Severity of Leukoaraiosis and Susceptibility to Infarct Growth in Acute Stroke

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Background and Purpose—Leukoaraiosis (LA) is associated with structural and functional vascular changes that may compromise tissue perfusion at the microvascular level. We hypothesized that the volume of LA correlated with the proportion of initially ischemic but eventually infarcted tissue in acute human stroke.

Methods—We studied 61 consecutive patients with diffusion-weighted imaging–mean transit time mismatch. All patients were scanned twice within 12 hours of symptom onset and between days 4 and 30. We explored the relationship between the volume of white matter regions with LA on acute images and the proportion of diffusion-weighted imaging–mean transit time mismatch tissue that progressed to infarction (percentage mismatch lost).

Results—Bivariate analyses showed a statistically significant correlation between percentage mismatch lost and LA volume ($r=0.33$, $P<0.01$). A linear regression model with percentage mismatch lost as response and LA volume, acute diffusion-weighted imaging and mean transit time volumes, age, admission blood glucose level, admission mean arterial blood pressure, etiologic stroke subtype, time to acute MRI, and time between acute and follow-up imaging as covariates revealed that LA volume was an independent predictor of infarct growth ($P=0.04$). The adjusted percentage mismatch lost in the highest quartile of LA volume was 1.9-fold (95% CI: 1.2 to 3.1) greater than the percentage mismatch lost in the lowest quartile.

Conclusion—LA volume at the time of acute ischemic stroke is a predictor infarct growth. Because LA is associated with factors that modulate tissue perfusion as well as tissue capacity for handling of ischemia, LA volume appears to be a composite predictive marker for the fate of acutely ischemic tissue. (Stroke. 2008;39:1409-1413.)

Key Words: acute stroke | cerebral infarct | diffusion-weighted imaging | leukoaraiosis | MRI

Leukoaraiosis (LA) is a descriptive term used to describe neuroimaging findings of diffuse hemispheric white matter abnormalities mainly characterized by loss of myelin and/or ischemic injury.1,2 The exact cause and pathophysiology of LA remain under active investigation, and most working definitions are operational in nature with numerous outstanding questions regarding the precise mechanisms of its occurrence and prognostic implications. LA exhibits a distinct pattern of distribution. It primarily occurs in the periventricular white matter and regularly spares the convoluted white matter, U-fibers, corpus callosum, internal capsule, anterior commissure, and the white matter of the brain stem.1 It is of note that periventricular white matter has its distinct blood supply characterized by multiple, parallel, penetrating, small arteries (100 to 170 μm in diameter) that arise from the pial vessels at almost right angles and run in a straight line toward the lateral ventricle.3 Arteries that supply the cortex and adjacent white matter, on the other hand, are often parallel to the cortical surface and exhibit fountain-like frequent ramifications.

In LA, the walls of penetrating arteries of the white matter are characteristically thickened and hyalinized. There is often arteriosclerotic narrowing, elongation, and tortuosity, yet occult occlusion or severe stenosis is rare.1,4 In addition, in brains with LA, the vascular density is diminished to approximately four fifths that of a normal brain.5 Furthermore, arteriosclerotic penetrating arteries in LA exhibit an inability to dilate in response to reduced blood flow.6 The cumulative effect of these factors is that the baseline cerebral blood flow in the white matter of brains with LA is depressed.7 It is, therefore, plausible to consider that compromised tissue perfusion at the macro- and microvascular level in LA can
result in adverse tissue outcome in acute cerebral ischemia. As an initial investigation into this question, we sought to determine the correlation between LA volume and the proportion of initially ischemic but eventually infarcted tissue in human acute ischemic stroke.

**Methods**

**Study Population**

The study population consisted of consecutive patients with acute ischemic stroke presenting to the emergency department who had diffusion-weighted (DWI) and perfusion-weighted MRI within 12 hours of symptom onset and a follow-up imaging between days 4 and 30. The study was a retrospective analysis of patients who were recruited as part of a prospective study (MRI Diffusion/Perfusion Mismatch in Human Acute Stroke) between 2000 and 2006. A portion of the study population has been previously published within the context of another study.8 Patients who had DWI/mean transit time (MTT) mismatch <20% of the DWI volume, patients who received thrombolytic therapy or investigational drugs, and patients in whom the assessment of final infarct volume was not possible due to extensive hemorrhagic conversion, massive brain edema, or brain surgery (hemicraniectomy) were excluded. The decision to use 20% as a mismatch threshold was based on our unpublished data indicating that the median interexaminer difference for DWI/MTT mismatch measurement was approximately 20%. Because the presence of a MTT defect that is larger than a DWI lesion was a requirement for inclusion, none of the study patients had been fully reperfused at the time of acute imaging. The study was conducted at a single academic center and the study protocol was approved by the local Institutional Review Board.

**Imaging**

Imaging was performed using 1.5-T whole body scanners (GE Signa; GE Medical Systems; or Siemens Sonata; Siemens Medical Solutions). The acute MRI consisted of fluid-attenuated inversion recovery (FLAIR) images, apparent diffusion coefficient maps, DWI, and MTT maps. DWI was obtained using echoplanar imaging with a repetition time of 5000 ms to 10 000 ms, an echo time of 71 ms to 125 ms, field of view of 22×22 cm, matrix of 128×128, slice thickness 5 mm to 6 mm with a 1-mm gap, and b values of 0 seconds/mm² and 1000 seconds/mm². Diffusion-weighted images were corrected for motion and eddy present distortions using a Linear Image Registration Tool (FLIRT 5.0; Oxford Centre for Functional Magnetic Resonance Imaging of the Brain).9 Isotropic DWI maps as well as apparent diffusion coefficient maps were computed from these images. Perfusion-weighted images were acquired using spin-echo and gradient-echo echoplanar imaging. Imaging parameters were repetition time 1500 to 1775 ms and echo time 18 to 75 ms with the same spatial resolution as for DWI. MTT maps were calculated using methods described previously.10 FLAIR images were acquired with a repetition time of 8002 to 10 002 ms, echo time of 125 to 145 ms, field of view of 22×22 cm, acquisition matrix of 256×256 pixels, and slice thickness 5 mm with a 1-mm gap. The follow-up study consisted of fast-spin echo T2-weighted images in 43 patients and noncontrast CT in 18 patients. Fast-spin echo T2-weighted images were acquired with a repetition time of 4000 ms to 6500 ms, echo time of 85 ms to 110 ms, field of view of 22×22 cm or 24×24 cm, acquisition matrix of 256×192 pixels or 320×256 pixels, and slice thickness of 5 mm to 6 mm with a 1-mm gap. The CT studies were performed by using a helical scanner (High-Speed Advantage; GE Medical Systems) with 5-mm contiguous axial images, 140 kVp, 170 mA, and 1-second rotation.

**Image Analysis**

Ischemic lesions on admission DWI and MTT maps and on follow-up images were manually outlined by 2 neuroradiologists using a commercial software program (ALICE; Hayden Image Processing Solutions). The volume of each outline was then calculated with the same software. The intraclass correlation coefficient for DWI and MTT volume estimates between examiners was 0.99 and 0.98, respectively.

LA was defined as regions of increased signal intensity on acute FLAIR images in the white matter that starts at the lateral ventricular border and extends up to the corticomedullary junction.11 The boundaries of LA were differentiated from the acute ischemic lesion by visually coregistering acute FLAIR images with the DWI. Discrete territorial brain lesions with well-defined borders that appear hyperintense on FLAIR images such as chronic subcortical infarcts and lacunar infarcts were not outlined. The volume of LA in the whole brain was calculated as described before by the use of a semiautomatic image display program (MIRcro).12 The interexaminer reliability of this technique was reported to be high (intraclass correlation coefficient=0.98).12 The LA volumes were normalized with respect to the intracranial area to correct for differences in head size using a previously validated method13,14:

\[
\text{Normalized leukoaraiosis volume} = \frac{\text{leukoaraiosis volume} \times \text{mean intracranial area of the population/ intracranial area of an individual patient}}{100}
\]

The intracranial area was measured by outlining the inner tabula on the midsagittal T1 images. The intraclass correlation coefficient for this technique was 0.92 according to a prior report.12 Tissue outcome was assessed by calculating percentage mismatch lost (PML), a composite measure of acute DWI/MTT and follow-up volumes. PML was estimated as follows (Figure):

\[
PML = \left( \frac{\text{follow-up volume} - \text{DWI volume}}{\text{MTT volume} - \text{DWI volume}} \right) \times 100
\]

**Statistics**

Bivariate analyses assessed the relationship between PML and the following clinical and imaging covariates that are related to PML: LA volume, time from symptom onset to acute MRI, acute DWI volume, acute MTT volume, time between acute and follow-up imaging, age, SSS-TOAST etiologic stroke subtype,15 admission blood glucose level, and admission blood pressure. Bivariate relationships were tested using Spearman’s correlation and Kruskal-Wallis test for situations in which the covariates were both continuous and one continuous and one categorical, respectively. A backward elimination regression model (P<0.10 used as retention criterion) with PML as response and all other clinical and imaging covariates as independent variables was developed. SSS-TOAST stroke subtype was introduced into the model as multiple dichotomous variables. Because PML did not conform to normal distribution, it was log-transformed before being introduced to the model. All numeric variables were expressed as mean±SD and median±interquartile range. A level of P≤0.05 was considered statistically significant. All statistical analyses were performed by SPSS 11.5.

**Results**

A total of 2832 consecutive patients with ischemic stroke were admitted during the study period. During the last 3.5 years of the study, a total of 1541 consecutive admissions were regularly entered into a stroke log. According to this log, patients were disqualified because of the following reasons: contraindication to MRI (156 patients), admission >12 hours of symptom onset (732 patients), inability to obtain MRI within the first 12 hours (218 patients), images of insufficient quality due to motion artifact or other reasons (14 patients), administration of thrombolytic or experimental treatment (169 patients), inability to get consent from patients (108 patients), and lost to follow-up (46 patients). The
remaining 98 of the 1541 patients had both acute and follow-up imaging per protocol. Twenty-three of the 98 patients were later excluded because they had massive edema or hemorrhagic conversion on follow-up imaging (15 patients) or underwent hemicranietomy (8 patients). From the 41-month period preceding the log, there were 54 additional eligible patients who were scanned per protocol. These 54 patients were identified using the same criteria as the later eligible patients who were scanned per protocol. These 54 additional patients were included in the present study.8 There was approximately 50% overlap between study populations of the 2 studies. When the original regression model was used LA volume only in the contralateral hemisphere was developed. In this model, LA volume was still an independent predictor of PML. Our group has previously shown that age is an independent predictor of PML in a cohort identified from the same prospective data pool used for the present study.8 There was approximately 50% overlap between study populations of the 2 studies. When the original regression model in this relatively new data set was repeated by removing LA volume from the model, age (P = 0.04), DWI volume (P = 0.05), and admission blood glucose (P = 0.03) appeared to be independent predictors of PML.

Discussion
In patients with acute ischemic stroke, tissue in regions where the perfusion is compromised but the apparent diffusion coefficient (and hence DWI) is normal is considered to be “at risk” for developing irreversible injury. The fate of such ischemic tissue within the diffusion–perfusion mismatch is complex and depends on many factors, including the timing of reperfusion, presence of collateral flow channels, time from symptom onset, comorbid conditions, and factors such as age that are associated with impaired tissue handling of ischemia.8,16–18 The data presented here demonstrate that LA volume is also associated with more tissue damage for a
given insult independent of initial insult size, age, admission blood glucose, admission blood pressure, and stroke subtype, suggesting that LA volume is an imaging marker for diminished ability to respond to an ischemic insult.

Recent studies highlighting LA as a risk factor for cognitive dysfunction\textsuperscript{19} and stroke\textsuperscript{20} have shifted its importance from an incidental radiological description to a radiological surrogate marker. LA is associated with increased mortality, increased cardiovascular morbidity, and unfavorable functional outcome in patients with stroke.\textsuperscript{21} LA is a composite product of multiple factors, which themselves appear to play a role in determining the tissue outcome after ischemia. LA may be a marker of compromised tissue perfusion because it is associated with a number of structural and functional vascular changes (arteriosclerotic narrowing, elongation, tortuosity, impaired autoregulation).\textsuperscript{1,4} In brains with extensive LA, the resting cerebral blood flow is reduced by up to 30\%\textsuperscript{,22} In addition to vascular alterations, LA is also associated with increased platelet activation\textsuperscript{23} and hypercoagulability,\textsuperscript{24} which can further complicate tissue perfusion in acute ischemic stroke. Vascular influences, although having an essential and central role, is not the sole determinant of adverse tissue outcome in cerebral ischemia in patients with LA. Low plasma levels of antioxidants,\textsuperscript{25} increased microglial activation,\textsuperscript{26} and blood–brain barrier dysfunction\textsuperscript{27} can contribute to worsened tissue outcome as a result of their association with LA. Furthermore, there is a strong correlation between LA volume and accepted cardiovascular risk factors: aging, chronic hypertension, diabetes mellitus, smoking, hypercholesterolemia, and coronary artery disease.\textsuperscript{28} Aging is associated with impaired cellular energy production, reduced clearance of oxygen-free radicals, and increased susceptibility to excitotoxicity.\textsuperscript{29} Advanced age is a predictor of increased conversion of ischemic tissue into infarction in acute human stroke.\textsuperscript{8} Likewise, patients with multiple stroke risk factors are more prone to less favorable outcome after stroke.\textsuperscript{30} Thus, there may be no single dominant mechanism by which LA influences tissue outcome and, therefore, it is plausible to presume that LA should be considered as a composite imaging marker for the likelihood of progression of tissue injury in acute stroke due to major cerebral artery occlusion. More definitive conclusions on the mechanism of relationship between LA and tissue outcome can be derived from analyses of larger data sets in which there are serial imaging data at multiple time points to assess the presence and timing of recanalization of arterial occlusion. Larger data sets may also provide insight into the association between LA volume and growth in lacunar infarcts, a subset that was disqualified because of the requirement that DWI/MTT mismatch should be >20\% of the DWI lesion volume in the present study.

Interindividual variation in LA volume appears to be strongly related to genetic variation. Estimates of the heritability of LA volume range between 55\% and 71\%\textsuperscript{,31,32} and preliminary studies of candidate genes have implicated variants in endothelial nitric oxide synthase G894T, angiotensin-converting enzyme I/D, angiotensin II type I receptor A1166C, paraoxonase, methylenetetrahydrofolate reductase C677T, and apolipoprotein E in its pathogenesis.\textsuperscript{33–35} Potential biological consequences of many of these genetic variants associated with LA such as decreased bioavailability of endothelial nitric oxide, increased angiotensin-converting enzyme levels, and maybe increased sensitivity to angiotensin are associated with poor collateral circulation,\textsuperscript{36,37} less salvageable ischemic tissue,\textsuperscript{37} and larger infarct volumes.\textsuperscript{38–40} Thus, LA is not only a composite marker of tissue susceptibility to ischemia or a unified marker of tissue susceptibility and structural or functional vascular insufficiency, but may also serve as a marker of genetic influences that regulate tissue perfusion as well as tissue resistance to ischemia.

Genetic variation may explain, in part, the high variability of stroke severity as well as tissue outcome, although expression of an imaging characteristic (phenotype) probably incorporates the effects of multiple environmental as well as genetic factors. LA, therefore, may represent an intermediate phenotype that links tissue outcome in acute stroke to genetic underpinnings, and this may in turn allow discovery of therapeutic approaches to modify the effects of the products encoded by implicated genes. Further studies are needed to confirm our findings and then clarify the exact role of genetic and acquired factors that link LA to unfavorable tissue outcome in patients with acute stroke.

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Disclosures

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References

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