excellent inter-rater reliability ($\kappa = 0.76$) in evaluating intracerebral hemorrhage.[17]

Defining Lacunar Disease/White Matter Hyperintensity Burden

On MRI, areas of restricted diffusion were identified on diffusion-weighted imaging. A symptomatic lacune was defined as a focal, diffusion-weighted imaging/T2-weighted hyperintense lesion, <2.0 cm,[18] in a classic location for small-vessel disease (thalamus, basal ganglia, subcortical white matter, pons, midbrain, medulla, cerebellum), corresponding to the acute neurological presentation. Territorial infarcts (eg, large-vessel middle cerebral artery occlusion with resulting ischemia of the lenticulostriates) were excluded. The extent of white matter hyperintensity (PVWMD) was reviewed from fluid-attenuated inversion recovery/T2-weighted images using the Cardiovascular Health Study (CHS) white matter rating scale and templates, with a range from 0 to 9 (9 representing the most severe confluent PVWMD).[19] For patients unable to undergo MRI, those with areas of hypodensity meeting the size criteria for lacunar stroke on computed tomography that corresponded to presenting symptoms were included.

Defining sICH/Microbleeds

Computed tomography was used to characterize the size and location of subcortical sICH. Cortical hemorrhages (defined as hemorrhages containing cortex that may or may not contain subcortical white matter but do not involve deep structures) were excluded, as was hemorrhagic conversion of ischemic stroke (blood present within a vascular distribution with a larger area of diffusion restriction on MRI). If there was debate on the origin of hemorrhage (cortical versus subcortical), T1- and T2-weighted MRI (obtained in most cases as part of routine clinical care) was reviewed.[16] Brain MRIs were also reviewed for the presence of cerebral microbleeds (punctate foci of increased susceptibility on susceptibility-weighted MRI).[8] These were characterized by presence, quantity (1, 2–5, 6–10, >10), and location (cortical, subcortical, both).

Statistical Analysis

Initial univariate analysis was performed using Student paired *t* tests (for continuous variables) and Fisher exact tests (for categorical variables). Covariates that were significant in univariate analysis were entered into a multivariable logistic regression analysis with sICH as the dependent variable along with age, sex, and severe PVWMD (thought to be potential clinical confounders although not significant in univariate analysis). Renal impairment and age were defined as serum creatinine >1.0 mg/dL and age ≥65 years (median values). ESR, LDL, and AST were evaluated per 10 U increase, whereas INR was evaluated per 0.1 U increase. Severe PVWMD was defined as a CHS grade ≥ 6. Microbleeds were evaluated by presence, number >5, and subcortical location (patients with cortical microbleeds only excluded).

Multivariable logistic regression was performed. Multiple models were generated. Model 1 contained demographics, presence of severe PVWMD, and presence of cerebral microbleeds. Model 2 added clinical variables including current tobacco use and systolic blood pressure. Diastolic blood pressure was dropped because of its collinearity with systolic blood pressure. Model 3 was the same as model 2 but also incorporated laboratory values: AST, INR, creatinine, LDL, and ESR. With each model, the sample size decreased because of missing data points. Identical models were generated to evaluate cerebral microbleeds >5 and subcortical microbleeds. A final model was created based on our initial hypotheses, incorporating demographics, PVWMD, microbleeds, renal function, ESR, and LDL.

Results

Final Included Cohort

We examined the charts of 2260 patients. The average age was 66.2 (SD, 15.3) years. Twenty-three percent were black and 47% were women. Five hundred seventy-one patients were included in the analysis after neuroimaging revealed subcortical lacune (n=352) or subcortical sICH (219). The majority of excluded patients had cortically based pathology (57%) or no visible lesion on imaging (12%). The remaining third were excluded for other reasons, such as presence of an underlying embolic cause on further workup. Baseline

demographics of the included cohort did not vary significantly from the entire cohort. Participant characteristics are displayed in the Table.

Factors Associated With Hemorrhage

Univariate Analysis—Black race (P=0.01), reported history of hypertension (P=0.004), elevated systolic blood pressure on admission (P<0.001), presence of cerebral microbleeds (P<0.001), elevated INR (P<0.001), elevated ESR (P<0.001), and elevated AST (P<0.001) were each associated with sICH in univariate analysis, whereas current tobacco use (P=0.006), decreased high-density lipoprotein (P=0.002), and elevated LDL (P<0.001) were each associated with ischemia.

Multivariable Modeling

1. Model 1 (n=419): Age ≥65 years (odds ratio [OR], 1.16; confidence interval [CI], 0.71–1.91), black race (OR, 1.67; CI, 1.00–2.78), and male sex (OR, 1.70; CI, 1.03–2.82) trended toward predicting sICH, whereas presence of microbleeds was a strong predictor of sICH (OR, 3.39; CI, 2.10–5.50), and severe PVWMD was significantly associated with ischemia (OR, 0.56 risk of sICH; CI, 0.32–0.98). When our hypothesized laboratory values of interest were added to the model (n=322), higher levels of ESR (OR, 1.19 per 10 mm/h increase; CI, 1.06–1.34) were associated with sICH, whereas elevated LDL was associated with ischemic infarct (OR, 0.93 risk of sICH per 10 mg/dL increase; CI, 0.86–0.99). Creatinine >1.0 mg/dL (OR, 1.01; CI, 0.53–1.92) was not a significant predictor of sICH or ischemia. With a lower sample size, the effect of all variables was attenuated: age ≥65 years (OR, 0.88; CI, 0.45–1.74), male sex (OR, 1.30; CI, 0.68–2.50), black race (OR, 1.46; CI, 0.74–2.90), presence of microbleeds (OR, 2.36; CI, 1.24–4.51), and severe PVWMD (OR, 0.79; CI, 0.39–1.59) although trends remained consistent.
2. Model 2 (n=319): When clinical variables were added to the model, the effect of systolic blood pressure (OR, 1.06 per 10 mm Hg increase; CI, 0.97–1.15) was attenuated, whereas current tobacco use (OR, 0.54 risk of sICH; CI, 0.29–1.01) neared significance.
3. Model 3 (n=292): The number of participants included fell significantly when all variables significant in univariate analysis were added into the model (Figure). The presence of cerebral microbleeds (OR, 2.19; CI, 1.18–4.07), elevated AST (OR, 1.2 per 10 U/L increase; CI, 1.04–1.38), elevated INR (OR, 1.06 per 0.1 U increase; CI, 1.01–1.11), and elevated ESR (OR, 1.20 per 10 mm/h increase; CI, 1.05–1.38) remained statistically significant predictors of sICH, whereas severe PVWMD (OR, 0.44 risk of sICH; CI, 0.21–0.92) predicted ischemia.

Subclinical Phenotype Predicts Symptomatic Phenotype—The presence of cerebral microbleeds (OR, 3.39; CI, 2.09–5.50) was a strong predictor of sICH, whereas severe PVWMD predicted ischemia (OR, 0.56 risk of sICH; CI, 0.32–0.98). This association was strengthened when the number of microbleeds was evaluated; subjects with >5 micro-

bleeds had an increased risk of sICH (OR, 4.11; CI, 1.96–8.59) and remained significant when individuals with only cortical microbleeds were removed (OR, 1.77; CI, 1.13–2.76).

Discussion

Hypertension is the major risk factor for a spectrum of ischemic and hemorrhagic subcortical cerebrovascular disease. In general, as vascular risk factors accumulate, the likelihood increases for any cerebrovascular event; however, we posit that specific factors shift the likelihood of an event in favor of either hemorrhage or ischemia. This retrospective analysis confirms that tobacco use and hyperlipidemia (as evidenced by an elevated LDL) are more strongly associated with the development of ischemic disease, whereas an elevated ESR is a highly significant predictor of sICH. Importantly, the nature of subclinical subcortical disease also seems to be strongly predictive of the type of symptomatic disease and may precede clinical events, offering an opportunity for more appropriate risk reduction.

Potential Underlying Mechanism for the Transition of Subclinical to Clinical Disease

The accumulation of specific risk factors may predispose an individual to all degrees of subcortical hemorrhage (micro-bleeds and sICH), but the intensity and duration may determine whether one accumulates asymptomatic microbleeds or experiences an sICH. Individuals with milder risk factors (better control) may develop poor small-vessel compliance over years, leading to tiny asymptomatic leaks (microbleeds) seen on susceptibility-weighted MRI. As microbleeds accumulate, the likelihood increases that one will expand, resulting in an sICH. In contrast, a greater number or more severe risk factors for a shorter period of time may lead to the rupture of vessels with relatively normal compliance, resulting in sICH without chronic leaking or microbleeds. In this study, the presence of cerebral microbleeds was a strong predictor of sICH, consistent with our hypothesis regarding the spectrum of hypertensive disease. We recognize that PVWMD rates were similar between the 2 groups in univariate analysis, but became a significant predictor of acute lacunes in multivariable modeling. This may be explained by the fact that many individuals with severe PVWMD and sICH also had microbleeds (44% of those with PVWMD ≥6 versus 24% with PVWMD <6). Adjusting for microbleeds showed apparent reverse confounding, demonstrating that PVWMD was in fact a risk factor for acute lacunes, independent of the absence of microbleeds alone.

Role of Kidney Disease and Chronic Inflammation in Hemorrhage

Other studies have suggested that individuals with renal impairment are at increased risk for systemic hemorrhage, cerebral microbleeds, and sICH.[13,17,20–28] In our study, an abnormal creatinine trended toward predicting sICH, although results did not reach statistical significance. One explanation may be the cross-sectional nature of our analysis. Renal impairment was defined based on a single measure at a single time point. It may be that the effect of kidney disease on hemorrhage risk is best seen over time and that excluding individuals with acute renal insufficiency or evaluating kidney disease longitudinally would have yielded different results. A prospective longitudinal study is currently underway.

In our study, we found that ESR, a marker of systemic inflammation, was actually significantly associated with hemorrhage compared with ischemia. The mechanism by which systemic inflammation may predispose to hemorrhage is unclear. Inflammation is important for the removal of debris and repair of damaged tissue, but these repair mechanisms can be dysfunctional in chronic inflammatory states.[29] Chronic inflammation may lead to increased blood–brain barrier permeability[30,31] through damage of the neurovascular unit (capillary endothelial cells, neurons, and non-neuronal cells that comprise the blood–brain barrier) without subsequent repair. This chronic vascular injury might result in low compliance and leaking of the vessels, predisposing to both asymptomatic (microbleed) hemorrhage and sICH. Elevated ESR levels can be seen in patients with chronic kidney disease[32,33]; however, there was no collinearity between the two in our population. Given the apparent association between elevated ESR and intracerebral hemorrhage, additional studies with pathological correlation to determine the underlying pathophysiologic mechanisms are needed.

Other Factors Predictive of Subcortical Hemorrhage

In univariate analysis, systolic blood pressure on admission was also significantly associated with hemorrhage. This effect was attenuated in multivariable regression, perhaps because of collinearity with PVWMD or decreased sample size. It is not surprising that higher levels of AST and INR were also associated with bleeding in both univariate and multivariate analyses, because one could hypothesize that both result in a relative hypocoaguable state that increases the chance for leaky vessels to hemorrhage. There are multiple potential underlying mechanisms. Unfortunately, given the retrospective nature of the analysis, we were unable to control for whether abnormal liver function tests or coagulation studies were associated with chronic alcohol use, hepatitis, other chronic viral infections, systemic anticoagulation, or the use of antiplatelet or statin therapy.

Study Limitations and Future Directions

Our study is not without limitations. First, it is a retrospective analysis of prospectively collected data, but includes a relatively small number of patients from a single institution. Second, there are likely other unmeasured confounders that we were unable to account for adequately (such as a reliable history of diabetes mellitus and medication use before admission). Finally, it is a cross-sectional analysis rather than a longitudinal study. Additionally, an association between cerebral microbleeds, inflammatory markers, and sICH does not necessarily indicate a causal pathway. However, such an association may indicate a potential mechanism that can be studied more. Even with these limitations, our data strongly suggest that the risk profile may be distinct for hemorrhagic versus ischemic complications of longstanding hypertension. Results must be prospectively validated and high-risk patients followed to determine potential use in clinical practice. This prospective validation is currently underway.

Conclusions

In patients with longstanding hypertension, there seems to be a distinct risk profile that separates those who will go on to develop symptomatic intracerebral hemorrhage from lacunar disease. Our data suggest that the presence of cerebral micro-bleeds and elevated

ESR is a strong predictor of future sICH. In the absence of microbleeds, severe PVWMD and elevated LDL strongly predict symptomatic lacunes.

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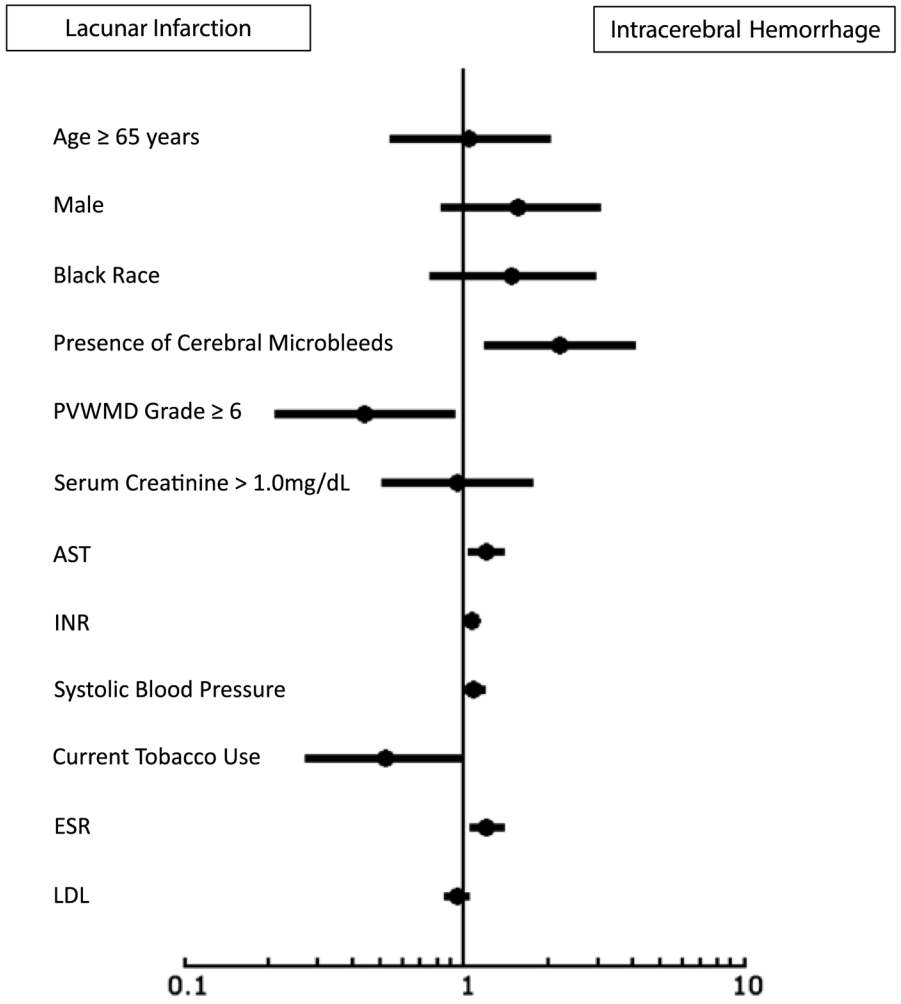

Figure.

Odds ratios for symptomatic intracerebral hemorrhage vs acute lacune based on clinical and radiographic factors. AST indicates aspartate transaminase; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; LDL, low-density lipoprotein; and PVWMD, periventricular white matter disease.

Table

Patient Characteristics

	Total	Lacune	sICH	*P* Value
n	571	352	219	
Age, mean (SD), y	65.8 (14)	66.3 (14)	65.0 (14)	0.28
Female sex, %	54%	53%	56%	0.48
Black race, %	27%	23%	34%	0.01
Reported history of hypertension, %	91%	90%	96%	0.004
Left ventricular hypertrophy, %	50%	47%	57%	0.06
SBP on admission, mean (SD), mm Hg	172 (35)	167 (31)	181 (39)	<0.001
Current tobacco use, %		39%	25%	0.006
Current alcohol use, %		41%	43%	0.60
Any cerebral microbleeds, %		22%	49%	<0.001
PVWMD ≥6, %		30%	30%	1.00
Hematocrit, mean (SD), %	40 (5)	41 (5)	40 (6)	0.19
Platelet count, mean (SD), K/mm^3	225 (71)	226 (67)	223 (76)	0.57
INR, mean (SD)	1.2 (0.7)	1.1 (0.4)	1.4 (0.9)	<0.001
Creatinine, mean (SD), mg/dL	1.3 (1.3)	1.2 (1.2)	1.4 (1.4)	0.16
ESR, mean (SD), mm/h	27 (23)	25 (20)	36 (30)	<0.001
HDL, mean (SD), mg/dL	46 (17)	44 (15)	50 (19)	0.002
LDL, mean (SD), mg/dL	108 (43)	113 (44)	97 (38)	<0.001
AST, mean (SD), U/L	29 (31)	22 (16)	40 (45)	<0.001
Glucose, mean (SD), mg/dL	155 (80)	152 (79)	161 (82)	0.21

AST indicates aspartate transaminase; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein; PVWMD, periventricular white matter disease; SBP, systolic blood pressure; and sICH, symptomatic intracerebral hemorrhage.