What Is the Significance of Leukoaraiosis in Patients With Acute Ischemic Stroke?

Malgorzata Wiszniewska, MD; Gérald Devuyst, MD; Julien Bogousslavsky, MD; Joseph Ghika, MD; Guy van Melle, PhD

Background: Leukoaraiosis (LA) may have specific clinical correlates in patients with stroke, but this is not well investigated, so that the significance of LA in patients with stroke remains unclear.

Methods: In a study of 2289 patients with a first-ever acute ischemic stroke, LA was noted in 149 by the use of baseline computed tomography of the brain. These patients were compared with the non-LA group. Statistical tests, including Fisher exact test or a $\chi^2$ test, were used to compare variables, and a multivariate approach using stepwise logistic regression was performed.

Results: Patients with LA were significantly older (73.7 vs 62.7 years; $P<.001$), and had a higher incidence of hypertension (72.5% vs 47.1%; $P<.001$) and subcortical or lacunar infarction (40.3% vs 25.4% and 21.5% vs 8.0%, respectively; $P<.001$) on neuroimaging studies, compared with the non-LA group. The most common cause of stroke in the LA group was presumed to be small-artery disease associated with hypertension (46% vs 13.5% in the non-LA group). Age and hypertension were very strongly associated with LA (respective odds ratios [95% confidence intervals], 1.06 [1.04-1.08] and 2.33 [1.60-3.39]). In addition to these risk factors, a close relationship was found between LA and nonsevere stenosis (<50%) of the internal carotid artery (odds ratio, 2.23 [95% confidence interval, 1.32-3.76]), although the significance of this association remains speculative. The outcome at 1 month after stroke was similar in both groups.

Conclusion: Our results provide further evidence that LA is related primarily to small-vessel disease.

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Leukoaraiosis (LA) is a term used to describe radiological abnormalities seen in the computed tomography (CT) of the brain in elderly patients as bilateral areas of hypodensity in the white matter of the cerebral hemispheres. This nonspecific radiological sign is also shown by magnetic resonance imaging (MRI) findings. Leukoaraiosis may be associated with cognitive dysfunction in nondemented elderly subjects, but is also found in patients with Alzheimer disease, vascular dementia, and stroke. Hypodensity of the cerebral white matter can also be found in some healthy elderly subjects. The clinical relevance and pathogenesis of LA remain unclear. Results of pathological studies consistently linked LA with demyelination, gliosis, necrosis, and cavitation, which are associated with atherosclerosis of small or large vessels. Similar pathologic features are found in arteriosclerotic vascular encephalopathy, orBinswanger disease. Opinions differ regarding the outcome of stroke in patients with LA. Although most authors agree about the major role of hypertension in LA, conflicting opinions prevail concerning the potential causality of cardiac disease or diabetes mellitus. However, all authors agree that frequency of LA increases with age. Our study was designed to elucidate the relationship between risk factors, atherosclerosis of extracranial arteries visualized using Doppler sonography, causes and features of stroke, and early stroke outcome in patients with acute ischemic stroke (AIS) and coexisting LA.

For editorial comment see page 925

RESULTS

Patients

From January 1, 1979, through December 31, 1996, 155 (6.8%) patients from the LSR were found to have LA, 149 (96.1%) with AIS and only 6 (3.9%) with hemorrhagic stroke. Those 149 patients with AIS and LA were compared with the 2140 patients with AIS without LA.
PATIENTS AND METHODS

PATIENTS

Patients were obtained from the Lausanne Stroke Registry (LSR) from January 1, 1979, through December 31, 1996. The LSR is a hospital-based registry, details of which have been reported elsewhere.\(^{25}\) Registered patients underwent routine examination using CT within 7 days of stroke (\(\leq 5\) examinations), Doppler ultrasonography with spectral analysis, 12-lead electrocardiography, 3-lead electrocardiography for at least 12 hours, and standard blood tests. Further investigations (eg, catheter angiography, 2-dimensional transthoracic or transesophageal echocardiography, and electrocardiographic Holter monitoring) were performed selectively. All patients with LA presenting with an AIS were included in the study. Leukoaraiosis was defined as bilateral, symmetrical diffuse or patchy abnormalities in the white matter around the frontal horn and/or the posterior part of the lateral ventricles (parieto-occipital) and in the centrum semiovale, ie, as poorly delineated low-density areas seen by means of CT findings (Figure 1, left), or as areas of high-signal intensity on T2-weighted MRI of the same region (Figure 1, right).\(^{1,10,13,15,22}\) An area was considered hypodense if its density was between those of normal white matter and cerebrospinal fluid. Only patients with clear-cut hypodensity of the white matter on CT or MRI findings were defined as having LA; purely periventricular lucencies were excluded.

METHODS

For all patients, risk factors such as age, sex, hypertension (blood pressure \(>160/90\) mm Hg on at least 2 measurements), diabetes mellitus, regular cigarette smoking (at least 5 cigarettes/d), hypercholesterolemia (fasting cholesterol level \(>6.5\) mmol/L [\(>250\) mg/dL]), history of cardiac disease, intermittent claudication, and history of transient ischemic attack were considered. Leukoaraiosis was advocated when carotid atherosclerotic plaques were present with a stenosis of less than 50% of lumen diameter reduction. (3) Small-artery disease was considered a potential cause of stroke (lacunar infarct) when the patient had long-standing hypertension, the infarct was limited to the territory of a deep perforating branch (brainstem and thalamic perforators), and the largest diameter of the infarction on MRI did not exceed 15 mm. (4) Atherosclerotic disease was advocated when carotid atherosclerotic plaques were present with a stenosis of less than 50% of lumen diameter reduction. (5) Other causes of stroke including coagulopathies, arterial dissection, and uncommon syndromes. (6) Cause of stroke was undetermined.

The functional status 1 month after stroke onset was measured using a 5-point scale, with 1 indicating no disability; 2, mild disability (return to all activities, although with difficulty); 3, moderate disability (return to daily activities with difficulty); 4, severe disability (impossible to return to daily activities); and 5, death. Patients with combined AIS and LA were compared with those without LA who were treated during the same time interval.

STATISTICAL METHODS

The distribution of risk factors in patients with AIS was compared between those with and without LA. Variables were compared using the Fisher exact test for dichotomous factors or a \(\chi^2\) test when more than 2 categories were present. Age distributions were compared by means of the Wilcoxon rank-sum test. To determine which factors were significantly associated with the presence of LA in a multivariate approach, a stepwise logistic regression was used in which all the risk factors significantly associated with LA and the Doppler finding were estimated. The factors remaining in the model and the odds ratios and corresponding 95% confidence intervals are given.

during the study interval. Table 1 shows the main characteristics of these patients.

RISK FACTORS

The risk factor profile for patients with or without LA is shown in Table 1. Patients in the LA group were older than those in the non-LA group (73.7 vs 62.7 years; \(P<.001\)), with a range considerably smaller for LA patients (<50%), moderate (50%-90%), or marked (>90%, including occlusion) stenosis.

Infarct topography was classified according to vascular territories, using templates developed in the LSR, ie, supratentorial (territory of the medial cerebral artery, anterior cerebral artery, or posterior cerebral artery), subcortical, multi-infarct, subcortical, or border zone.\(^{21}\) Diagnostic criteria for stroke mechanisms and etiology have been published elsewhere, as well as the general findings of the LSR.\(^{25}\) In summary, patients with stroke were divided by cause into the following etiologic groups: (1) Large-artery disease (artery-to-artery embolism or hemodynamic-related hypoperfusion) was related to atherosclerotic stenosis (>50% of lumen diameter reduction) of ICAs, VAs, and the basilar artery. (2) The cardiac sources of stroke included atrial fibrillation, sick sinus syndrome, severely reduced left ventricular function (or regional wall akinesia after myocardial infarction), intracardiac thrombi or tumors, right-to-left shunts, wall aneurysms, prosthetic aortic or mitral valves, and endocarditis. (3) Small-artery disease was considered a potential cause of stroke (lacunar infarct) when the patient had long-standing hypertension, the infarct was limited to the territory of a deep perforating branch (brainstem and thalamic perforators), and the largest diameter of the infarction on MRI did not exceed 15 mm. (4) Atherosclerotic disease was advocated when carotid atherosclerotic plaques were present with a stenosis of less than 50% of lumen diameter reduction. (5) Other causes of stroke including coagulopathies, arterial dissection, and uncommon syndromes. (6) Cause of stroke was undetermined.

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hematocrit levels, ischemic heart disease, atrial fibrillation, or a history of transient ischemic attack between groups. Patients with LA had a significantly higher prevalence of diabetes mellitus (22.8% vs 15.1%; Table 1). Intermittent claudication was less frequent in the LA than in the non-LA group (2.0% vs 6.4%; \( P = .03 \)); the former group also contained significantly fewer smokers (16.1% vs 29.7%; \( P < .001 \)).

### NEUROLOGIC SYMPTOMS

The incidence of pure hemiparesis or isolated ataxia was significantly higher in the LA group (53.0% or 6.7% vs 30.1% or 2.7% in the non-LA group). These symptoms are typical for lacunar infarcts, which were diagnosed in 21.5% of the LA group and in only 8.0% of the non-LA group. A statistically significant lower number of patients with LA had combinations of symptoms (\( P = .001 \)), i.e., motor plus sensory deficit (14.1% vs 23.6%) or sensory-motor deficit plus hemianopia (5.4% vs 12.4%). Isolated hemianopia was not seen in patients with LA. A smaller percentage of patients with LA presented with aphasia (global and sensitive), whereas a higher percentage had dysarthria; the difference was not statistically significant (\( P = .07 \)). There was no difference in frequency of agnosia or apraxia between groups.

### OUTCOMES

Outcomes for patients with and without LA are shown in Table 2. A good outcome (no or mild disability) was seen in 62.5% of the LA group compared with 64.5% in the non-LA group. A poor outcome (severe disability or death) was comparatively lower in the LA group (6.7% vs 11.9%), but the difference was not statistically significant (\( P = .15 \)). The outcome was independent of the territory of infarct (\( \chi^2 \) test, \( P = .16 \)).

### VASCULAR TERRITORY OF INFARCTION

The topography of ischemic strokes is essentially constituted by supratentorial infarcts in the LA (61.7%) and non-LA groups (71.2%), but the frequencies in superficial and subcortical infarctions were quite different between groups. Indeed, superficial ischemic strokes were found in 21.5% and 45.8% of the LA and non-LA groups, respectively; subcortical ischemic strokes, 40.3% and 25.4% of the LA and non-LA groups, respectively. These differences were statistically significant (\( P < .001 \)). Another significant difference between LA and non-LA groups was the prevalence of multi-infarct, which was found in 21.5% and 8.0% of the groups, respectively. No differences were seen between infarcts in the subtentorial region (15.4% of the LA group vs 18.5% of the non-LA group) or in border zones (1.3% of the LA group vs 2.3% of the non-LA group).

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**Table 1. Characteristics of Patients With AIS With and Without LA**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LA (n = 149)</th>
<th>Non-LA (n = 2140)</th>
<th>( P )†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>73.7</td>
<td>62.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>77 (51.7)</td>
<td>803 (37.5)</td>
<td>.01</td>
</tr>
<tr>
<td>Male</td>
<td>72 (48.3)</td>
<td>1337 (62.5)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>108 (72.5)</td>
<td>1007 (47.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>24 (16.1)</td>
<td>636 (29.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>34 (22.8)</td>
<td>324 (15.1)</td>
<td>.02</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>32 (21.5)</td>
<td>578 (27.0)</td>
<td>.15</td>
</tr>
<tr>
<td>Hematocrit above 0.45</td>
<td>22 (14.8)</td>
<td>342 (16.0)</td>
<td>.80</td>
</tr>
<tr>
<td>History of transient ischemic attack</td>
<td>38 (25.5)</td>
<td>419 (20.0)</td>
<td>.09</td>
</tr>
<tr>
<td>Cardiac ischemic history</td>
<td></td>
<td></td>
<td>.50</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>23 (15.4)</td>
<td>247 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction and cardiac insufficiency</td>
<td>7 (4.7)</td>
<td>162 (7.6)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>20 (13.4)</td>
<td>243 (11.4)</td>
<td>.40</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>3 (2.0)</td>
<td>137 (6.4)</td>
<td>.03</td>
</tr>
</tbody>
</table>

*LA indicates acute ischemic stroke; LA, leukoaraiosis. Unless otherwise indicated, data are given as number (percentage) of patients.
†Fisher exact test for dichotomous factors and a \( \chi^2 \) test when more than 2 categories existed. Age was compared by the Wilcoxon rank-sum test.
CAUSES OF ISCHEMIC STROKE

Causes of ischemic stroke included large-artery disease, cardioembolic origin, small-vessel disease, atherosclerotic disease, rare causes, and undetermined causes in 11.5%, 11.0%, 46.0%, 13.0%, 7.5%, and 11.0% in the LA group, respectively, and 20.0%, 26.0%, 13.5%, 11.0%, 14.0%, and 15.5% in the non-LA group, respectively.

CARDIAC FINDINGS

Cardiac findings are summarized in Table 3. Similar results were seen between groups for all findings except left ventricular hypertrophy. Signs of left ventricular hypertrophy were present in 22 (14.8%) of 149 patients in the LA group, but in only 150 (7.0%) of 2140 in the non-LA group (P = .002).

DOPPLER ULTRASOUND OF THE ICAS AND VAS

Doppler ultrasound was performed on all 149 patients with AIS (Table 4 and Table 5). The most frequent finding was a mild stenosis (<50%) of both ICAs. Table 5 reveals a highly statistically significant (P < .001) difference between LA and non-LA groups due mainly to a higher percentage of mild ICA stenosis (<50%) and a remarkably low percentage of marked ICA stenosis (>90% and occlusion) in the LA compared with the non-LA group. As discussed in the multivariate analysis, mild ICA stenosis is a major discriminator between LA and non-LA groups.

MULTIVARIATE LOGISTIC REGRESSION ANALYSIS

A stepwise logistic regression was used to evaluate the risk of LA based on all the significant factors (Table 1) and the Doppler ultrasound findings (Table 5). Age, sex, hypertension, diabetes mellitus, smoking, and mild stenosis of the ICA were used in the model. Sex, smoking, and diabetes mellitus were excluded, which should be interpreted as meaning that their contribution is probably non-significant in the presence of the other factors, as a result of our findings that only age, hypertension, and mild ICA stenosis have significant correlation with LA (Table 6). Hypertension and mild stenosis have very similar statis-
Our study shows similar results concerning the association of LA with age, but not with sex. As in the Copenhagen Stroke Study and that of Fazekas and coworkers, our study showed women with LA to be older than men with LA; therefore, it is age, and not sex, that is related to LA.

We also observed that factors other than age were correlated with LA. An important relationship was found between LA and 2 other risk factors, ie, hypertension and mild stenosis in the ICAs. In our study, both risk factors were independent, but when associated, there was significant correlation between hypertension and LA. Furthermore, a clear relationship was also found between LA and mild stenosis of the ICAs (<50%), as diagnosed using results of Doppler ultrasound examination (odds ratio, 2.23 [Table 6]). This latter association occasionally has been reported in the literature. In 1988, Fazekas et al suggested that obstructive extracranial carotid artery disease therefore did not seem to play a role in the development of WMLs on MRI with aging. Heindel et al also reported no correlation between angiographically documented severe stenoses of extracranial carotid arteries and white matter hyperintensities on MRI in subjects with overt cerebrovascular disease. However, the association between WMLs on MRI and mild extracranial carotid artery disease as found by Fazekas et al and in our study led to 3 considerations. First, as proposed by Fazekas et al and Mohr and Pessin, our study led to 3 considerations. First, as proposed by Fazekas et al and Mohr and Pessin, this association could signify a higher risk for stroke in people with these unilateral plaques to bilateral stenoses of up to 50% of the vessel diameter in subjects with white matter lesions (WMLs), whereas higher-grade carotid stenoses were not detected in subjects with WMLs on MRI. Fazekas et al also reported no correlation between angiographically documented severe stenoses of extracranial carotid arteries and white matter hyperintensities on MRI in subjects with overt cerebrovascular disease. However, the association between WMLs on MRI and mild extracranial carotid artery disease as found by Fazekas et al and in our study led to 3 considerations. First, as proposed by Fazekas et al and Mohr and Pessin, this association could signify a higher risk for stroke in people with these...

Table 4. Extracranial Cerebral Artery Disease in Patients With AIS and Leukoaraiosis*

<table>
<thead>
<tr>
<th>Artery</th>
<th>Doppler Ipsilateral</th>
<th>Doppler Contralateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA normal with VA normal</td>
<td>19 (12.8)</td>
<td>25 (16.8)</td>
</tr>
<tr>
<td>ICA stenosis &lt;50% with VA normal</td>
<td>92 (61.7)</td>
<td>92 (61.7)</td>
</tr>
<tr>
<td>ICA stenosis 50%-90% with VA normal</td>
<td>5 (3.4)</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>ICA stenosis &gt;90% with VA normal</td>
<td>7 (4.7)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>ICA normal with minor VA abnormality</td>
<td>21 (14.1)</td>
<td>26 (17.4)</td>
</tr>
<tr>
<td>ICA normal with major VA abnormality</td>
<td>5 (3.4)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* AIS indicates acute ischemic stroke; ICA, internal carotid artery; and VA, vertebral artery.

Table 5. Comparison of Doppler Ultrasonographic Findings Between Patients With AIS With and Without LA*

<table>
<thead>
<tr>
<th>Artery</th>
<th>Doppler Ipsilateral, No. (%) of Patients</th>
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<tr>
<td>ICA normal with VA normal</td>
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* AIS indicates acute ischemic stroke; LA, leukoaraiosis; ICA, interval carotid artery; and VA, vertebral artery. Overall χ², P < .001.

Table 6. Multiple Logistic Regression Analysis of the Influence of Age, Hypertension, and Mild ICA Stenosis on Incidence of Leukoaraiosis*

<table>
<thead>
<tr>
<th>Factors</th>
<th>Leukoaraiosis, OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06 (1.04-1.08)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.33 (1.60-3.39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stenosis ICA &lt;50%</td>
<td>2.23 (1.32-3.76)</td>
<td>.003</td>
</tr>
</tbody>
</table>

* OR indicates odds ratio; CI, confidence interval; and ICA, internal carotid artery.

Figure 3. Calculated probability of leukoaraiosis with age.
MRI findings, because minor vessel wall lesions suffice to promote a cerebrovascular event. Second, the difference for age between patients with and without LA could constitute a biased patient selection. Patients with stroke and severe carotid atherosclerotic disease being significantly younger, MRI of the brain cannot reveal WMLs as observed in older patients. Third, another but more speculative mechanism could be that cerebral small arteries in subjects with severe atherosclerosis of the carotid and major cerebral arteries may have been protected from extensive loss of medial smooth muscles as proposed by Masawa et al25 in a study of 121 autopsied brains. The hypothesis of Masawa et al,32 that patients with severe carotid atherosclerosis could avoid wall damage of intracerebral arteries although they had clinical hypertension, is based on the following 2 possible mechanisms: (1) inhibition of medial necrosis by hyperlipidemia (mechanism still unclear) and (2) decreased tensile stress of the wall associated with reduced blood perfusion due to severe atherosclerotic ICA stenosis. However, the hypothesis of Masawa et al25 remains speculative, whereas capsular lacuna can be found in patients with severe internal carotid stenosis.33 Another consideration is the association of WMLs on MRI with lacunar stroke, which is well established but was observed to be variable,34 suggesting that WMLs and lacunar infarct could be due to different mechanisms. Nevertheless, the marked progression of WMLs in connection with lacunar stroke suggests a similar underlying vasculopathy.35 Nearly half of the strokes in our LA group were attributed to lacunar infarcts, whereas, as observed in our patients with stroke and LA, Boiten et al36 showed that patients with lacunar infarct had significantly lesser degrees of ICA stenoses in comparison with patients with nonlacunar infarct. The recent study of Mantyla et al37 revealed that patients with lacunar infarcts more often had moderate or severe WMLs than patients with cortical infarctions. Moreover, their study reported that the difference in the extent of WMLs in patients with lacunar compared with nonlacunar infarcts was highly significant. These observations support the view that small-vessel disease is the common underlying abnormality behind lacunar lesions and WMLs.38

In contrast to previous reports,12,23,24 but in agreement with observations of Tarvonen-Schroder,13 Miyao,11 and van Swieten14 et al, we found no relationship between LA and myocardial ischemia. Similarly, we found no relationship between LA and intermittent claudication, the latter being even less frequent in the LA group. In our study, in contrast to the findings of Jorgensen et al,10 we found no relationship between LA and atrial fibrillation. Furthermore, very few of the patients in the LA group were smokers. Our study shows that among all cerebrovascular risk factors, arteriosclerosis of the ICA plays the most important role in the potential cause of LA.

Contrary to the findings of van Zagten et al,13 our study showed that diabetes mellitus was more frequent in patients with LA. Although this relationship was not seen in logistic regression analyses, it remains possible that diabetes mellitus may play a role in LA through small-vessel disease. Ylikoski and coworkers44 found that, in patients aged 56 to 72 years, MRI periventricular hyperintensity significantly correlated with diabetes mellitus. Further studies are needed to make this point clearer.

Leukoaraiosis has been reported to be associated with Binswanger disease.19,20,22 In our study, the most frequent ischemic lesions in patients with LA were found in subcortical white matter, followed by lacunar lesions. In our study, early functional stroke outcome was not influenced by the presence of LA. This is in agreement with Jorgensen and coworkers,10 but contrasts with a study of 215 patients with stroke and lacunar infarct, in whom a poorer prognosis was reported for patients with LA in terms of mortality and daily living activities.17 In our study, the incidence of death was lower in the LA than in the non-LA group. Our study confirms that LA in patients with stroke does not cause a poorer progressive factor for daily living activities. Although our study highlights specific correlates of LA in patients with acute stroke, it also underlines the absence of suggestive clinical findings or prognostic consequences associated with LA soon after stroke.

In conclusion, LA does not aggravate the outcome of stroke. Hypertension and age seem to be major risk factors for LA. Patients with LA and stroke had significantly more lacunar strokes and mild ICA stenoses (<50%). These findings provide further evidence of the concept that LA is primarily related to small-vessel rather than large-artery disease.

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REFERENCES


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