Leukoaraiosis on Magnetic Resonance Imaging Correlates With Worse Outcomes After Spontaneous Intracerebral Hemorrhage

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Background and Purpose—Leukoaraiosis (LA) is associated with dementia, ischemic stroke, and intracerebral hemorrhage (ICH), but there are few data on how LA might impact outcomes after acute ICH. We tested the hypothesis that the severity of LA on magnetic resonance imaging is related to worse functional outcomes after spontaneous ICH.

Methods—We prospectively identified patients with spontaneous acute ICH. LA was identified on magnetic resonance imaging and its severity was graded using the Fazekas method to include a score for the deep white matter and periventricular regions. Outcomes were obtained at 14 days, 28 days, and 3 months with the modified Rankin Scale (mRS; a validated scale from 0 [no symptoms] to 6 [dead]) and analyzed with multivariate logistic regression.

Results—Higher Fazekas total (periventricular plus deep white matter) score correlated with higher mRS score at 14 days (P=0.02) and 3 months (P=0.02). This relationship was driven by the periventricular score, for which higher score (more severe disease) correlated with higher National Institute of Health Stroke Scale at 14 days (P=0.03), and higher mRS score at 14 days (P<0.001), 28 days (P=0.004), and 3 months (P=0.005). A higher (more severe) Fazekas periventricular score was associated with dependence or death at 3 months (odds ratio, 1.8 per point; 95% confidence interval, 1.02–3.1; P=0.04) after correction for the ICH score.

Conclusions—Increased LA is an independent predictor of worse functional outcomes in patients after spontaneous ICH. The pathophysiology associating LA with worse outcomes requires further study. These data may improve prognostication and selection for clinical trials. (Stroke. 2013;44:642-646.)

Key Words: functional recovery ■ intracerebral hemorrhage ■ leukoaraiosis ■ magnetic resonance imaging ■ outcomes ■ white matter disease

Intracerebral hemorrhage (ICH) affects 37,000 to 67,000 people in the United States each year, and has a high risk of disability and death. Only 20% of ICH patients are functionally independent at 6 months and less than half of patients survive up to 1 year. Establishing potentially modifiable predictors of poor outcome is key to identifying patients who may benefit from increased screening or selection for clinical research.

Leukoaraiosis (LA) is a neuroimaging finding of white matter changes thought to be a result of ischemic injury and demyelination. LA is a common finding on brain imaging studies in the elderly and is related to ischemic stroke. ICH, global functional decline, and dementia. LA and ICH share several risk factors in common (hypertension, cerebrovascular disease), and may share a common underlying pathological mechanism involving microangiopathy. Microbleeds, which may predispose patients to ICH, are associated with more severe LA. Additionally, LA is an independent risk factor for warfarin-related ICH and spontaneous ICH after thrombolysis for ischemic stroke. LA may predispose patients to ICH, whereas LA is related to worse outcomes in ischemic strokes, its potential impact on outcomes in ICH is uncertain. We tested the hypothesis that severity of LA is associated with worse functional outcomes in patients after spontaneous ICH.

Materials and Methods

Study Population

In a prospective fashion, we consecutively recruited patients with ICH. All salvageable patients underwent magnetic resonance imaging (MRI) (Figure 1), and their characteristics have been previously described. All cases were prospectively diagnosed by a board-certified vascular neurologist and had acute symptoms consistent with ICH and a diagnostic computed tomography scan. Patients with ICH attributed to trauma, hemorrhagic conversion of ischemic strokes, and structural lesions were excluded. The likely cause of...
ICH was prospectively determined by a board-certified vascular neurologist. All patients with ICH were admitted to the neurological intensive care unit with a standardized order set in the electronic medical record. We prospectively recorded baseline demographics, medical history, and clinical data, including the National Institute of Health Stroke Scale (NIHSS) score and ICH score. The ICH score is a previously validated clinical scale for outcomes, composite of level of consciousness, intraventricular hemorrhage, infratentorial location, large hematoma size, and old age.22,23 We performed volumetric assessment of hematoma size from computed tomography scans with a computerized workstation as previously described.24

The study was approved by the Northwestern University Institutional Review Board. Written informed consent to collect data and clinical outcomes was obtained from the patient or a legally authorized representative in all cases, except when the patient died in hospital or no representative could be located for an incapacitated patient. In that case, the Institutional Review Board approved data collection in a registry without consent.

Data Recording
MRI scans were obtained from salvageable patients, with sequences including fluid-attenuated inversion recovery (FLAIR), T2/turbo spin echo, T1 and T2 gradient echo, B1000, diffusion-weighted imaging, and apparent diffusion coefficient map. The MRI was reviewed and interpreted by a neurologist blinded to clinical outcomes. LA was identified as white matter hyperintensities on FLAIR images. Its severity was graded within the region starting at the lateral ventricular borders extending out to the cortico-medullary junction. FLAIR hyperintensities involving the convolutional white matter, U fibers, corpus callosum, and chronic infarcts that clearly follow a vascular territory were not regarded as LA. Chronic lacunar infarcts appear dark on T1-weighted and FLAIR sequences, and were not regarded as LA.22,23 FLAIR signal contiguous to the area of hemorrhage, which may represent edema, was not regarded as LA. Periventricular (PV) hyperintensity was graded as 0=absent, 1=caps or pencil-thin lining, 2=smooth halo, or 3=irregular PV hyperintensity extending into the deep white matter (DWM). Separate DWM hyperintensity was graded as 0=absent, 1=punctuate foci, 2=smooth halo, or 3=large confluent areas.26 This scale previously has been validated as a reliable measure for degree of LA with good interrater reliability.27–30 and has been used extensively to grade severity of LA in stroke and in epidemiological studies.5,17,20,30

Follow-up
The NIHSS score was recorded at 14 days by a certified examiner. The modified Rankin Scale (mRS) scores were prospectively recorded at 14 days, 28 days, and 3 months with a validated questionnaire.31,32

Statistical Analysis
Normally distributed variables were compared with t test, and non-normally distributed variables were compared with Mann–Whitney U test or Kruskal–Wallis H test as appropriate. Correlations for non-normally distributed data were evaluated with Spearman ρ. We performed logistic regression for poor outcome, defined as mRS score of 4 through 6 (dependent or worse), typical for clinical studies of ICH.33 We checked for statistical interactions when appropriate. Statistics were performed with standard commercial software (IBM SPSS version 20).

Results
Demographics
Demographic and characteristic differences of included and excluded patients are compared in Table 1. Included patients generally had moderately severe symptoms on admission (median NIHSS, 6) and a history of hypertension. MRI scans were obtained at a median of 1.8 (95% confidence interval [CI], 0.9–4) days after ICH symptoms onset. Patients who were not included (101) had larger hematoma volume, a worse clinical examination at baseline (NIHSS), and were likely to require constant care or be dead at 14 days.

Univariate Associations With LA
PV and DWM LA were common in the sample. Eighty-four patients (88%) in the sample had some level of PV disease, of which 30% was scored as severe. Demographics are shown in Table 2. There was no correlation between any Fazekas score and initial or final hematoma volume on computed tomography scan (P>0.1). There was no association between any Fazekas score and acute infarction (decreased diffusion) on MRI.

Fazekas total score (DWM plus PV) was correlated with mRS score at 14 days (P=0.02) and 3 months (P=0.02), driven by the PV score. Correlations between PV score, DWM score, and each individual outcome are presented in Tables III–V in the online-only Data Supplement.

The Fazekas PV score was correlated with the NIHSS score at 14 days (P=0.03), and the mRS score at 14 days (P=0.001), 28 days (P=0.004), and 3 months (P=0.005). Higher scores (more severe disease) were correlated with worse outcome (Figure 2). The Fazekas DWM score was not correlated with outcomes (P>0.1 for all).

Multivariate Models for LA and Outcomes
In logistic regression, higher (worse) Fazekas PV score was associated with greater odds of poor outcomes at 3 months (1.8 per grade; 95% CI, 1.02–3.1; P=0.04) after correction for the composite ICH score (1.9 per point; 95% CI, 1.2–3.2; P=0.006). Each increased point on the Fazekas PV score was associated with increased odds of dependence or death at 3 months. Neither hypertension nor diabetes mellitus significantly added to the model (P>0.5 for both).

We then repeated the analysis excluding patients with mRS score of 6 (death). At 28 days, there were 79 patients with mRS scores of 0 through 5 who could be analyzed. Both the composite ICH score (odds ratio [OR], 2.1 per point; 95% CI, 1.3–3.6; P=0.004) and PV score (OR, 1.8 per point; 95% CI, 1.06–3.2; P=0.03) were associated with increased odds of functional dependence (mRS score 4 or 5, as opposed to
mRS score 0 through 3). At 3 months, there were 73 patients with mRS of 0 through 5 available for analysis, but neither the composite ICH score (OR, 1.6 per point; 95% CI, 0.9–2.8; \( P=0.1 \)) nor PV score (OR, 1.5 per point; 95% CI, 0.8–2.9; \( P=0.1 \)) was associated with dependence in this post hoc analysis of survivors.

**Discussion**

In this prospectively ascertained cohort with blinded assessment of LA scores, we found that LA was common in patients with spontaneous ICH, and that PV LA severity was associated with greater odds of dependence or death at 3 months after spontaneous ICH. This correlation persisted after adjusting for the ICH score, which itself is a powerful predictor of outcomes.\(^{22,23}\) These data suggest that LA may be an important prognostic factor and imply that strategies to prevent LA formation or progression may significantly improve functional outcomes in patients after ICH. Because LA may indicate areas of demyelination, ischemia, or injury, it is unknown whether LA could be ameliorated, although preventing or minimizing LA might lead to improved clinical outcomes. Hypertension and age have been independently associated with LA progression,\(^{34}\) so treating hypertension may be a potential strategy to reduce the severity of LA. There are conflicting data regarding associations between LA and smoking, diabetes mellitus, dyslipidemia, coronary artery disease, and large vessel atherosclerotic disease.\(^{35–37}\) There have been no randomized prospective trials to study the effect of risk factor reduction on LA progression.

LA may be a manifestation of small vessel disease.\(^{38}\) LA and chronic white matter infarcts may coexist on MRI imaging, but their risk factor profiles seem to differ. Age and hypertension are most strongly associated with LA, whereas hyperlipidemia, diabetes mellitus, and coronary artery disease are more associated with isolated lacunar infarction,\(^{39}\) suggesting a difference in pathogenesis.

Areas of LA may have decreased neuronal connectivity,\(^{40}\) which may lead to poor brain compensation and recovery.\(^{6,33}\) Arsva et al\(^{4}\) suggested that areas of LA may contain decreased blood flow and poor collateral compensation,\(^{41}\) which may lead to ischemic stroke extension. We were unable to confirm that LA was associated with hematoma volumes or decreased diffusion on MRI in patients with acute ICH. Because LA also

<table>
<thead>
<tr>
<th>Variable</th>
<th>N, %</th>
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<tbody>
<tr>
<td>Age, y</td>
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<tr>
<td>Ethnicity</td>
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<td>South Asian</td>
<td>1</td>
</tr>
<tr>
<td>Women</td>
<td>48</td>
</tr>
<tr>
<td>Diabetes mellitus by history</td>
<td>23 (24)</td>
</tr>
<tr>
<td>Hypertension by history</td>
<td>75 (79)</td>
</tr>
<tr>
<td>Dementia or memory loss before ICH</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Coronary artery disease by history</td>
<td>17 (18)</td>
</tr>
<tr>
<td>Alcohol misuse</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Warfarin use before admission</td>
<td>6 (6)</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>4 (4)</td>
</tr>
<tr>
<td>GCS on admit</td>
<td>14 (12–15)</td>
</tr>
<tr>
<td>NIHSS on admit</td>
<td>6 (2–14)</td>
</tr>
</tbody>
</table>

| Fazekas periventricular score |      |
| 0 (no disease) | 11 (12) |
| 1 (caps, pencil-thin) | 27 (28) |
| 2 (smooth halo) | 32 (34) |
| 3 (irregular, extends to DWM) | 25 (26) |

| Fazekas deep white matter score |      |
| 0 (no disease) | 15 (16) |
| 1 (punctate) | 33 (35) |
| 2 (beginning confluence) | 31 (33) |
| 3 (extensive, confluent) | 16 (17) |

DWM indicates deep white matter; GCS, Glasgow coma scale; ICH, intracerebral hemorrhage; and NIHSS, National Institute of Health Stroke Scale.

Values are mean±SD or median (quartile 1–quartile 3).
relates to poor outcomes after ischemic stroke, the underlying pathophysiology may be similar in ICH. The precise mechanisms by which LA mediates poor outcomes are unclear and require further investigation.

The association between LA severity and worse outcomes was evident in PV disease but not DWM disease. Interestingly, a similar anatomic differentiation has been seen in cognitive decline. The white matter adjacent to the ventricles contains cholinergic fibers that extend to the cerebral cortex. It also has a high density of long association fibers that connect more distant cortex, whereas the subcortical DWM carries more U fibers, or short association fibers, that link adjacent gyri. Interruption of ascending PV pathways may disturb cognitive functioning relatively more, and could potentially lead to worse functional outcome. Unfortunately, the mRS does not contain detailed information about cognition, so the direct causes of disability are not clear. Data on domain-specific function would be helpful, and this is a topic for future research.

Dementia may confound the association between LA and outcomes. It is unlikely to be a confounder here, however, because dementia before ICH was uncommon in our cohort. Another potential limitation is that we only performed MRI in salvageable patients, and so the impact of LA in devastated patients is not clear from these data. This may represent some bias, because more severe LA may be associated with mortality.

In summary, we found that PV LA is an independent predictor of functional outcome in patients with spontaneous acute ICH. More LA was independently associated with worse functional outcomes at 3 months. The pathophysiology of LA in patients with LA and its putative mechanisms require further dedicated study. The prevention and treatment of LA may improve outcomes after ICH.

Disclosures
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References


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