Leukoaraiosis Correlates With Cerebral Hypoperfusion in Vascular Dementia

Jun Kawamura, MD; John Stirling Meyer, MD; Yasuo Terayama, MD; and Susan Weathers, MD

Leukoaraiosis quantified by computerized densitometric measurements of reduced Hounstield numbers was correlated with local cerebral blood flow on the same computed tomographic images of 35 patients with multi-infarct dementia and 16 age-matched elderly normal volunteers. The ratio for area of frontal leukoaraiosis to total area of parenchyma among the patients was significantly greater than that among the normal volunteers (5.8±2.3% compared with 3.1±1.3%, p<0.001). Severity of leukoaraiosis around the frontal horns of the lateral ventricles correlated significantly with severity of leukoaraiosis of the centrum semiovale adjacent to the bodies of the lateral ventricles. Cerebral blood flow values for all representative cerebral regions except the parietal white matter were reduced among the patients compared with the normal volunteers. Multivariate regression analysis revealed that reduced cerebral perfusion in the putamen and thalamus correlated significantly with the severity of leukoaraiosis. Cerebral hypoperfusion in territories supplied by deep penetrating arteries may contribute to the pathogenesis of leukoaraiosis. (Stroke 1991;22:609–614)

A reas of abnormal density in the periventricular white matter are sometimes detected by either computed tomography (CT) or magnetic resonance imaging (MRI) among elderly normal subjects; such abnormalities are detected more frequently among patients with strokes and vascular dementia. Hachinski et al1 proposed the term "leuko-araiosis" for these white matter abnormalities to emphasize that both their clinical relevance and their pathogenesis were unknown. A number of reports indicate that leukoaraiosis is regularly associated with aging, risk factors for stroke, minor neurologic signs, subtle cognitive impairments, or dementia, and the authors of these reports added an ischemic origin for leukoaraiosis.2-9 However, quantitative reductions of cerebral blood flow (CBF) have seldom been correlated with the severity of leukoaraiosis.10-13

The present study was designed to elucidate relations that may exist between quantitative measures of cerebral perfusion and severity of leukoaraiosis among patients with vascular dementia compared with age-matched normal volunteers. Stable xenon CT provided measurements of local cerebral blood flow (LCBF) on the same noncontrasted CT slices that were subjected to quantification of any leukoaraiosis by densitometry.

Subjects and Methods

Thirty-five patients with multi-infarct dementia (MID) (mean±SD age 68.5±10.9 [range 37-92] years) and 16 neurologically and cognitively normal age-matched volunteers (mean±SD age 67.2±10.5 [range 57-86] years) participated. They signed informed consent according to protocols approved annually by the Institutional Review Board of this Department of Veterans Affairs Medical Center. All subjects underwent similar assessments including physical and neurologic examinations, the Cognitive Capacity Screening Examination (CCSE),14,15 Hachinski Ischemic Index scoring,16,17 and laboratory tests.

In the patients, dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders.18 Among high school graduates, CCSE scores of <25 correlate well with other psychological and behavioral test scores indicating cognitive impairments and provide a simple but reliable index for quantifying dementia.13 Diagnosis of MID required focal neurologic signs, a Hachinski Ischemic Index score of >7, and a CCSE value of <25. Table 1 classifies the types of strokes present according to recommendations of the National Institute of Neu...
 TABLE 1. Presence of Risk Factors and Classification of Strokes in 35 Patients With Multi-infarct Dementia

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>26</td>
<td>74</td>
</tr>
<tr>
<td>Heart disease</td>
<td>19</td>
<td>54</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>20</td>
<td>57</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12</td>
<td>34</td>
</tr>
<tr>
<td>Smoking</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>Classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar stroke</td>
<td>25</td>
<td>71</td>
</tr>
<tr>
<td>Lacunar stroke + ICA stenosis or occlusion</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>Atherothrombotic stroke + ICA</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

ICA, internal carotid artery.

rological Disorders and Stroke\(^1^9\) and lists associated risk factors. Occlusion or stenosis of the internal carotid arteries was considered present when ultrasonography or angiography disclosed occlusion or stenosis of \(\geq 80\%\).

Criteria for the normal volunteers included 1) a normal neurologic examination, 2) normal cognitive function including a CCSE score of \(\geq 27\), 3) the absence of a history of stroke and other neuropsychiatric disorders, and 4) exclusion by CT and/or MRI of intracranial abnormalities other than age-related cerebral atrophy.

The LCBF was measured by serial CT scanning while the subject inhaled 27% stable xenon as a contrast agent for 8 minutes (Xe CT-CBF method). Details of the method have been reported.\(^2^0\) LCBF values were measured on brain slices that included the frontal, temporal, and occipital cortex, the caudate nucleus, the putamen, and the thalamus parallel to the orbitomeatal line. Additionally, in 13 patients with MID and eight normal volunteers, LCBF values were also measured in slices 10 mm above the basal ganglia that included the lateral ventricles and parietal cortex.

After two baseline unenhanced CT scans for each slice were obtained, seven serial CT scans were recorded at 1-minute intervals between the second and eighth minutes of xenon gas inhalation using one of two high-resolution rapid CT scanners (Somatom DR Version H, Siemens Medical Systems, Inc., Iselin, N.J., or Picker Synerview SX 1200, Picker International, Inc., Cleveland, Ohio). End-tidal partial pressures for xenon gas and carbon dioxide (\(\text{PECO}_2\)) were recorded on a polygraph.

The LCBF values were generated by a desktop computer programmed to use the two baseline scans and seven enhanced scans to determine multiple tissue xenon saturation curves as required by Kety's formula. The original CT images (512×512 pixels) were compressed to 128×128 pixels before calculating the LCBF values, using precalculation and postcalculation smoothing (3×3 pixels). LCBF values were computed for 11 representative regions for each hemisphere (total of 22 regions, including the frontal, temporal, parietal, and occipital cortex, the caudate nucleus, putamen, and thalamus, the frontal, parietal, and occipital white matter, and the internal capsular white matter). The electroencephalogram (EEG) and electrocardiogram were monitored throughout the LCBF measurements.

Limitations of the Xe CT-CBF method include the anesthetic effects of xenon gas, errors due to CT noise, motion artifacts, tissue overlap, and radiation exposure. However, measurement errors were reduced by using high-resolution rapid CT scanners combined with a relatively low concentration of xenon gas as described previously.\(^2^0\)

The Hounsfield number for each CT pixel was obtained from the two baseline CT images at each of the two levels used for LCBF measurements. To determine the upper- and lower-threshold Hounsfield numbers for leukoaraiosis, two of us determined them independently by computerized densitometry in two patients with mild and severe leukoaraiosis compared with young normal controls. The independent determinations were found to be in good agreement with the lower threshold, assigned as 25 Hounsfield units, and the upper threshold assigned as 34.
Leukoaraiosis was therefore quantified as a Hounsfield number between 25 and 34 determined by computerized densitometry. Areas of leukoaraiosis adjacent to the anterior horns of both lateral ventricles and anterior to the heads of both caudate nuclei at the level of the basal ganglia (LA-1) and areas of leukoaraiosis adjacent to the bodies of the lateral ventricles 10 mm above the LA-1 level (LA-2) were quantified by computerized densitometry. Severity of leukoaraiosis was expressed as the percentage ratio for the area of leukoaraiosis to the total area of the cerebral parenchyma at the two different levels. The standard deviation of the Hounsfield number was 0.2 when a CT phantom was scanned 11 times, indicating adequate reproducibility of the CT scanners for densitometry.

Data are presented as mean±standard deviation. Statistical analyses were performed using Student's t test and multiple regression analysis.

Results

Figure 1 displays zones of leukoaraiosis detected at LA-1 level in a 59-year-old woman with mild MID. Figure 2 illustrates plain CT images and the corresponding LCBF maps for a 92-year-old woman with severe MID. CT scanning revealed multiple cerebral
Leukoaraiosis has been defined by Hachinski et al. as "abnormal regions of white matter disclosed by CT or MRI." Since that provocative report, a number of studies have indicated relations between leukoaraiosis and advanced age, risk factors for stroke, focal neurologic signs, cognitive impairments, and cerebral hypoperfusion. However, to our knowledge there have been no investigations in which the severity of leukoaraiosis was quantified by densitometry. We made such quantification, providing an objective method for analyzing the relations of leukoaraiosis to cerebral perfusion and other relevant factors. Computerized densitometry has technical limitations, which include tissue overlap or partial volume effects in regions near the ventricles or calcification in the choroid plexus. However, we avoided such regions as much as possible when choosing representative volumes of white matter.

The reported frequency of leukoaraiosis among normal subjects has varied from 9% to 22%. These differences are related to differences in selection of the cohorts of "normals" studied and to differences in the associated risk factors for stroke. Leukoaraiosis has consistently been reported to be more frequent among demented patients. Our results are consonant with these semiquantitative observations and confirm that the frequency and severity of leukoaraiosis are much greater among MID patients than among age-matched normal controls.

When LCBF and leukoaraiosis were quantified on the same CT slices among our patients with MID, the severity of frontal leukoaraiosis correlated best with reduced LCBF in the thalamus and putamen. At least two pathogenetic mechanisms may be considered to explain such relations between frontal leukoaraiosis and reduced perfusion of the subcortical gray matter. The first consideration is that the territories supplied by deep penetrating cerebral arteries include the putamen, thalamus, and periventricular white matter and that ischemia within these territories will be responsible for changes in the deep periventricular white matter because of the well-known poor collateral blood supply of these regions. This consideration is supported by the studies of Awad et al. who reported that MRI-demonstrated lesions of the white matter were associated with thickening of their supplying arterial walls as well as with vascular ectasia and dilated periventricular spaces. Atrophic perivascular demyelination accompanied by thickening of the arterial walls was also reported by Kirkpatrick and Hayman in neuro-pathologic studies of white matter changes recognized as leukoaraiosis by neuroimaging. Likewise,
Thalamus with leukoaraiosis. Meyer et al. concluded that white matter lesions functionally interrupt cortico- and subcortical connections in patients with leukoaraiosis, presumably due to Binswanger's subcortical arteriosclerotic encephalopathy because of prominent cortical hypoperfusion and hypometabolism in the frontal cortex. On the other hand, similar PET studies reported by others have described decreased CBF and increased oxygen extraction fractions within the frontal cortex of subjects with leukoaraiosis, supporting an ischemic hypothesis for its pathogenesis. In our age-matched normal volunteers, correlations were not found between the severity of leukoaraiosis and reductions of LCBF, indicating that the process, if present, is less severe than in patients with MID.

Based on LCBF comparisons between patients with MID and those with Alzheimer's disease, evidence was reported previously that the pathogenetic mechanisms for leukoaraiosis among the former apparently differ from those among the latter, in whom Wallerian degeneration may be an important contributing factor. Taken together, currently available information suggests that several factors contribute to the pathogenesis of leukoaraiosis and that these factors may become mutually deleterious. These factors include 1) ischemia in the territory of the deep penetrating arterioles due to either atherosclerosis or amyloid angiopathy, 2) selective vulnerability of the white matter due to its poor collateral circulation, 3) decreased local metabolic demand due to neuronal disconnections, and 4) Wallerian degeneration.

In conclusion, multivariate analysis shows best correlations between putamen-thalamic hypoperfusion and the severity of leukoaraiosis. Cerebral hypoperfusion and ischemia may contribute to the

### Table 2. Multiple Regression Analysis for Severity of Frontal Leukoaraiosis Correlated With Local Cerebral Blood Flow for Thalamus and Putamen Among Patients With Multi-Infarct Dementia

<table>
<thead>
<tr>
<th>Region</th>
<th>Partial Regression Coefficient</th>
<th>Standardized Partial Regression Coefficient</th>
<th>Partial Correlation Coefficient</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>-0.0858</td>
<td>-0.4500</td>
<td>-0.4579</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Putamen</td>
<td>-0.1337</td>
<td>-0.3889</td>
<td>-0.4067</td>
<td>&lt;0.025</td>
</tr>
</tbody>
</table>

**Figure 4.** Scatterplot of ratios for area of leukoaraiosis at level of basal ganglia (LA-1) and at level of bodies of lateral ventricles (LA-2) to total parenchyma area among patients with multi-infarct dementia (MID) and age-matched normal volunteers. Ratios at both LA-1 and LA-2 were greater among patients with MID than among age-matched normal volunteers (p<0.001 for LA-1).

**Figure 5.** Bar graph of mean±SD local cerebral blood flow (LCBF) values for 11 representative brain regions in 35 patients with multi-infarct dementia (filled bars) compared with 16 age-matched normal volunteers (open bars). FC, frontal cortex; TC, temporal cortex; PC, parietal cortex; OC, occipital cortex; CAU, caudate nucleus; PUT, putamen; THA, thalamus; FW, frontal white matter; PW, parietal white matter; OW, occipital white matter; INT, internal capsule. LCBF values for all regions except PW were significantly less in patients than in normals. ***p<0.01, ****p<0.001 different from age-matched normal volunteers by Student's t-test.
pathogenesis of leukoaraiosis, but disconnections of the cortical and subcortical gray matter projection systems aggravate leukoaraiosis by decreasing local metabolic demands, which may eventually lead to cognitive impairments.

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References


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