Leukoencephalopathy in Patients With Ischemic Stroke

J. Bogousslavsky, MD, F. Regli, MD, and A. Uske, MD

Thirty-one (16 women, 15 men; mean age 68 years) of 1,000 consecutive patients with an ischemic stroke investigated systematically with computed tomography (CT), Doppler, electrocardiography (ECG), and biological tests had a diffuse hypodensity of the cerebral hemispheric white matter on CT, a sign indicative of leukoencephalopathy. In 25 of the 31 patients, the acute infarct was deep. Leukoencephalopathy was more frequent in patients with a deep infarct (8%) than in patients in whom the cortex was involved (0.8%) (p<0.01). A history of progressive intellectual impairment (23%) and the finding of a mild or moderate impairment, or severe dementia (84%) were more frequent in study patients (p<0.05) than in 31 sex- and age-matched controls with an acute infarct of same size and topography but without leukoencephalopathy. A history of hypertension (81%) and high blood pressure on admission (166 ± 19/96 ± 12 mm Hg) were the most common risk factors and were more frequent in study patients (p<0.05) than in controls. On the other hand, study patients had a <50% stenosis or occlusion of the carotid artery (13%) less often than controls (35%) (p<0.05). Diabetes (23%), elevated blood cholesterol (13%), hematocrit >45% (23%), smoking (32%), and myocardial ischemia by history or ECG (45%) did not differ. These findings suggest that hypertension may be more strongly associated with leukoencephalopathy than with deep infarcts. In acute stroke patients, leukoencephalopathy on CT should not be considered a fortuitous finding.

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Binswanger1 in 1894 reported 8 cases of what he termed "encephalitis subcorticalis progressiva," in which white matter changes were prominent and attributed to vascular changes. The clinical picture associated a slow mental deterioration with "apoplectic attacks." The concept of Binswanger's disease has since been used to describe a leukoencephalopathy (LE) of the elderly with chronic hypertension, which has been related to progressive arteriosclerosis involving the deep medullary branches in the white matter of the cerebral hemispheres.2-4 Recently, patients with a suggestive clinical picture who showed hypodense hemispheric white matter on computed tomography (CT) have been diagnosed to have Binswanger's disease, sometimes with pathologic verification.5-11 However, the neuropathologic findings (gliosis, demyelination, and chronic edematous changes often intermingled with small infarcts and cysts) are not specific.12-14 For this reason, Binswanger's disease as a clinicopathologic entity has been questioned,15,16 and it has been suggested that the condition does not differ from multi-infarct dementia with multiple lacunes.4,15 Moreover, a diffuse hypodensity of the white matter on CT has been reported in normotensive, apparently healthy people17-19 as well as in patients with proven Alzheimer's disease in the absence of significant cerebrovascular changes.18-20 However, although the finding of diffuse lucency of the cerebral white matter on CT may be fortuitous in some patients and reflect only an aging process,18 the same finding in a subpopulation of patients with specific cerebrovascular problems may bear a clinical significance. We have evaluated the significance of diffuse lucency of the white matter on CT in patients admitted to our department for an acute ischemic stroke.

Subjects and Methods

All patients with diffuse hypodensity in the hemispheric white matter among the last 1,000 patients admitted following ischemic stroke were selected from our stroke data registry. All patients with stroke were investigated using a standard protocol including CT, Doppler ultrasound with frequency spectral analysis, electrocardiography (ECG), fasting blood cholesterol, and other screening blood analyses. The following parameters could be assessed in the patients with LE: vascular risk factors such as hypertension, diabetes mellitus, cigarette use, ischemic heart disease, cardiac dysrhythmia; previous stroke, transient ischemic attack (TIA), myocardial infarction; blood pressure on admission; clinical findings; ischemic heart disease and dysrhythmia on ECG; topography of cerebral infarcts on CT; and patency of the carotid arteries on Doppler ultrasound.

A diagnosis of LE was made when two investigators independently found that the white matter of the cerebral hemispheres, including not only the periventricular white matter but also the core of the centrum semiovale, was hypodense on CT. Patients with multiple sclerosis, history of acute anoxia, radiation LE, leukodystrophy, and other known nonvascular causes of LE

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were found. For Doppler ultrasound, 5 categories of findings on the internal carotid artery were used: 0–49% stenosis of the lumen diameter, 50–74% stenosis, 75–89% stenosis, 90–99% stenosis, and occlusion.

Mental status (orientation, memory, language, constructional ability, abstraction, and calculation) was assessed systematically in all patients with an acute stroke admitted to our service using a standard battery of tests. Four categories of neuropsychological impairment were used, based on cognitive deficit and interference with independent living: no impairment, mild impairment (cognitive deficit but no interference with activities of daily living), moderate impairment (some disability due to cognitive impairment), and severe dementia (unable to perform activities of daily living).

To assess the role of risk factors in the genesis of LE, a retrospective case–control study was performed. The control group consisted of sex- and age- (± 2 years) matched patients with ischemic stroke, who were thereafter matched for topography and size of the acute cerebral infarct on CT. This matching eliminated the bias due to the selective impact of some risk factors on the location of cerebral infarction; for instance, patients with small deep infarcts are more often expected to be hypertensive than patients with cortical infarcts. Thus, the controls were the same age and sex, with an acute cerebral infarct similar to that of the study patients, but without LE on CT. Statistical analysis was completed using the χ² test, Fisher’s test, and analysis of variance.

Results

Sixteen women and 15 men (mean age 68 years, not different between sexes) displayed LE, a diffuse hypodensity in the hemispheric white matter in all patients, which predominated anteriorly (15 patients) more often than posteriorly (2 patients).

Clinical Characteristics

The presenting stroke was in the deep middle cerebral artery (MCA) territory in 21, the superficial MCA territory in 4, the brainstem in 2, the thalamus in 2, the superficial posterior cerebral artery (PCA) territory in 1, and the complete PCA territory in 1 patient. Twelve study patients had suffered previous cerebrovascular events consisting of carotid stroke in 6, vertebrobasilar stroke in 2, and isolated TIAs in 4. Seven study patients complained of progressive memory and intellectual impairment that developed over 1–2 years. One of these 7 study patients, plus another study patient without mental deterioration, also had gait disturbances that progressed over the year before admission. On admission, 13 study patients had the following clinical features of a lacunar syndrome: pure motor hemiparesis (6), ataxic hemiparesis (3), pure sensory stroke (3), and nonproportional pure motor hemiparesis (1). Four study patients had features compatible with a "lacunar state:” involuntary laughing and crying in 2, marche à petits pas in 2, and bilateral facial or lingualopharyngeal weakness in 2. One study patient had urinary incontinence. No study patient had parkinsonian features, but 2 had dystonic posturing of the upper limbs as a consequence of the presenting stroke. Neuropsychological testing showed normal results for age in only 5 study patients; 9 were mildly impaired, 14 moderately impaired, and 3 severely demented. These findings differed strikingly from those among the controls, who showed normal results in 17, mild impairment in 8, moderate impairment in 4, and severe dementia in 2 (p < 0.01). Also, none of the controls had a history of recent progressive mental impairment (p < 0.05).

On CT, 11 study patients had > 1 infarct (8 patients had 2, 2 patients had 3, and 1 patient had 4). Eighty percent of the infarcts were deep while 20% involved the cerebral cortex. In the total group of 1,000 patients with ischemic stroke, LE was more frequent in the 230 patients in whom the stroke was due to a deep infarct (8%) than in the 770 patients in whom the stroke was due to a superficial or global infarct (0.8%) (p < 0.0001).

Risk Factors

The risk factors are summarized in Table 1. Hypertension was the main risk factor (81%) and the only risk factor that was more frequent in the study patients than in the controls (p < 0.05). On history, elevated blood pressure had been present for 12 ± 7 years in the 25 study patients with hypertension; this did not differ from the 13 controls with hypertension (11 ± 6 years). Blood pressure on admission was 166 ± 19/96 ± 12 mm Hg in the study patients vs. 156 ± 14/85 ± 8 mm Hg in the controls (p < 0.05). In patients with known hypertension, there was a moderate difference in the blood pressure on admission between the study patients (170 ± 17/99 ± 10 mm Hg) and the controls (166 ± 19/95 ± 14 mm Hg), but this was not significant. The duration of diabetes mellitus did not differ between the study patients (13 ± 5 years) and the controls (12 ± 7 years).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Study Patients</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension*</td>
<td>25 (81%)</td>
<td>13 (42%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>7 (23%)</td>
<td>6 (19%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cigarette smoking*</td>
<td>10 (32%)</td>
<td>13 (42%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia†</td>
<td>4 (13%)</td>
<td>3 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit &gt; 45%</td>
<td>7 (23%)</td>
<td>10 (32%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Old myocardial infarct‡</td>
<td>2 (6%)</td>
<td>2 (6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Isolated angina</td>
<td>6 (19%)</td>
<td>5 (16%)</td>
<td>NS</td>
</tr>
<tr>
<td>ST-T changes on ECG</td>
<td>9 (29%)</td>
<td>12 (39%)</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation§</td>
<td>3 (10%)</td>
<td>4 (13%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*By history.
†> 6.5 mmol/l (fasting).
‡Older than 6 months in all patients.
§By history or on electrocardiogram.
Table 2. Internal Carotid Artery Doppler for Patients With Leukoencephalopathy and Controls

<table>
<thead>
<tr>
<th>Study patients</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or &lt; 50% stenosis</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>50–74% stenosis</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>75–99% stenosis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Occlusion</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Doppler Findings in the Internal Carotid Artery

Only 4 study patients showed a ≥ 50% stenosis or an occlusion of the internal carotid artery, which was unilateral in all cases (Table 2). Compared with the controls, the study patients less often had a ≥ 50% stenosis or occlusion of the internal carotid artery (p < 0.05). No case with reversed ophthalmic flow and normal internal carotid artery signal (suggesting intracranial carotid obstruction) was encountered.

Discussion

Our results suggest that in patients with an acute ischemic stroke, the finding on CT of diffuse lucency in the white matter of the cerebral hemispheres is usually not fortuitous, and that it may be associated with a particular subgroup of patients with specific risk factors. The role of chronic hypertension in the pathogenesis of vascular LE has been emphasized previously in patients with progressive dementia who showed periventricular white matter changes on CT or at autopsy.5,7,11,12,14,16,22-27 However, in patients selected only for the CT appearance of white matter hypodensity, hypertension has not been found more commonly than in control patients without white matter lucency.28 It is not our purpose to challenge the idea that an aspect of LE may be found on CT or nuclear magnetic resonance imaging (NMRI)29,30 of normal elderly people, but our findings do suggest that in the setting of ischemic stroke, such a CT appearance is strongly associated with a chronically elevated blood pressure. This association does not solely reflect concomitant lacunar infarction since the controls with infarcts of similar topography and size but no LE were less often hypertensive than the study patients. Other risk factors, such as diabetes mellitus, cigarette smoking, hypercholesterolemia, high hematocrit, atrial fibrillation, and ischemic heart disease, were not significantly associated with LE in our ischemic stroke population.

It is interesting that LE correlated inversely with the finding of a ≥ 50% stenosis or an occlusion of the internal carotid arteries on Doppler ultrasound. Angiographic findings in a series of patients with vascular LE have been reported in only 2 previous studies.5,9 In one study,1 of 8 angiographed patients among 11 with LE showed a stenosis of the internal carotid artery; in the other study,9 no narrowing lesion was found in 3 patients who had a 4-vessel angiogram. However, the frequency of carotid obstruction in consecutive stroke patients with LE has never been assessed. Our results suggest that < 15% of these patients have a hemodynamically significant lesion in the carotid artery. Thus the pathogenesis of the LE seen in our patients differs from that of the strictly periventricular leukomalacia reported by De Reuck and Schaumburg11 and De Reuck and Van der Eecken12 distal to carotid artery obstruction in adults with concomitant severe cardiac hypotension. In these latter cases, the leukomalacia was probably of hemodynamic origin and corresponded to watershed infarction. In our patients there was no clinical evidence of episodes of acute hypotension, and the carotid arteries were usually permeable, suggesting another mechanism as the origin of LE. With regard to the strong association between LE and chronic hypertension found in our patients, the leukoencephalopathy may correspond to a phenomenon of chronic distal ischemia with a distorted blood–brain barrier14 due to progressive arteriosclerosis in the end arterioles of the white matter medullary branches. However, the occurrence of incomplete infarction with demyelination in the setting of chronic cerebral hypoperfusion remains a very controversial issue because it has not been clearly substantiated that a chronically lowered cerebral blood flow could in itself lead to morphologic damage.

Dementia has been considered to be the cardinal clinical feature of so-called Binswanger’s disease,5,7,13,14 although nondemented patients may have similar CT findings.18,19,20 Our results show that LE in patients with ischemic stroke is significantly associated with intellectual deterioration.

In elderly hypertensive patients admitted with a stroke, an underlying LE may be suspected on clinical grounds before CT. In these patients, further investigations are unlikely to disclose an etiologically significant cardiac or carotid lesion. The strong association between LE and hypertension warrants vigorous management of high blood pressure in these patients, which may possibly alter the progression of LE with stabilization of the neuropsychological dysfunction.

References

Bogousslavsky et al. Leukoencephalopathy and Stroke


**KEY WORDS** • stroke • leukoencephalopathy • dementia • cerebral infarct • hypertension
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