Extensive Leukoaraiosis Is Associated With High Early Risk of Recurrence After Ischemic Stroke

Gyeong-Moon Kim, MD, PhD; Kwang-Yeol Park, MD; Ross Avery, BS; Johanna Helenius, MD; Natalia Rost, MD; Jonathan Rosand, MD, MSc; Bruce Rosen, MD, PhD; Hakan Ay, MD

Background and Purpose—The integrity of white matter tracts connecting different parts of the brain is important for rapid compensation for the lost function from ischemic stroke. Impaired white matter reserve capacity secondary to leukoaraiosis may facilitate detection of new symptomatic ischemic events that would otherwise remain inconspicuous after an initial ischemic stroke. We sought to identify whether the extent of leukoaraiosis was a predictor of risk of early stroke recurrence.

Methods—We used Cox regression analysis in consecutive patients with ischemic stroke to determine the relationship between leukoaraiosis burden and symptomatic stroke recurrence within 90 days. We graded total leukoaraiosis, periventricular leukoaraiosis, and subcortical leukoaraiosis using the Fazekas scale as mild (<2) and extensive (≥2) on fluid-attenuated inversion recovery images obtained within 72 hours of stroke onset in the hemisphere contralateral to acute stroke.

Results—There were 106 recurrent events in 2378 patients. The cumulative incidence of recurrence was 5.9% at 90 days. Kaplan–Meier estimate of recurrence-free survival rate was lower in patients with extensive leukoaraiosis (P=0.04) and extensive periventricular leukoaraiosis (P=0.02) but not in extensive subcortical leukoaraiosis (P=0.09). Multivariable Cox regression analysis revealed a hazard ratio of 1.50 (95% confidence interval, 1.00–2.25) for extensive leukoaraiosis, 1.67 (95% confidence interval, 1.11–2.51) for extensive periventricular leukoaraiosis, and 1.42 (95% confidence interval, 0.94–2.12) for extensive subcortical leukoaraiosis.

Conclusions—The extent of leukoaraiosis independently predicts 90-day recurrent stroke risk after ischemic stroke. This suggests that leukoaraiosis may be used for risk stratification in ischemic stroke. (Stroke. 2014;45:00-00.)

Key Words: leukoaraiosis ■ magnetic resonance imaging ■ stroke
did not undergo an MRI study and patients who did not exhibit an acute infarct on diffusion-weighted MRI (DWI). The study was approved by the local Human Studies Committee.

We collected data on published predictors of short-term stroke recurrence from an institutional database maintained by stroke-trained physicians. These predictors included age, sex, history of stroke, or transient ischemic attack within a month preceding the index stroke, admission National Institute of Health Stroke Scale score, thombolytic treatment, carotid or cardiac intervention, and pathogenic stroke subtype determined using the Causative Classification of Stroke (CCS) system. We also collected data on vascular risk factors that are known to confer increased stroke risk over the long term. These risk factors included hypertension (blood pressure, \( \geq 140/90 \) mmHg on repeated measurements or prior use of antihypertensive medication), diabetes mellitus (fasting blood glucose level, \( \geq 126 \) mg/dL on repeated measurements or the use of medications to lower blood glucose), atrial fibrillation, coronary artery disease, current smoking, and distant history of prior stroke (>1 month). Time of index stroke was determined based on careful interview with patients and reliable observers. In patients with uncertain onset of stroke, the time at which the patient was last known to be free of the signs and symptoms of the stroke was considered to be the time of onset.

**Image Acquisition and Analysis**

MRI was performed within 24 hours of admission by 1.5T GE Signa (GE Medical Systems, Milwaukee, WI) or Siemens Sonata (Siemens Medical Solutions, Erlangen, Germany) scanners. Image acquisition and processing protocols were previously described in detail. We defined leukoaraiosis as hyperintense lesions on axial T2 fluid-attenuated inversion recovery (FLAIR) images that are located in the region starting at the lateral ventricular border and extending up to the corticomedullary junction. Hyperintense lesions involving the convolutional white matter, U-fibers, corpus callosum, internal capsule, and anterior commissure were not regarded as leukoaraiosis. The boundaries of leukoaraiosis were differentiated from the acute ischemic lesion by visually coregistering FLAIR images with DWI. Discrete territorial brain lesions with well-defined borders that seemed hyperintense on FLAIR images, such as chronic subcortical infarcts and lacunar infarcts, were not considered leukoaraiosis. We graded leukoaraiosis in the hemisphere contralateral to acute stroke using the Fazekas scale. In patients with bihemispheric infarcts, we performed leukoaraiosis ratings in the hemisphere with lower burden of acute infarcts. On the basis of visual assessment of FLAIR images, we further categorized leukoaraiosis into periventricular leukoaraiosis (PLA) and subcortical leukoaraiosis (SLA). PLA indicated white matter hyperintensities exclusively located around the lateral ventricles (0: absent, 1: caps or pencil lining, 2: smooth halo, 3: irregular periventricular hyperintensity extending into deep white matter). SLA denoted white matter hyperintensities in the centrum semiovale and the corona radiata (0: absent, 1: punctate foci, 2: beginning confluence of foci 3: large confluent areas). Total leukoaraiosis score was calculated by summing up the scores for PLA and SLA and changed between 0 and 6. Large regions of leukoaraiosis that started from the ventricular border and extended into the deep white matter were classified as both PLA and SLA. We computed a receiver operating characteristics curve for total leukoaraiosis score and stroke recurrence and identified that the optimal operating point on this curve corresponded to the score of 2. Based on this, we dichotomized leukoaraiosis according to its severity as mild (Fazekas scores of 0 or 1) and extensive (Fazekas scores of 2). Extensive total leukoaraiosis was defined as having either PLA≥2 or SLA≥2. We tested inter-rater reliability of dichotomized leukoaraiosis ratings between 2 investigators (J.H. and G.-M.K.) in a set of 100 consecutive patients using \( \kappa \) statistics. The \( \kappa \) coefficient for PLA and SLA were 0.97 and 0.96, respectively. All leukoaraiosis ratings were done blind to recurrent stroke status.

**Follow-up Assessment**

The outcome variable was recurrent ischemic stroke within 90 days of index stroke. Recurrent stroke was defined as clinical deterioration caused by a new infarct that was spatially distinct from the index lesion. All recurrent events were confirmed by brain imaging. Clinical worsening because of brain edema, hemorrhagic transformation of the index lesion, and other metabolic and systemic causes were not considered as recurrence. Follow-up data on stroke recurrence were collected through inspection of inpatient medical record notes and outpatient assessment notes by investigators who were blinded to leukoaraiosis information on baseline MRI. All recurrent events were adjudicated by a separate investigator using the same data sources (H.A.).

**Statistical Analyses**

Statistical analyses explored relationships between leukoaraiosis and 90-day stroke recurrence. We made univariate comparisons between patients with and without recurrent stroke using Cox regression analysis. We used independent \( t \) tests or the Mann–Whitney \( U \) tests for continuous variables and Pearson \( \chi^2 \) and Fisher exact tests for categorical variables to compare patients with and without complete follow-up. We constructed a multivariable Cox proportional hazard model where time to recurrent stroke was the response and variables that were associated with leukoaraiosis or stroke recurrence with a univariate \( P \) value <0.1 were covariates. We performed Kaplan–Meier analysis and log-rank test to assess the predictive value of leukoaraiosis for early risk of stroke recurrence in each pathogenic category. Results were presented as hazard ratio with 95% confidence interval (CI). Values of \( P<0.05 \) were considered statistically significant. All statistical analyses were performed using a commercially available software (SPSS for Windows, version 13.0; SPSS, Chicago, IL).

**Results**

**Study Population and Follow-up Events**

A total of 3269 consecutive patients were admitted with diagnosis of ischemic stroke during the study period. We excluded 538 patients who were admitted after 72 hours of symptom onset. We also excluded 281 patients in whom MRI was not performed because of contraindications, such as metal implants, 28 patients in whom MRI was not deemed to be necessary by the treating physician (often because there was another MRI obtained at an outside center before coming to the Massachusetts General Hospital), and 44 patients in whom FLAIR images were not acquired. The remaining 2378 patients comprised the study population.

The median age of the study population was 70 years (interquartile range, 58–80 years), and the median time from onset to MRI was 10 hours (interquartile range, 5–21 hours). Complete 90-day follow-up data were available in 1736 patients (73%). In the remaining 27%, median follow-up was 7 days (interquartile range, 4–21 days). Patients with incomplete follow-up were older and more likely to have CCS subtype of small artery occlusion. The Fazekas score and other baseline characteristics listed in Table 1 were similar between patients with and without complete follow-up.

A total of 106 patients developed recurrent ischemic stroke within 90 days of index ischemic stroke. The cumulative incidence of recurrence by the Kaplan–Meier estimate was 1.8% at 7 days, 2.6% at 14 days, and 5.9% at 90 days. Baseline demographic and clinical characteristics of the cohort are summarized in Table 1. Patients with recurrent stroke were more likely to have high blood pressure at admission, prior stroke, or transient ischemic attack within the month preceding the index stroke, chronic
Leukoaraiosis and Pathogenic Stroke Subtypes

Because PLA attained higher statistical significance in prior analyses, we further explored associations between PLA

Table 2. Leukoaraiosis and 90-Day Stroke Recurrence

<table>
<thead>
<tr>
<th>Leukoaraiosis</th>
<th>Recurrence (%), (n=106)</th>
<th>No Recurrence (%), (n=2272)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive LA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (n=1322)</td>
<td>50 (47.2)</td>
<td>1272 (56.0)</td>
<td>0.074</td>
</tr>
<tr>
<td>Positive (n=1056)</td>
<td>56 (52.8)</td>
<td>1000 (44.0)</td>
<td></td>
</tr>
<tr>
<td>Extensive PLA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (n=1424)</td>
<td>53 (50.0)</td>
<td>1371 (60.3)</td>
<td>0.034</td>
</tr>
<tr>
<td>Positive (n=954)</td>
<td>53 (50.0)</td>
<td>901 (39.7)</td>
<td></td>
</tr>
<tr>
<td>Extensive SLA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (n=1631)</td>
<td>67 (63.2)</td>
<td>1564 (68.8)</td>
<td>0.222</td>
</tr>
<tr>
<td>Positive (n=747)</td>
<td>39 (36.8)</td>
<td>708 (31.0)</td>
<td></td>
</tr>
</tbody>
</table>

PLA indicates periventricular leukoaraiosis; and SLA, subcortical leukoaraiosis.
and pathogenic subtype of index stroke. The 90-day cumulative stroke rate by the Kaplan–Meier estimate varied by pathogenic CCS subtype (log-rank test, \(P<0.001\); Table 4). Similarly, the prevalence of extensive PLA also varied by CCS subtype (log-rank test, \(P<0.001\)). There was disconcordance between the baseline risk by CCS subtype and the prevalence of extensive PLA. For instance, extensive PLA was more prevalent in small artery occlusion (51%) where the risk of recurrence was lowest (1.0%), whereas it was less prevalent in the category of other uncommon causes (18%) where the risk was highest (12.7%). To characterize CCS subtype–leukoaraiosis–recurrence relationship further, we calculated hazard ratio for 90-day recurrence by extensive PLA in each CCS category. The effect of extensive PLA on stroke recurrence tended to be higher in CCS subtypes with greater baseline risk \((P=0.1)\); there was more than 2-fold difference in hazard ratio by PLA between the highest and the lowest risk CCS subtypes (Table 4).

**Discussion**

Increasing leukoaraiosis burden, whether measured among a cross section of healthy adults, or measured among patients with ischemic stroke, has substantial negative consequences on brain function. Leukoaraiosis is associated with progression of cognitive impairment, gait abnormalities, poor functional outcome, increased mortality, higher risk of hemorrhage after thrombolysis, and long-term recurrence after ischemic stroke.8–13 This study extends our knowledge on the relationship between leukoaraiosis and ischemic stroke by showing that leukoaraiosis is also a risk factor for early stroke recurrence. After controlling for initial stroke severity, conventional stroke risk factors, underlying stroke mechanism, and preventive stroke treatment, patients with extensive leukoaraiosis were 1.5× more likely to have another ischemic stroke in the short-term than those without extensive leukoaraiosis.

Extensive leukoaraiosis in the periventricular location was associated with slightly more prominent increase in risk of early recurrence when compared with subcortical location. This finding is consistent with prior observations in other conditions; the extent of PLA when compared with SLA more strongly correlates with cognitive decline in the non-demented elderly population,14–16 progression from mild cognitive impairment to Alzheimer disease,17 burden of aortic atherosclerosis,18 poor functional outcome after stroke,11 and risk of recurrent hemorrhage in patients with lobar intracerebral hemorrhage.19 It has been suggested that SLA predominantly disrupts the short association fibers that connect adjacent gyri to each other, whereas PLA affects the long association fibers that connect multiple distant cortical areas and is, therefore, more likely to interfere with cognitive and executive functions.20 Alternatively, SLA and PLA may be representing pathophysiologically different states with different burden of injury in the white matter. In support of this, recent evidence suggests that PLA is primarily associated with diminished cerebral vasomotor reactivity and subsequent cerebral hypoperfusion,21 whereas SLA is associated with microangiopathy.22

The exact mechanism by which leukoaraiosis confers increased risk of short-term stroke recurrence is not known. The severity of leukoaraiosis is, in part, influenced by vascular risk factors, such as hypertension, advanced age, diabetes mellitus, and smoking. However, the association between leukoaraiosis and recurrent stroke risk cannot be explained solely on the basis of shared risk factors because the present study and previously published studies clearly indicate that leukoaraiosis is a predictor of stroke risk even after controlling for
vascular risk factors.\textsuperscript{2,13,15,23} Of note, none of the conventional factors except for hypertension that confer an increased risk in the long-term predicted stroke recurrence in the short-term in the present study, consistent with the notion that leukoaraiosis influences short-term risk of recurrent stroke through other mechanisms. Prior studies have suggested that the extent of leukoaraiosis can negatively affect the brain’s capacity to tolerate an ischemic insult; among patients with cerebral ischemia, those with extensive leukoaraiosis are more likely to develop completed cerebral infarction,\textsuperscript{6} and among patients with acute infarction, those with extensive leukoaraiosis are more likely to develop severe and persistent clinical deficits.\textsuperscript{1,2} Given that asymptomatic new infarcts are substantially more common, as much as 17\times more common—than symptomatic infarcts during the first few days after an ischemic stroke,\textsuperscript{24} impaired ability of the brain to tolerate ischemia and its reduced capacity to compensate for the lost function in the presence of extensive leukoaraiosis could potentially facilitate conversion of asymptomatic infarcts into symptomatic infarcts. In support of this view, procedures that are associated with high risk of embolism to the brain, such as carotid artery stenting,\textsuperscript{25,26} carotid endarterectomy,\textsuperscript{26,27} and total aortic arch replacement,\textsuperscript{28} confer a higher perioperative risk of symptomatic stroke in patients with extensive leukoaraiosis when compared with those with less severe leukoaraiosis. In the International Carotid Stenting Study (ICSS), patients with extensive leukoaraiosis (as defined by age-related white matter changes score, \( \geq 5 \)) were 1.5\times more likely to develop periprocedural infarction on DWI after stenting than those with lower leukoaraiosis scores.\textsuperscript{26} In the present study, patients with high-risk pathogeneses for asymptomatic recurrence, such as large artery atherosclerosis or acute arterial dissection, had 2 to 3\times higher odds of symptomatic recurrence in the presence of extensive leukoaraiosis when compared with those with lower leukoaraiosis scores.\textsuperscript{26} In the present study, patients with high-risk pathogeneses for asymptomatic recurrence, such as large artery atherosclerosis or acute arterial dissection, had 2 to 3\times higher odds of symptomatic recurrence in the presence of extensive leukoaraiosis when compared with those with lower leukoaraiosis scores.\textsuperscript{26} The strengths of this study are large sample size, large number of outcome events, comprehensive diagnostic assessment, rigorous identification of pathogenic stroke subtypes using the CCS system, MRI-based assessment of leukoaraiosis, and imaging confirmation of recurrent events. There are limitations as well. Because this was not a prospective

| Table 4. Baseline Risk, Prevalence of PLA, and Hazard Ratio of PLA in Each Pathogenic Category |
|----------------------------------|------------------|-----------------|------------------|
| CCS Subtypes                  | Estimated 90-D Recurrence Rate, % | Prevalence of Extensive PLA, % | HR by Extensive PLA for Early Recurrence (95% CI) |
| Large artery atherosclerosis    | 11.4 (41)         | 2.22 (1.23–3.99) |
| Cardioaortic embolism          | 3.8 (42)          | 1.88 (0.93–3.83) |
| Small artery occlusion         | 1.0 (51)          | 0.87 (0.05–13.8) |
| Other uncommon causes          | 12.7 (18)         | 2.05 (0.80–5.30) |
| Undetermined                   | 2.7 (34)          | 0.85 (0.16–4.62) |

CCS indicates Causative Classification of Stroke; CI, confidence interval; HR, hazard ratio; PLA, periventricular leukoaraiosis; and SLA, subcortical leukoaraiosis.
longitudinal study, we were not able to collect 90-day follow-up data in all of the subjects. The extent of leukoaraiosis and independent predictors of stroke recurrence (hypertension, National Institute of Health Stroke Scale score, chronic stroke, and CCS subtypes of large artery atherosclerosis, and other uncommon causes), however, did not substantially differ between patients with and without complete follow-up, arguing against selection of a particular risk population. Although the 90-day cumulative estimate for recurrent stroke (5.9%) was comparable with the published rates in prospective longitudinal series,29,30 we think this rate slightly underestimates the true clinical recurrence rate in our population because we did not consider clinical stroke events that are not accompanied by new, clinically relevant, and spatially distinct infarct as recurrence. We note the importance of radiographic confirmation in diagnosis of clinical recurrence for future studies that intend to replicate our results. In this study, we focused on symptomatic events. Future studies with serial imaging could identify whether leukoaraiosis burden is also a risk factor for asymptomatic infarcts. We used a dichotomized visual rating scale for leukoaraiosis. Although quantitative assessment of leukoaraiosis load would provide more information, qualitative assessment allows the identification of high-risk individuals on the basis of readily available leukoaraiosis information in a typical clinical setting. Although the relationship between leukoaraiosis and early stroke recurrence was statistically significant, the correlation was not perfect. The lack of a clear dose-dependent effect of leukoaraiosis might be because of small number of patients in the higher leukoaraiosis load strata. Alternatively, severe strokes occurring in the presence of extensive leukoaraiosis would mask new symptoms in an event of recurrent infarction and thereby lead to underestimation of symptomatic recurrence rate.1,6

Several characteristics derived from the neuroimages of patients with acute ischemic stroke seem to predict risk of early stroke recurrence. These include multiple acute infarcts, simultaneous acute infarcts in both hemispheres or in both anterior and posterior circulations, multiple infarcts of different ages (combination of acute and subacute infarcts), and isolated cortical location of an infarct.21 We now describe a fifth imaging predictor. The difference between leukoaraiosis and the other imaging predictors is that the latter predictors are primarily based on DWI. Infarcts on DWI are highly subject to changes in their number and pattern during the acute phase. In contrast, leukoaraiosis on FLAIR images is a relatively stable and easily measurable parameter with acceptable inter- or intraobserver reliability. It requires further studies to show whether leukoaraiosis confers prognostic information that is not conveyed by other imaging predictors and thus provides added value in risk-stratification after ischemic stroke.

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Disclosures

Dr Ay is responsible for ensuring that full disclosures appear on the article and that the page proof reflects the disclosures listed. The other authors report no conflicts.

References


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Supplemental material

**Supplementary Table I:** Fazekas score and 90-day stroke recurrence.

<table>
<thead>
<tr>
<th>Fazekas Score</th>
<th>Extensive LA</th>
<th>Extensive PLA</th>
<th>Extensive SLA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recurrence</td>
<td>No Recurrence</td>
<td>Recurrence</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>0</td>
<td>4 (3.8)</td>
<td>216 (9.5)</td>
<td>9 (8.5)</td>
</tr>
<tr>
<td>1</td>
<td>15 (14.2)</td>
<td>308 (13.6)</td>
<td>44 (41.5)</td>
</tr>
<tr>
<td>2</td>
<td>31 (29.2)</td>
<td>757 (33.3)</td>
<td>42 (39.6)</td>
</tr>
<tr>
<td>3</td>
<td>18 (17.0)</td>
<td>352 (15.5)</td>
<td>11 (10.4)</td>
</tr>
<tr>
<td>4</td>
<td>24 (22.6)</td>
<td>310 (13.6)</td>
<td>-</td>
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<tr>
<td>5</td>
<td>11 (10.4)</td>
<td>165 (7.3)</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>3 (2.8)</td>
<td>165 (7.3)</td>
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