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 Hounsfield 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 adduced 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 noncontrast 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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Classification</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<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 vasculitis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

ICA, internal carotid artery.

FIGURE 1. Baseline unenhanced computed tomogram showing zones of frontal leukoaraiosis at level of basal ganglia as measured by computerized densitometry in patient with mild multi-infarct dementia (59-year-old woman with hypertension and 40-year history of heavy cigarette smoking who suffered from small lacunar infarcts). Regions with leukoaraiosis having Hounsfield numbers between 25 and 34 are displayed in green (arrow). Ratio of area of leukoaraiosis to area of total parenchyma for this level is 8.31%.
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
infarcts in the cortex and subcortical gray matter bilaterally accompanied by leukoaraiosis. LCBF measurements demonstrated prominent and patchy reductions of cerebral perfusion throughout both hemispheres, particularly in the left parietotemporal cortex and thalamus.

Figure 3 shows a significant correlation between the ratios of leukoaraiosis area to total parenchyma area for both LA-1 and LA-2 among the eight normal volunteers and the 13 patients with MID in whom two slices were examined ($r=0.938$, $p<0.001$). Figure 4 compares the ratios of leukoaraiosis area to total parenchyma area for LA-1 among all 35 patients with MID and all 16 age-matched normal volunteers and the ratios for LA-2 in those in whom it was measured. Ratios for both LA-1 and LA-2 were greater among the patients with MID than among the normal volunteers ($p<0.001$ for LA-1).

Figure 5 compares LCBF values for the 11 representative brain regions of the patients with MID and the normal volunteers. LCBF values for all regions except the parietal white matter were significantly less in the patients with MID than in the normal volunteers.

The associations of LCBF among nine representative cerebral regions to the severity of frontal (LA-1) leukoaraiosis were assessed by multiple linear regression analysis. The coefficient of determination ($R^2$) was 0.593, $R^2$ adjusted for degrees of freedom was 0.567, and the multiple correlation coefficient was 0.770; the results were significant ($p<0.001$, F test). Among the initial nine independent (explanatory) variables (LCBF value for each region), LCBF values for either the thalamus or the putamen correlated significantly with the severity of leukoaraiosis at LA-1 (Table 2), indicating that among patients with MID, reduced cerebral perfusion in either the putamen or the thalamus correlates with the severity of frontal leukoaraiosis. Among the normal volunteers, significant correlations were not observed between LCBF and the severity of leukoaraiosis, which was mild.

The PECO$_2$ did not differ significantly between the normal volunteers (32.9±2.5 mm Hg) and the patients with MID (32.1±2.4 mm Hg), nor were there significant differences in mean arterial blood pressure between the two groups (normal, 95±8 mm Hg; MID, 99±13 mm Hg). There were no changes in EEG recordings before or during the inhalation of xenon gas.

Discussion

Leukoaraiosis has been defined by Hachinski et al$^1$ 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.$^2-^5$ 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.$^2-^4$ Leukoaraiosis has consistently been reported to be more frequent among demented patients.$^1,^12$ 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$^{21}$ 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$^{23}$ in neuropathologic 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-

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>

subcortical connections in patients with leukoaraiosis, presumed to be due toBinswanger'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 describe 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 putamenothalamic hypoperfusion and the severity of leukoaraiosis. Cerebral hypoperfusion and ischemia may contribute to the
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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Key Words: cerebral blood flow • leukoencephalopathy • dementia
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