Development and Progression of Leukoaraiosis in Patients With Brain Ischemia and Carotid Artery Disease

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Background and Purpose—Leukoaraiosis (LA) or the presence of white matter changes, a frequent finding on brain CT scans of elderly individuals, is a risk factor for stroke and vascular death. The aim of the study was to seek development and progression of LA and associated risk factors in patients with symptomatic carotid artery disease.

Methods—Presence and extent of LA were determined on entry and follow-up CT scans from 685 patients in the North American Symptomatic Carotid Endarterectomy Trial.

Results—Among 596 patients without LA at entry, 107 (18.0%) developed restricted LA and 18 (3.0%) developed widespread LA during a mean follow-up of 6.1 years (range, 3.0 to 9.6 years). Older age was associated significantly with LA development ($P<0.001$). History of hypertension, diabetes mellitus, ischemic heart disease, and intermittent claudication had weak associations with LA development. During follow-up, 36.0% of patients who developed LA had 1 or more strokes, particularly of the lacunar type, in comparison to 23.5% of patients who did not develop LA ($P=0.01$). In patients who developed LA, the percentage with small deep infarcts (diameter ≤1.5 cm) increased from 34.4% on entry to 45.6% on follow-up CT scans compared with no increase (20.4% and 20.4%, respectively) in patients who did not develop LA. Among 89 patients who had restricted LA at entry, 28 (31.5%) progressed to widespread LA. Progression was associated with occurrence of strokes.

Conclusions—LA is common in elderly patients with symptomatic cerebrovascular disease. Its development and progression are associated with higher occurrence of strokes, mainly of the lacunar type. (Stroke. 2003;34:1913-1917.)

Key Words: carotid endarterectomy | leukoaraiosis | prognosis | stroke | white matter

Leukoaraiosis (LA), or the presence of diffuse white matter changes, is frequently observed on CT scans of elderly individuals, particularly those with dementia or a history of stroke or hypertension.1,2 The presence of LA is associated with an increased risk of stroke and vascular death.1,3–5 Yet not much is known about the development of LA and in particular the underlying mechanisms and risk factors. The aim of the study was to seek development and progression of LA, as well as associated risk factors, in patients with symptomatic carotid artery disease who were followed prospectively for ≥3 years.

Subjects and Methods
All patients were recruited by the North American Symptomatic Carotid Endarterectomy Trial (NASCET). This was a multicenter, randomized trial designed to determine the role of carotid endarterectomy for symptomatic patients with carotid artery disease. Full details of the trial protocol have been published.6 In brief, patients with transient or nondisabling retinal or hemispheric ischemic events and angiographically determined carotid artery disease were recruited within 180 days of their last ischemic event, provided that there was no cardiac source of embolism or any life-threatening or other disabling condition that could interfere with the interpretation of outcome events.

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. Hard copies of all angiograms and CT scans were sent to the central office, where they were reviewed independently and in a blinded fashion by the study neuroradiologist (A.J.F.). Patient follow-up consisted of examinations by a stroke neurologist at 30 days, every 3 months in the first...
year, and every 4 months thereafter. The territory and type of stroke (ischemic or hemorrhagic) occurring during follow-up were reviewed centrally. The cause of each ischemic stroke was designated as either large artery, lacunar, or cardioembolic. Lacunar strokes were defined by criteria of classic lacunar syndromes, with or without radiological deep lesions no more than 1 cm in diameter.7 Cardioembolic strokes were defined by a combination of clinical and echocardiographic criteria. Ischemic strokes without a lacunar or cardioembolic origin were classified as large-artery strokes.8

Three neurologists (J.Y.S, O.R.B, S.A.) centrally reviewed the scans for the purpose of identifying LA according to a published rating scale.9 Our first study reported no association between LA and the severity of carotid artery stenosis.2 Our second study of 2618 patients who had a good-quality entry CT scan in the NASCET identified LA as a risk factor for stroke and vascular death.6 In the present study patients were identified from the group of 2618 who had a follow-up CT scan performed ≥3 years from their time of entry, either as requested (but not mandated) by the protocol at the end of the trial (exit CT scan) or for reasons other than for the evaluation of a stroke outcome. Some participating centers did not perform any exit CT scans. Patients who were studied only by MRI at the time of follow-up were excluded from the present study because their findings were not comparable to the entry CT scans. All follow-up CT scans were reviewed blindly and rated by the same observers (J.Y.S, O.R.B, S.A.) using the same method as in the previous studies.2,5,9 In brief, LA was assessed by a scale that required separate evaluation of the anterior and posterior locations using 3 sequential CT scan slices. 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, whereas “widespread” LA involved the entire region from the lateral ventricle to the cortex. 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 cm and those with diameters >1.5 cm. Because LA was previously shown to be unrelated to the degree of carotid artery stenosis,2 the present study used the binary factor “stenosis ≥70% in either carotid artery” in all analyses.

Results

Of the 2618 patients who had good-quality CT scans available for review at entry into the NASCET, 354 had restricted and 139 had widespread LA.3 A total of 1469 patients had a follow-up CT scan, 45 had MRI only, and 1104 had no follow-up brain imaging. Of the 1469 patients, the present study focused primarily on the 596 patients who had no LA at entry and had a follow-up CT scan ≥3 years later. A secondary analysis was performed on the 89 patients who had restricted LA on their entry scan. Excluded from the present study were 33 patients who had widespread LA on both their entry and exit scans, 104 patients whose only follow-up CT scans were done because of stroke outcomes, and 647 patients whose follow-up CT scans were all done within 3 years of the entry scan. The mean time interval between the entry and follow-up CT scans for the 685 (596 + 89) patients in the present study was 6.1 years (SD 2.0; median, 6.0; range, 3.0 to 9.6 years), and there was no difference between those without LA and those with restricted LA at entry.

Among the 596 patients without LA at entry, 107 (18.0%) developed restricted LA and 18 (3.0%) developed widespread LA during follow-up. The mean time interval between the entry and follow-up CT scan for the 125 patients who developed LA was 6.4 years and was similar to the mean time interval of 6.1 years for the 471 patients who did not develop LA (P = 0.17). The most statistically significant baseline characteristic associated with LA development was age (Table 1). The mean age of patients who developed LA was 66.8 years in comparison to 62.9 years in those who did not develop LA (P < 0.001). History of hypertension, diabetes mellitus, myocardial infarction or angina, and intermittent claudication had weak associations with LA development.

History of hyperlipidemia was inversely associated. Over the course of follow-up, 36.0% of patients who developed LA had 1 or more strokes in comparison to 23.5% of patients who did not develop LA (Table 2). Even after adjustment for all baseline characteristics listed in Table 1 in a logistic regression analysis (including older age and severe carotid stenosis), patients who developed LA were 1.5 times more likely to have had a stroke (95% CI, 1.0 to 2.4). Patients who developed LA were also more likely to have multiple strokes. The distribution of stroke origin differed slightly

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Leukoaraiosis During Follow-Up, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 471)</td>
</tr>
<tr>
<td>Assaigned to carotid endarterectomy</td>
<td>50.3</td>
</tr>
<tr>
<td>Male sex</td>
<td>65.4</td>
</tr>
<tr>
<td>Age ≥65 y</td>
<td>44.4</td>
</tr>
<tr>
<td>Presenting event nondisabling stroke‡</td>
<td>41.0</td>
</tr>
<tr>
<td>Presenting hemisphere ischemic event§</td>
<td>74.5</td>
</tr>
<tr>
<td>History of smoking within past year</td>
<td>43.7</td>
</tr>
<tr>
<td>History of:</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>56.9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16.8</td>
</tr>
<tr>
<td>Myocardial infarction or angina</td>
<td>36.1</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>13.8</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>36.3</td>
</tr>
</tbody>
</table>

LA in either carotid artery

*P value computed from a chi-square statistic comparing two groups.
‡Mean age of patients: 62.9 and 66.8 years, respectively; *P value < 0.001.
§Nondisabling stroke, not transient ischemic attack.
§Hemisphere, not retinal ischemic event.

Table 2. Comparison of Groups on the Basis of Stroke Outcomes

<table>
<thead>
<tr>
<th>Number of Strokes During Follow-Up</th>
<th>Leukoaraiosis During Follow-Up, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 471)</td>
</tr>
<tr>
<td>None</td>
<td>76.5</td>
</tr>
<tr>
<td>1</td>
<td>17.6</td>
</tr>
<tr>
<td>2 or more</td>
<td>5.9</td>
</tr>
</tbody>
</table>

*P value refers to the overall association between leukoaraiosis during follow-up and number of strokes during follow-up, computed from a chi-square statistic.
There were too few stroke outcomes to analyze their cause.

Times more likely to have had a stroke (95% CI, 0.5 to 5.6).

Progression to widespread LA was associated with the occurrence of strokes. Patients who progressed were 1.7 times more likely to have had a stroke (95% CI, 0.5 to 21.1%).

Although the percentage of patients with cortical lesions increased from 34.4% to 45.6% in patients who developed LA.

The frequency of deep infarcts was similar on the entry and follow-up CT scans in patients who did not develop LA during follow-up (Table 4). In contrast, the percentage of patients with small deep infarcts (diameter ≤1.5 cm) increased from 34.4% to 45.6% in patients who developed LA. Although the percentage of patients with cortical lesions increased over the period of follow-up, the percentages were similar between the 2 groups of patients (Table 4).

Among the 89 patients who had restricted LA at entry, 28 (31.5%) progressed to widespread LA during follow-up. There were no statistically significant differences in baseline patient characteristics between the 28 patients who progressed and the 61 who did not progress to widespread LA. Progression to widespread LA was associated with the occurrence of strokes. Patients who progressed were 1.7 times more likely to have had a stroke (95% CI, 0.5 to 5.6). There were too few stroke outcomes to analyze their cause.

**TABLE 4. Findings on Entry and Follow-Up CT Scans**

<table>
<thead>
<tr>
<th>CT Scan Findings</th>
<th>Leukoaraiosis During Follow-Up, %</th>
<th>No</th>
<th>Yes</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep infarct on entry CT scan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>76.6</td>
<td>63.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter ≤1.5 cm</td>
<td>20.4</td>
<td>34.4</td>
<td>0.004*</td>
<td></td>
</tr>
<tr>
<td>Diameter &gt;1.5 cm</td>
<td>3.0</td>
<td>2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep infarct on follow-up CT scan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>77.9</td>
<td>52.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter ≤1.5 cm</td>
<td>20.4</td>
<td>45.6</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Diameter &gt;1.5 cm</td>
<td>1.7</td>
<td>2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical lesion present on entry CT scan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.4</td>
<td>13.6</td>
<td>0.31†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical lesion present on follow-up CT scan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23.4</td>
<td>27.2</td>
<td>0.37†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P value refers to the overall association between leukoaraiosis during follow-up and deep infarct, computed from a chi-square statistic.

†P value computed from a chi-square statistic comparing 2 groups.

There were no apparent differences in the distribution of deep infarcts between the entry and follow-up CT scans in patients who did and did not progress.

**Discussion**

The present study showed that 21.0% of the patients with symptomatic carotid artery disease at a mean age of 64 years developed LA over an average of 6.1 years, and 31.5% progressed from restricted to widespread LA. The development of LA was associated with a higher frequency of multiple strokes, particularly of the lacunar type. This is the first study to report on the development and progression of LA as well as on the clinical outlook for patients exhibiting this lesion during a long follow-up period. The importance of the observations is strengthened by the fact that the acquisition of follow-up CT scans was not related to stroke outcomes.

A previous small study on the natural history of LA reported similar results. Twenty-six percent of 107 stroke patients who were followed for 3 years had LA progression on brain CT scans (average rate of 8.7% per year). However, these results are difficult to interpret because 15% of the patients had LA at study entry. A 3-year brain MRI study of an elderly cohort reported 17.9% progression of white matter hyperintensities, which was not associated with any clinical symptoms. The present study observed an average rate of development of 3.5% per year and progression of 5.2% per year. As supported by the present study, it is known that the extent of LA is related to age, and its prevalence on CT scans in patients with symptomatic cerebrovascular disease is approximately 15% to 20%. The association between small deep infarcts and LA development is not surprising because deep infarcts, lacunar strokes, and even silent infarcts are known to be associated with LA and may share a common mechanism of small-artery disease. In conclusion, LA is common in elderly patients with symptomatic cerebrovascular disease. Its development and progression are associated with higher occurrence of strokes, mainly of the lacunar type.

**Acknowledgments**

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The Progression of Leukoaraiosis

Leukoaraiosis (LA), the presence of rarefaction of the white matter originally described on CT\(^1\) but now more commonly recognized on MRI, was originally largely ignored as an inconsequential finding seen in association with cerebrovascular disease. More recently, it has become clear that LA impairs cognition.\(^2\) When LA is sufficiently prominent to be seen on CT, its associated cognitive impairment is readily detected. When seen only on MRI, a more sensitive technique, more sensitive cognitive tools are needed.\(^3\) At least as important is the effect of one cognitive disorder to accelerate another, and LA may causally accelerate the progression of Alzheimer disease, for example.\(^4\) LA is therefore not the unimportant phenomenon it was once considered.

LA encompasses a wide range of histological changes ranging from local edema\(^5\) to demyelination, loss of axons and oligodendroglia, and mild reactive gliosis without cavitation but does not include frank infarction. The mechanism is not considered to be chronic low perfusion as cerebral blood flow in affected areas lies within normal limits at rest or is modestly decreased in proportion to tissue loss. There is, however, clear evidence of diminished perfusion reserve.\(^6,7\) and it is hypothesized that episodic mild ischemia occurs as a result of intermittent changes in cerebral perfusion pressure. The process has been termed “incomplete infarction.”\(^8\) That extensive areas of LA may be seen without local evidence of completed ischemic events has led to the suggestion that part of the mechanism may be increased blood-brain barrier permeability leading to leakage of serum proteins, which are known to be toxic.\(^9\)

Its new-found importance means that LA has been investigated to only a limited extent. NASCET has already shown that LA is not associated with carotid stenosis but that it is a risk factor for stroke.\(^10\) While NASCET used only CT and did not assess cognition, the data presented in the accompanying article by Streifler et al are invaluable for 2 reasons. The first is the very long follow-up available with a mean of 6.4 years, which is double that of the closest previous data. They have shown that 21% of those without LA at entry developed this during the study and that 31.5% of those with LA at entry deteriorated from this point of view. These data will be of great use in determining sample sizes for future studies of the prevention of progression of LA.

Of at least equal importance are the insights into the etiology of LA that the study provides. These are striking by their relative absence in that the traditional risk factors such as age, hypertension, and diabetes are all identified but are remarkably weak. If traditional vascular risk factors offer only part of the explanation for LA, where might the rest of the explanation be found?

One possible explanation comes simply from the study design. The study was concerned primarily with carotid stenosis and did not look in detail at dysrhythmias or other causes of episodic hypotension, which are one postulated mechanisms by which LA might develop.\(^11\) Clearly, if a risk factor was not studied, then its effects cannot be analyzed. Curious in this regard is the previously demonstrated lack of association of carotid stenosis with LA; if episodic hypoperfusion truly was a mechanism by which LA develops, it would be expected that the territory supplied by severely stenosed carotids would be especially vulnerable, and yet this is not the case. This mechanism may therefore be weaker than has been supposed and in any case is certainly not yet proven.

The other insight comes from Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL).\(^12\) This is numerically unimportant when set against the total burden of cerebrovascular disease but is important because it shows that specific diseases of small vessels causing progressive occlusion can and do exist. Furthermore, there may well be at least 2 such conditions since an autosomal recessive condition associated with lumbago and alopecia has been described in Japan.\(^13\) It is the common experience of practicing neurologists that from time
to time they see patients with considerable LA in the absence of much in the way of vascular risk factors. The converse is also true, that patients are seen with extensive risk factors, particularly hypertension, but who have little if any LA. These observations can be tied together by the hypothesis that the ability of patients’ small deep arteries to resist the consequences of hypertension and other risk factors varies; CADASIL is an extreme, but buried within the general non-CADASIL population there may well be other single-gene causes of “fragile” vessels or polygenetic factors producing a continuum of susceptibility. Given that LA predicts lacunar stroke, cognitive decline, and dementia and that it is common, the time is now ripe to look pathologically and genetically at patients with LA (and those with extensive risk factors but no LA) with a view to identifying and ultimately treating 1 or more as yet unrecognized conditions affecting small cerebral arteries.

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References
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