Prognostic Importance of Leukoaraiosis in Patients With Symptomatic Internal Carotid Artery Stenosis

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Background and Purpose—Leukoaraiosis (LA) is a frequent finding on brain CT scans. This study examined patients with LA and symptomatic internal carotid artery disease.

Methods—Patients in the North American Symptomatic Carotid Endarterectomy Trial were evaluated for the extent of LA. Long-term prognosis and perioperative risk associated with carotid endarterectomy were assessed.

Results—Among 2618 patients, 493 had LA: 354 restricted and 139 widespread. Patients with LA were older, had a history of hypertension, had more hemispheric ischemic events (particularly stroke), and had small, deep brain infarcts. The 3-year risks of stroke for medically treated patients were 20.2% (no LA), 27.3% (restricted LA), and 37.2% (widespread LA) (P<0.01). For surgically treated patients, the risks were 14.2%, 25.4%, and 33.6%, respectively (P<0.001). With widespread LA, occurrence of disabling strokes doubled in medical patients and tripled in surgical patients. The 30-day perioperative risks of any stroke or death for surgical patients with 50% to 99% internal carotid artery stenosis were 5.3% (no LA), 10.6% (restricted LA), and 13.9% (widespread LA). Despite higher perioperative risk, endarterectomy reduced the absolute 3-year risk of stroke ipsilateral to the symptomatic 50% to 99% stenosed artery by 11.6% (P=0.46) for patients with widespread LA, 7.6% (P=0.39) with those with restricted LA, and 10.9% (P<0.001) for those with no LA.

Conclusions—In patients with a transient ischemic attack or nondisabling stroke associated with internal carotid artery disease, presence of LA was associated with an increased risk of any stroke and of disabling or fatal stroke. Patients with widespread LA had the worst prognosis. Despite the higher perioperative risk, endarterectomy reduced the risk of stroke.

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Key Words: carotid endarterectomy • leukoaraiosis • prognosis • stroke

Leukoaraiosis (LA) describes white-matter changes observed on cross-sectional images of the brain. It is a common finding in elderly people without neurological disease but is particularly frequent among those with dementia and stroke. LA has been associated with increased risks of stroke, vascular death, dementia, gait apraxia, and intracerebral hemorrhage during anticoagulation therapy. With the increasing age of the world’s population, the prevalence of LA will increase and will become more clinically important in the geriatric population.

LA is a heterogeneous entity with an unclear pathogenesis. The term was coined to differentiate the neuroimaging findings from the omenous neuropathological entity Binswanger’s disease. Evidence suggests that LA may be linked to cerebral ischemia; however, no association with the extent of carotid artery disease has been found. LA can be evaluated on brain CT scans or MRI. On CT scans, its prevalence in stroke patients ranges between 4% and 44%, whereas on MRI, because of its high sensitivity, its prevalence is reported to be as high as 100%.

The primary aim of the present study was to examine the risk of stroke in a large group of patients with LA who had recent ischemic symptoms attributable to carotid artery disease. The secondary aim was to examine in these patients the perioperative risk and long-term benefit of carotid endarterectomy, the risk of vascular death, and the incidence of lacunar stroke.

Patients and Methods

All patients in the present study were recruited by the North American Symptomatic Carotid Endarterectomy Trial (NASCET).
This multicenter, randomized trial was designed to determine the role of carotid endarterectomy for symptomatic patients with angiographically documented internal carotid artery (ICA) disease. Full details of the study protocol, including the effectiveness of endarterectomy, have been published. In brief, patients with transient retinal or nondisabling hemispheric ischemic events were randomized into the trial within 180 days of their event, provided that they had neither a cardiac source of embolism nor any life-threatening or other disabling condition that would contraindicate endarterectomy or interfere with the interpretation of outcome events and were mentally competent to sign an informed consent. All patients had a detailed history and physical examination at baseline, including routine blood tests, ECG, chest x-rays, cerebral angiogram, and a CT scan of the head. Relatively few patients had an MRI scan.

Hard copies of CT scans were sent to the central office, where they were first reviewed for the presence of brain infarcts by the trial neuroradiologist (A.J.F.), who was blinded to the clinical data. Three neurologists (J.Y.S., O.R.B., S.A.) reviewed the CT scans for the presence and extent of LA in each hemisphere; they also were blinded to the clinical data. Interrater agreement for grading the extent of LA between the neuroradiologist and neurologists was estimated from 120 CT scans to be 0.85 as measured by an intraclass correlation coefficient. LA was assessed by a scale that requires separate evaluation of the anterior and posterior locations with 3 sequential CT scan slices. Details of this method have been described previously. LA was identified by the presence of poorly delineated hypodense lesions, unlike the sharply defined, low-density lesions within a specific arterial territory characteristic of an infarct. The extent of LA was considered to be restricted when the lesions were confined to the region adjoining the ventricles (Figure 1a), whereas widespread LA involved the entire region from the lateral ventricle to the cortex (Figure 1b). Patients with LA in either hemisphere were categorized according to the greatest extent of LA in the 2 hemispheres. The presence of deep and cortical infarctions was also recorded. Deep infarcts were divided into those with diameters ≤1.5 and those >1.5 cm. Only patients with a good-quality CT scan were included in the present study. Patients who only had MRI were excluded because there were few of them and because the 2 imaging modalities are not comparable when relating the presence and degree of LA to neurological impairments because of the greater sensitivity of MRI to even very subtle changes.

Follow-up of the NASCET patients consisted of examinations by a stroke neurologist at 30 days, every 3 months in the first year, and every 4 months thereafter. All strokes were reported, and the territory, type, and severity were recorded. Strokes were considered disabling if patients had a modified Rankin score of ≥3 at 90 days. The underlying cause of death was indicated. All strokes and deaths were adjudicated by a central office committee.

Associations between baseline patient characteristics and the extent of LA were assessed by use of a χ² test. The prognostic impact of LA on the risk of stroke was assessed with Kaplan-Meier event-free survival analyses (including a log-rank test to compare groups) and Cox proportional-hazards regression modeling. The analyses also counted all deaths and all strokes (regardless of location) that occurred during the 30-day perioperative period for patients who had endarterectomy. All deaths and all strokes were also counted during a comparable 32-day period after randomization for the patients treated medically because the median time from randomization to endarterectomy in the surgical arm was 2 days. The risk of lacunar stroke, based on a clinical-radiological definition, was also assessed.

Results

Of the 2885 patients enrolled in NASCET between 1988 and 1996 and followed up until the end of 1997, the present study reports on the prognosis of the 2618 patients who had good-quality CT scans available for review; 186 patients had a baseline MRI scan only, 56 patients had a CT scan of poor quality, and 25 CT scans were unavailable for review. Among

Figure 1. CT slice through (a) the frontal horns of the lateral ventricles showing bilateral anterior “restricted” LA (arrows) with low densities in the deep white matter adjacent to the frontal horns and (b) the bodies of the lateral ventricles showing bilateral, anterior, and posterior widespread LA (arrows) with low densities adjacent to the ventricles, in the deep white matter, and extending to subcortical white matter.
the 2618 patients, 354 (13.5%) had restricted LA, and 139 (5.3%) had widespread LA. The remaining 2125 patients (81.2%) had no evidence of LA. Patient characteristics are shown in Table 1. Patients with some extent of LA were more likely to be older than those without LA. In addition, presenting hemisphere ischemic events, history of hypertension (including elevated systolic blood pressure), and the presence of deep brain infarcts on the CT scan were associated with increasing extent of LA. History of recent smoking and hyperlipidemia were less prevalent in LA patients.

The 3-year risk of any stroke, and separately for disabling or fatal stroke, increased with more extensive LA in both medically and surgically treated patients (Table 2) and regardless of ICA stenosis category (Figure 2). Medically

### Table 1. Comparison of Groups on the Basis of Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Extent of LA, %</th>
<th>None (n=2125)</th>
<th>Restricted (n=354)</th>
<th>Widespread (n=139)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assigned to carotid endarterectomy</td>
<td></td>
<td>49.5</td>
<td>51.1</td>
<td>50.4</td>
<td>0.84</td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td>69.7</td>
<td>71.5</td>
<td>63.3</td>
<td>0.20</td>
</tr>
<tr>
<td>Age, y*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td></td>
<td>43.9</td>
<td>26.8</td>
<td>19.4</td>
<td></td>
</tr>
<tr>
<td>65–74</td>
<td></td>
<td>44.6</td>
<td>51.7</td>
<td>53.2</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>≥75</td>
<td></td>
<td>11.5</td>
<td>21.5</td>
<td>27.4</td>
<td></td>
</tr>
<tr>
<td>Presenting event nondisabling stroke‡</td>
<td></td>
<td>42.6</td>
<td>50.8</td>
<td>51.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Presenting hemisphere ischemic event§</td>
<td></td>
<td>75.8</td>
<td>83.6</td>
<td>83.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure &gt;160 mm Hg</td>
<td></td>
<td>18.6</td>
<td>24.3</td>
<td>25.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure &gt;90 mm Hg</td>
<td></td>
<td>11.7</td>
<td>12.7</td>
<td>13.0</td>
<td>0.80</td>
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<tr>
<td>Smoking within past year</td>
<td></td>
<td>44.8</td>
<td>36.7</td>
<td>33.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>59.0</td>
<td>62.4</td>
<td>75.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>21.1</td>
<td>25.4</td>
<td>16.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Myocardial infarct or angina</td>
<td></td>
<td>37.7</td>
<td>44.6</td>
<td>39.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td></td>
<td>15.2</td>
<td>15.5</td>
<td>16.6</td>
<td>0.90</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td>35.2</td>
<td>27.4</td>
<td>30.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Stenosis ≥70% in either carotid artery</td>
<td></td>
<td>32.3</td>
<td>28.3</td>
<td>28.1</td>
<td>0.21</td>
</tr>
<tr>
<td>Deep infarct on CT scan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td></td>
<td>75.6</td>
<td>52.3</td>
<td>51.8</td>
<td></td>
</tr>
<tr>
<td>Diameter ≤1.5 cm</td>
<td></td>
<td>21.3</td>
<td>46.0</td>
<td>44.6</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Diameter &gt;1.5 cm</td>
<td></td>
<td>3.1</td>
<td>1.7</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Cortical lesion on CT scan</td>
<td></td>
<td>16.9</td>
<td>20.1</td>
<td>20.9</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*Mean ages of patients: 65.0, 68.4, and 70.0 years, respectively; P<0.001.
†Value refers to the overall association between extent of LA and the characteristic.
‡Nondisabling stroke, not transient ischemic attack.
§Hemisphere, not retinal ischemic event.

### Table 2. Kaplan-Meier 3-Year Risk of Outcome Event

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>Medically Treated Patients, Extent of LA, %</th>
<th>Surgically Treated Patients, Extent of LA, %</th>
<th>None (n=1073)</th>
<th>Restricted (n=173)</th>
<th>Widespread (n=69)</th>
<th>P*</th>
<th>None (n=1052)</th>
<th>Restricted (n=181)</th>
<th>Widespread (n=70)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any stroke</td>
<td></td>
<td></td>
<td>20.2</td>
<td>27.3</td>
<td>37.2</td>
<td>0.01</td>
<td>14.2</td>
<td>25.4</td>
<td>33.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disabling or fatal stroke</td>
<td></td>
<td></td>
<td>8.1</td>
<td>11.8</td>
<td>17.4</td>
<td>0.05</td>
<td>7.4</td>
<td>12.8</td>
<td>24.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vascular death†</td>
<td></td>
<td></td>
<td>5.0</td>
<td>5.0</td>
<td>6.7</td>
<td>0.77</td>
<td>3.6</td>
<td>6.8</td>
<td>10.1</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*P Values calculated from a log-rank test comparing 3 groups separately for medically and surgically treated patients.
†Not including fatal stroke; otherwise, vascular death resulted from cardiovascular or peripheral vascular causes.
treated patients with widespread LA had almost twice the risk of stroke as patients without LA. The risk of vascular death (not including fatal stroke) was similar for medically treated patients but increased with the extent of LA for surgically treated patients (Table 2).

In terms of the number of strokes over the 3-year follow-up period in medically treated patients, 8.7% of the patients with widespread LA had ≥2 strokes compared with 3.5% of the patients with restricted LA and 3.9% of patients without LA. (P=0.14, χ² test comparing 3 proportions). When lacunar stroke was used as the outcome, the 3-year risks for medically treated patients with no, restricted, and widespread LA were 4.3%, 5.5%, 5.6%, respectively (P=0.69, log-rank test comparing 3 risks).

Analyses of the risk of any stroke, and separately for disabling or fatal stroke, were repeated with Cox regression. After all patient characteristics listed in Table 1 were taken into account, LA remained a significant risk factor for any stroke (P<0.001 for 2-df likelihood ratio test from Cox regression) and for disabling or fatal stroke (P<0.001). Compared with medically treated patients without LA, the adjusted hazard ratio for any stroke for medically treated patients with restricted LA was 1.1 (95% CI, 0.8 to 1.6); for medically treated patients with widespread LA, it was 1.6 (95% CI, 1.1 to 2.5). For surgically treated patients, the adjusted hazard ratio for any stroke for restricted LA was 1.7 (95% CI, 1.1 to 2.4) and 2.5 (95% CI, 1.6 to 4.0) for widespread LA compared with surgically treated patients without LA. For the outcome of disabling or fatal stroke, the adjusted hazard ratios for medically treated patients with restricted LA were 1.2 (95% CI, 0.7 to 2.1) and 1.7 (95% CI, 0.9 to 3.4) for widespread LA compared with medically treated patients without LA. For surgically treated patients, the adjusted hazard ratios were 1.6 (95% CI, 0.9 to 2.6) for restricted LA and 3.1 (95% CI, 1.8 to 5.5) for widespread LA compared with surgically treated patients without LA.

A striking finding was that a large portion of the risk in surgically treated patients was due to outcome events occurring during the perioperative period (the 30 days after endarterectomy), with higher risks associated with more extensive LA (Figure 3, bars for surgically treated patients).

For patients with 50% to 99% ICA stenosis, the risk of perioperative stroke and death was 5.3% for patients without LA and 10.6% for those with restricted LA and increased to 13.9% for those with widespread LA (P=0.03, log-rank test comparing 3 risks). For patients with <50% ICA stenosis, the perioperative risk again was at its highest among patients with widespread LA (P<0.001, log-rank test comparing 3 risks). The extent of LA remained a significant independent risk factor for perioperative risk after accounting for all patient characteristics listed in Table 1 (P=0.003 for 2-df likelihood ratio test from Cox regression). The adjusted hazard ratios were 1.7 (95% CI, 0.9 to 3.1) for restricted versus no LA and 3.4 (95% CI, 1.7 to 6.6) for widespread versus no LA.

Despite the higher perioperative risk of stroke or death, endarterectomy reduced the absolute 3-year risk of ipsilateral stroke in the 50% to 99% ICA stenosis category by 11.6% (95% CI, −9.6% to 32.8%; P=0.46) for patients with widespread LA and by 7.6% (95% CI, −4.8% to 20.0%; P=0.39) for those with restricted LA, although the reductions did not reach statistical significance because of the small sample size. The absolute risk reduction with widespread LA was similar to that of patients without LA (10.9%; 95% CI, 6.7% to 15.1%; P<0.001). For patients with <50% ICA stenosis and LA, the 3-year risks of ipsilateral stroke in the surgically treated group exceeded the medically treated risks, yielding a net harm from endarterectomy.

Discussion

In this study involving the largest number of patients published in the literature with recent ischemic symptoms attributable to a diseased carotid artery and LA, the results demonstrated that LA was associated with an increased risk of stroke. This risk increased with an increasing extent of LA for both medically and surgically treated patients regardless of the degree of ICA stenosis. For surgically treated patients with widespread LA, more than a tripling in perioperative stroke and death was observed. However, compared with
medically treated patients with 50% to 99% ICA stenosis, there was a similar absolute reduction in 3-year ipsilateral stroke risk of \(\approx 10\%\) at all levels of LA. The reason for not observing a more sizeable absolute risk reduction with more extensive LA appeared to be as follows. Whereas the 3-year risk of ipsilateral stroke increased for medically treated patients, there was an approximately matching increase in the perioperative risk for surgically treated patients. The reason for the increase in perioperative risk is unknown. For patients with \(< 50\%\) ICA stenosis, endarterectomy was of no benefit and was harmful for patients with any extent of LA. Such patients should not be subjected to endarterectomy.

An increase in disabling or fatal strokes in patients with LA was observed, more so in those with extensive LA. This observation was not unexpected because LA results at least in part from previous ischemic insults, a consequence of arterioles being affected by stroke risk factors. Alteration of blood flow autoregulation has been recognized in this condition.\(^6\) During the follow-up period of the present study, only a minority of the patients experienced lacunar strokes. This was expected in this population with significant carotid stenosis whose common outcome events were large-artery strokes. Although most risk factors for strokes, old age in particular, were more prevalent in patients with LA, history of smoking and hyperlipidemia were less prevalent. The lower prevalence may be related to an early harvesting effect, whereby those who had these risk factors had already died.\(^19\)

The stroke results from the present study are consistent with previous reports that assessed LA on CT scans. In the Dutch TIA Trial, the presence of LA was associated with a 15% risk of stroke in 337 patients compared with 8.0% in 2680 patients without LA.\(^7\) In a Japanese study of 215 patients with lacunar infarctions, the 95 patients with LA had a significant increase in the risk of recurrent stroke or death.\(^8\) An Italian study of patients with any kind of motor impairment observed that the 6-year cumulative risk of stroke and myocardial infarction was 69% for the 31 patients with LA compared with only 36% for the 68 patients without LA.\(^9\) In another Italian study of 216 patients, the risk of vascular death for the 90 LA patients was almost 3-fold higher than for patients without LA.\(^10\) The present study observed an association between LA and small deep infarction, as have other studies.\(^7,9,20,21\)

In conclusion, patients with LA in the presence of 50% to 99% ICA stenosis faced a higher risk of stroke than patients without LA, whether treated medically or surgically. In all instances, the risk increased with more extensive LA. Strokes were 1.6 times more likely to occur in medically treated patients with widespread LA than without LA and 2.5 times more likely to occur in surgically treated patients with widespread LA. Nevertheless, endarterectomy reduced the risk of stroke for these patients because of the higher risk of stroke if left to medical treatment alone. Despite the presence of LA, patients with symptomatic ICA stenosis should be considered for carotid endarterectomy but must be advised that the perioperative risk facing them is twice as high in the presence of restricted LA and 3 times as high in the presence of widespread LA than for patients without LA.

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References
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