Hemorrhage Burden Predicts Recurrent Intracerebral Hemorrhage After Lobar Hemorrhage

Steven M. Greenberg, MD, PhD; Jessica A. Eng, BA; MingMing Ning, MD; Eric E. Smith, MD; Jonathan Rosand, MD, MS

Background and Purpose—Small asymptomatic cerebral hemorrhages detectable by gradient-echo MRI are common in patients with intracerebral hemorrhage (ICH), particularly lobar ICH related to cerebral amyloid angiopathy (CAA). We sought to determine whether hemorrhages detected at the time of lobar ICH predict the major clinical complications of CAA: recurrent ICH or decline in cognition and function.

Methods—Ninety-four consecutive survivors of primary lobar ICH (age ≥55) with gradient-echo MRI at presentation were followed in a prospective cohort study for 32.9±24.0 months. A subset of 34 subjects underwent a second MRI after a stroke-free interval of 15.8±6.5 months. Study endpoints were recurrent symptomatic ICH or clinical decline, defined as onset of cognitive impairment, loss of independent functioning, or death.

Results—The total number of hemorrhages at baseline predicted risk of future symptomatic ICH (3-year cumulative risks 14%, 17%, 38%, and 51% for subjects with 1, 2, 3 to 5, or ≥6 baseline hemorrhages, P=0.003). Higher numbers of hemorrhages at baseline also predicted increased risk for subsequent cognitive impairment, loss of independence, or death (P=0.002) among subjects not previously demented or dependent. For subjects followed after a second MRI, new microhemorrhages appeared in 17 of 34 and predicted increased risk of subsequent symptomatic ICH (3-year cumulative risks 19%, 42%, and 67% for subjects with 0, 1 to 3, or ≥4 new microhemorrhages, P=0.02), but not subsequent clinical decline.

Conclusions—Hemorrhages identified by MRI predict clinically important events in survivors of lobar ICH. Detection of microhemorrhages may be useful for assessing risk in ICH patients and as a surrogate marker for clinical studies. (Stroke. 2004;35:1415-1420.)

Key Words: hemorrhage ▪ amyloid ▪ magnetic resonance imaging, gradient echo ▪ dementia

Growing evidence has implicated deposition of β-amyloid in cerebral vessels, defined as cerebral amyloid angiopathy (CAA), as an important cause of both intracerebral hemorrhage (ICH)1 and cognitive impairment.2,3 ICH associated with CAA often recurs, with highest risk among individuals with the apolipoprotein E (APOE) ε2 or ε4 alleles.4 In the absence of noninvasive methods for detecting cerebrovascular amyloid, these multiple CAA-related hemorrhages in lobar brain regions serve as the primary means for diagnosing CAA during life.5

Cerebral hemorrhages associated with CAA can be relatively large and symptomatic or small and clinically silent. The small “microhemorrhages” consist pathologically of collections of hemosiderin-laden macrophages, often associated with diseased blood vessels. Microhemorrhages in CAA and other cerebrovascular disorders can be sensitively imaged by gradient-echo or T2*-weighted MRI.7 Using gradient-echo MRI, we have demonstrated that microhemorrhages are common in patients with CAA-related symptomatic ICH8 and that new microhemorrhages occur in approximately half of lobar ICH patients over a 17-month follow-up even in the absence of new clinical symptoms.9

The high frequency of microhemorrhages in CAA raises questions about the clinical importance of these lesions, either as direct contributors to CAA-related impairment or indirect markers of the disease’s course and prognosis. Therefore, we undertook a prospective cohort study of survivors of lobar ICH with gradient-echo MRI at presentation. We sought to address (1) whether microhemorrhages and larger symptomatic ICHs share a similar distribution in the brain or risk factors such as APOE genotype, and (2) whether the number of old hemorrhages or the incident appearance of new microhemorrhages predict future events such as recurrent symptomatic ICH, cognitive impairment, or functional decline.

Methods

Patient Recruitment and Follow-Up
Subjects were prospectively enrolled in a longitudinal cohort study of survivors of primary lobar hemorrhage as described6 (Figure 1).
Briefly, subjects were recruited from consecutive patients age ≥55 years admitted to Massachusetts General Hospital (MGH) for lobar ICH between July 1994 and March 2002. Subjects were excluded for hemorrhages in deep hemispheric regions such as basal ganglia, thalamus, or definite secondary cause of ICH. Survivors of lobar ICH who underwent MRI with gradient-echo sequences within 90 days of their index ICH were considered eligible. Of 213 potentially eligible patients who survived at least 30 days after primary lobar ICH, 127 underwent gradient-echo MRI. Fourteen of these patients were excluded for MRI occurring more than 90 days after presentation; 5 because MRI images were not available or interpretable, and 11 because the patient or family could not be reached for clinical follow-up information. An additional 3 subjects with CAA-related perivascular inflammation were excluded because of the markedly different course associated with this syndrome, leaving a final prospective cohort of 94 survivors of primary lobar ICH with available baseline gradient-echo MRI and follow-up clinical data. Of the 94 subjects, 90 were white and 4, African American.

Baseline clinical information was obtained as described with-out knowledge of radiographic or genetic results. Clinical data collected and recorded at the time of index presentation included demographic information, history of hypertension, diabetes mellitus, coronary artery disease or previous symptomatic ICH or ischemic stroke. Data on prior history of cognitive impairment or inability to live independently were determined by interviews with patients and caregivers (see below) as well as review of medical records. DNA was prepared from blood samples and APOE genotype determined by the polymerase chain reaction/restriction enzyme method. DNA samples were available from 81 of the 94 subjects in the cohort (including all 34 subjects who underwent a follow-up MRI scan as described under MRI Detection of Hemorrhages); subjects without DNA samples declined consent for genotyping or were not available for blood draw during their hospitalization.

Follow-up clinical data were obtained by systematic telephone interviews performed at 6-month intervals through June 2003 for a mean follow-up period from presentation to last interview or study endpoint of 32.9±24.0 months. During the interview, the patient, caregiver, or both were questioned regarding the appearance of symptoms suggestive of incident stroke, decline in memory, language or other cognitive functions, or loss of independent functional status over the previous 6-month interval. Questions on functional status followed the structured interview proposed for the modified Rankin Scale with a modified Rankin Scale score of ≥3 considered to represent functional dependence. Cognitive status was systematically assessed by asking informants to compare the subject’s ability to perform a list of daily cognitive tasks involving memory, praxis, calculation, or reasoning with his or her baseline 5 to 10 years prior to the index event. Cognitive impairment was defined as the presence of deficits in memory or other cognitive areas sufficient to interfere with tasks of daily living.

This study was performed with approval and in accord with guidelines of the institutional review boards of MGH and with informed consent of all participating subjects or family members.

MRI Detection of Hemorrhages
MRI with axial gradient-echo images (TR 750/TE 50/5 to 6-mm slice thickness/1 mm interslice gap) was performed as described using a 1.5-T superconductive magnet. Hemorrhages (defined as rounded foci hypointense on gradient-echo sequences and distinct from vascular flow voids, leptomeningeal hemosiderosis, or nonhemorrhagic subcortical mineralization) were recorded according to size (microhemorrhages defined as ≤5 mm in diameter, macrohemorrhages >5 mm in diameter) and cortical lobe in which they were centered. We have previously demonstrated high interrater reliability (intraclass correlation coefficient 0.97) for counting hemorrhagic lesions. All MRI analyses were performed and recorded without knowledge of clinical or genetic information.

Participants were encouraged to return for additional research MRI scans 12 to 18 month following their baseline scans. Of 36 subjects who returned for follow-up MRI, 1 was excluded from analysis because of a symptomatic ICH prior to the second MRI and 1 because of absent clinical follow-up information, leaving 34 subjects to be analyzed for the effects of new microhemorrhages without clinical recurrent ICH. These 34 subjects were younger (71.0 versus 75.7 years, P=0.005) and had more hemorrhages at baseline (median 3 versus median 2, P=0.02) than the remainder of the cohort, but did not differ by sex, hypertension, APOE genotype, previous cognitive impairment, or the occurrence of preindex symptomatic ICH. The mean interval between the baseline and follow-up MRI in the 34 subjects was 15.8±6.5 months. New microhemorrhages were identified by comparison of initial and follow-up scans without knowledge of clinical or genetic information as described and their locations recorded.

Statistical Methods
The total number of hemorrhagic lesions (microhemorrhages plus macrohemorrhages) was displayed in categories defined by cut-points (1, 2, 3 to 5, and ≥6) chosen at the beginning of the statistical analysis to divide the 94 subjects approximately into quartiles. Significance testing for these lesions was performed with the nonparametric Wilcoxon rank sum test because of their skewed distributions. Similarly, categories for the number of new hemorrhagic lesions were initially defined with cut-points of 0, 1 to 3, and ≥4 new hemorrhages and the rank sum test used for statistical significance. The relationship between hemorrhages at baseline and appearance of new hemorrhages was examined with a nonparametric rank sum test for trend across categories of baseline hemorrhages. Age at index ICH was analyzed as both a continuous variable and a dichotomous variable categorized by the median age of the cohort (<75 versus ≥75). APOE genotype was analyzed as a categorical variable according to the presence or absence of the e2 or e4 alleles, the e3/e3 genotype serving as reference. Multivariable analysis of the presence or absence of new hemorrhages was performed using multiple logistic regression to control for the time interval between the baseline and follow-up scans and the category of baseline hemorrhages.
We used the Kaplan-Meier method to estimate the cumulative proportion of patients with 2 prespecified outcomes during follow-up: (1) recurrent symptomatic ICH, and (2) clinical decline, defined as incident cognitive impairment, loss of functional independence, or death among subjects not cognitively impaired or dependent prior to or within 30 days after their index ICH. Survival time was calculated from date of initial MRI scan for analysis of baseline hemorrhages or from date of follow-up MRI for analysis of new hemorrhages. Survival was calculated until the date of recurrent hemorrhage or the last known date without recurrence for analysis of recurrent ICH, or till date of death, estimated date of incident cognitive impairment, or estimated loss of independent functioning for analysis of clinical decline. Significance testing was performed by the log-rank test for dichotomous variables. Significance testing for outcome as a function of baseline or new hemorrhages was performed by Cox proportional hazards regression model, with the categories of hemorrhage counts chosen as the independent variable in order to limit the effect of outlying values of hemorrhage counts on the analysis. Hazard ratios (HR) with 95% CI were calculated by Cox regression model; analyses of new hemorrhages also included a term for the length of interval between the baseline and follow-up MRIs.

All analyses were performed with Stata software (Stata Corporation). All significance tests were 2-tailed.

### Results

**Correlates of Baseline and New Hemorrhages**

The total number of macrohemorrhagic and microhemorrhagic lesions identified by gradient-echo MRI in consecutive elderly survivors of lobar ICH ranged from 1 to 35. Even in this cohort selected for the presence of symptomatic ICH, microhemorrhages were nearly 2.5-fold more common than macrohemorrhages (Table 1). The distribution among the cortical lobes for the 2 classes of hemorrhages was similar (Table 1). Among potential predictors of total hemorrhages at baseline, there was no association with age, sex, APOE genotype, or the presence of vascular risk factors such as hypertension (Table 2), diabetes, coronary disease, or previous stroke (data not shown). Individuals with cognitive impairment prior to their index ICH showed a trend (P=0.066) toward more hemorrhages at baseline (median 3, interquartile range 2 to 5) than those without prior cognitive impairment (median 2, interquartile range 1 to 4).

Among 34 subjects who underwent a follow-up research MRI scan after an approximately 16 month stroke-free interval, 17 (50%) demonstrated between 1 and 16 new microhemorrhages (Table 3). Larger numbers of hemorrhages at baseline and the presence of APOE ε2 or ε4 allele significantly predicted the appearance of new hemorrhages. New hemorrhages appeared in 13 of 19 (68%) carriers of APOE ε2 or ε4 compared with only 4 of 15 (26%) of those with the ε3/ε3 genotype (odds ratio 6.6, 95% CI 1.2 to 38.3, controlling for baseline hemorrhages and duration between scans). Age, sex, and, vascular risk factors, again, showed no association with appearance of new microhemorrhages.

### Table 1. Distribution of Macrohemorrhages and Microhemorrhages in 94 Consecutive Survivors of Lobar ICH

<table>
<thead>
<tr>
<th>N of Lesions (% of Total)</th>
<th>Frontal</th>
<th>Parietal</th>
<th>Temporal</th>
<th>Occipital</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrohemorrhages</td>
<td>36 (31)</td>
<td>23 (20)</td>
<td>28 (24)</td>
<td>29 (25)</td>
<td>116</td>
</tr>
<tr>
<td>Microhemorrhages</td>
<td>69 (24)</td>
<td>55 (19)</td>
<td>84 (30)</td>
<td>75 (27)</td>
<td>283</td>
</tr>
</tbody>
</table>

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### Table 2. Total Hemorrhages at Baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>N of Patients (%) in Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of hemorrhagic lesions:</td>
<td>1</td>
</tr>
<tr>
<td>Total cohort</td>
<td>94</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;75 years</td>
<td>47</td>
</tr>
<tr>
<td>≥75 years</td>
<td>47</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>43</td>
</tr>
<tr>
<td>Male</td>
<td>51</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>48</td>
</tr>
<tr>
<td>Present</td>
<td>46</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>76</td>
</tr>
<tr>
<td>Present</td>
<td>18</td>
</tr>
<tr>
<td>Previous ICH</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>87</td>
</tr>
<tr>
<td>Present</td>
<td>7</td>
</tr>
<tr>
<td>APOE Genotype</td>
<td></td>
</tr>
<tr>
<td>ε3/ε3</td>
<td>44</td>
</tr>
<tr>
<td>ε2/ε2 or ε4/ε−</td>
<td>37</td>
</tr>
</tbody>
</table>

Total percentages may not equal 100 because of rounding.
Risk of Recurrent ICH or Clinical Decline

Recurrent lobar ICH occurred in 27 of 94 (28%) subjects in the cohort, a mean of 20.8 ± 16.7 months following index presentation. The number of hemorrhages on the baseline scan was a significant predictor of time until recurrence (Figure 2A). The cumulative risk of recurrent ICH at 3 years of follow-up increased from 14% for subjects with only 1 hemorrhage at baseline to 17% for those with 2 hemorrhages, 37% for 3 to 5 hemorrhages, and 51% for 6 or more hemorrhages (HR 1.7, 95% CI 1.2 to 2.4 for each increase in category). This association remained independent in multivariable analysis controlling for previously defined risk factors for recurrent ICH: APOE genotype and history of previous ICH (HR 1.5, 95% CI 1.1 to 2.2, P = 0.03). Among the 34 subjects with follow-up MRI scans following a stroke-free interval, recurrent ICH occurred in 11 (32%), a mean of 16.1 ± 10.4 months after the second MRI. Subjects with new hemorrhages on the follow-up scan also demonstrated increased risk for early recurrence (Figure 2B). Cumulative risk of recurrent ICH 3 years after the follow-up scan was 19% for those with no new hemorrhages, 42% for 1 to 3 new hemorrhages, and 67% for 4 or more new hemorrhages (HR 3.0, 95% CI 1.2 to 7.3 for each increase in category controlling for the interval between MRI scans; HR 2.6, 95% CI 1.0 to 6.7 controlling in addition for APOE genotype and history of prior ICH).

We also examined the effect of baseline hemorrhages on the incidence of cognitive impairment, functional dependence or death among the 53 subjects in the cohort who survived their index ICH without the immediate occurrence of 1 of these events. During subsequent follow-up, 19 of the 53 (36%) developed cognitive impairment, loss of functional independence, or death at a mean 27.9 ± 17.1 month. Greater numbers of hemorrhages at baseline predicted increased hazard for these clinical events as well (Figure 3A; HR 1.7, 95% CI 1.2 to 2.4 for each increase in category). Baseline hemorrhages were associated with clinical decline even among subjects without recurrent ICH (HR 2.3, 95% CI 1.3 to 4.2, P = 0.005), indicating that this association was not primarily driven by risk of subsequent ICH. The number of new hemorrhages during follow-up was not predictive of clinical decline in the subset of 24 subjects with serial MRI scans not rendered cognitively impaired or dependent by their index events (Figure 3B).

### TABLE 3. New Hemorrhages at Follow-Up

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients, N</th>
<th>Patients in Category, N (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of new hemorrhagic lesions:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cohort</td>
<td>34</td>
<td>17 (50)</td>
<td></td>
</tr>
<tr>
<td>Age &lt;75 years</td>
<td>27</td>
<td>12 (44)</td>
<td></td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>7</td>
<td>5 (71)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>12 (63)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>5 (33)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>17</td>
<td>7 (41)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>17</td>
<td>10 (59)</td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>30</td>
<td>16 (53)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>4</td>
<td>1 (25)</td>
<td></td>
</tr>
<tr>
<td>Previous hemorrhagic stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>28</td>
<td>15 (54)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>6</td>
<td>2 (33)</td>
<td></td>
</tr>
<tr>
<td>APOE genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε3/ε3</td>
<td>15</td>
<td>11 (73)</td>
<td></td>
</tr>
<tr>
<td>ε2/ε or ε4/ε</td>
<td>19</td>
<td>6 (32)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic lesions at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>6 (75)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>3 (60)</td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>8</td>
<td>6 (75)</td>
<td></td>
</tr>
<tr>
<td>≥6</td>
<td>13</td>
<td>2 (15)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Kaplan-Meier estimates of rate of recurrent lobar ICH. Data are stratified according to the number of hemorrhages detected on baseline MRI (A) or the number of new hemorrhages detected on follow-up MRI (B). Testing for significance is by Cox proportional-hazards regression model on the designated categories; the analysis in B also controls for the time interval between the 2 MRI scans.
vascular lesions in general 19,20 and CAA in particular 2,3 are
cognition. Several large studies have indicated that cerebro-
orrhages are instead a marker of other pathologies associated
with CAA such as neuritic plaques,14 white matter dam-
unclear whether these findings reflect a direct effect of
disabled or cognitively impaired by their index ICH. It is
significant predictor of subsequent clinical decline in subjects not
survivors of an initial lobar hemorrhage. Early recurrence was
associated with both the number of hemorrhages at baseline
and the rate of new hemorrhage appearance over a follow-up
interval. The most plausible interpretation of these data are
that MRI-detectable hemorrhages are a marker of the severity
and aggressiveness of the underlying vascular disease and,
thereby, predict risk of recurrent ICH.

The number of total hemorrhages was also marginally
associated with previous cognitive impairment and a signifi-
cant predictor of subsequent clinical decline in subjects not
disabled or cognitively impaired by their index ICH. It is
unclear whether these findings reflect a direct effect of
hemorrhage burden on neurologic function, or if microhem-
orrhages are instead a marker of other pathologies associated
with CAA such as neuritic plaques,14 white matter dam-
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vascular lesions in general19,20 and CAA in particular2,3 are
risk factors for cognitive impairment, especially in the setting
of concomitant Alzheimer disease (AD) pathology. Our study
raises the possibility that microhemorrhages may be one of
the manifestations of advanced CAA that contribute to
clinical impairment. The rate of new microhemorrhage emer-
gence did not predict decline, suggesting a role for total lesion
burden, rather than rate of appearance as the determinant of
their effects on cognitive and behavioral function.

We found that new microhemorrhages, like recurrent symp-
tomatic lobar ICH,4 occur with increased frequency in carriers of
the APOE ε2 or ε4 alleles. Previous studies of APOE and CAA
have identified an association between APOE ε4 and extent of
vascular amyloid,21–23 and between APOE ε2 and CAA-related
vessel breakdown.24,25 It is therefore plausible that these alleles
mark lobar ICH patients with more severe CAA pathology and,
therefore, increased risk for new vessel rupture.

A potential weakness in this study is the uncertainty of the
diagnosis of cognitive impairment. The proportion of patients
diagnosed with dementia varies sharply according to how it is
defined;26 studies also indicate that cognitive impairment
presents with different clinical characteristics in vascular
disease compared with AD.27 Because of the further limita-
tions of a telephone-based rather than in-person follow-up
scheme, we chose to prespecify a broad clinical endpoint that
included loss of functional independence and death in addi-
tion to cognitive impairment. We note that any errors in
classification according to these endpoints should bias toward
a null result rather than a spurious association. The mecha-
nism for the association between multiple hemorrhages and
clinical decline remains to be determined, but does not appear
to require recurrent symptomatic ICH, as the association
remained present among subjects without clinical recurrence.

Our results have potential implications for the treatment of
patients with lobar ICH. The decision to prescribe antiplatelet
or anticoagulant treatment for prevention of thromboembo-
lism, for example, depends substantially on the patient’s risk
for ICH.28 It is therefore plausible that information from
gradient-echo MRI might affect the risk-benefit calculation
for anticoagulation or antiplatelet treatment in specific clin-
cal situations.

These findings also offer support for use of hemorrhages
detected by MRI as a surrogate outcome marker in studies of
CAA. All available evidence suggests that microhemorrhages
occur by the same mechanisms as larger symptomatic hem-
orrhages: the 2 types of hemorrhages demonstrate similar
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Discussion

A major finding from this analysis is that hemorrhages
detected by MRI predict risk of future symptomatic ICH in
survivors of an initial lobar hemorrhage. Early recurrence was
associated with both the number of hemorrhages at baseline
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interval. The most plausible interpretation of these data are
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and aggressiveness of the underlying vascular disease and,
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Figure 3. Kaplan-Meier estimates of rate of cognitive impair-
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significance testing performed in A and B as described in Figure 2.

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References


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