Relation of Leukoaraiosis to Lesion Type in Stroke Patients

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Nonspecific periventricular white matter lucencies on computed tomograms (leukoaraiosis) were found in 141 (38%) of 367 patients with ischemic or hemorrhagic strokes. Patients with leukoaraiosis were significantly older than those without it and were significantly more likely to have hypertension, diabetes mellitus, general vascular disease, and lacunar infarcts on computed tomograms but were less likely to have cortical infarcts. Because many of these variables may be mutually dependent, we performed a logistic regression analysis examining all clinical and computed tomographic variables. The analysis demonstrated that increasing age, lacunar infarcts, and hemorrhages were significant determinants of leukoaraiosis; cortical infarcts were also significantly, but negatively, correlated with leukoaraiosis. In patients with hemorrhages, leukoaraiosis occurred significantly more often when aneurysms or arteriovenous malformations were not demonstrated. These findings suggest that in patients with cerebrovascular disorders leukoaraiosis is associated with small-vessel disease. (Stroke 1990;21:890-894)

Periventricular white matter lucencies on computed tomograms (CT scans) in the absence of hydrocephalus or well-defined white matter diseases such as multiple sclerosis and leukodystrophies has been called leukoaraiosis. This condition has been demonstrated in 1-5% of patients investigated with CT for several reasons and is associated with increasing age, hypertension, and a history of cerebrovascular disease. Pathologic examination of the white matter shows diffuse and patchy demyelination, with hypertrophic arterioles and widened perivascular spaces.

The clinical and pathologic features of patients with cerebrovascular disease and leukoaraiosis suggest that the latter is associated with small- rather than large-vessel disease. Leukoaraiosis may therefore be more common in patients with the types of lesions that are mainly associated with small-vessel disease (lacunes and spontaneous intracerebral hematomas not associated with arteriovenous malformations [AVMs]) than in patients with cortical infarcts or hemorrhages from AVMs. To test this hypothesis we studied a number of clinical and CT features of 367 hospitalized patients with various types of stroke.

Subjects and Methods

Our study was cross-sectional, with both clinical and CT data collected retrospectively from standard patient files and CT scans. However, before the patient files and CT scans were studied, strict criteria for relevant data were formulated.

We included all patients discharged from the Departments of Neurology or Neurosurgery during 1985-1987 with a final diagnosis of cerebral infarction or spontaneous intracerebral hemorrhage who had a clinically relevant lesion demonstrated by CT. Clinical data retrieved from the patient files included age, sex, presence of hypertension (defined as a history of treatment for or a diagnosis during admission of hypertension, based on the continuing presence of elevated blood pressure that called for treatment), presence of diabetes mellitus (defined as a history of treatment for or a diagnosis during admission of diabetes mellitus, based on the continuing presence of elevated serum glucose levels that called for treatment), and presence of vascular disease (defined as a history of angina, myocardial infarction, congestive heart failure, intermittent claudication, or vascular surgery).

We studied the CT scans of all patients. All CT scans were made ≤1 week after admission on either a Philips Tomoscan 350 (Eindhoven, the Netherlands) or a Siemens Somatom DR3 (Uithoorn, the Netherlands). Hard copies of unenhanced CT scans were studied jointly by two observers who were blinded to the clinical data except for the patient's age. All ischemic and hemorrhagic lesions present on each CT scan were described as intracerebral hem-
TABLE 1. Prevalence of Leukoaraiosis According to Demographic and Clinical Features of 367 Patients With Cerebrovascular Disease

<table>
<thead>
<tr>
<th>Features</th>
<th>Leukoaraiosis</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent (n=226)</td>
<td>Total (AT-141)</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Women</td>
<td>102</td>
<td>45</td>
</tr>
<tr>
<td>Hypertension</td>
<td>90</td>
<td>40</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>43</td>
<td>19</td>
</tr>
</tbody>
</table>

*p<0.001 different from absent by two-sample t test.
t3§p<0.001, 0.023, 0.002, respectively, different from absent by Fisher's exact test.

orraghe(s) (punctate hemorrhages in a hypodense area compatible with hemorrhagic infarction were scored as infarcts); cortical infarct(s), defined as any infarct that included part of the cortical surface of the brain (cerebellar infarcts were scored as cortical infarcts); subcortical infarct(s), defined as subcortical infarcts with a diameter of >2 cm; lacunar infarct(s), defined as subcortical infarcts with a diameter of <2 cm in the basal ganglia or paraventricular regions (brainstem infarcts were scored as lacunar infarcts); and leukoaraiosis, defined as the presence of poorly delineated hypodense areas around the frontal horns and/or around the posterior part of the lateral ventricles. An area was considered hypodense if its density was between that of normal white matter and that of the cerebrospinal fluid. Abnormal white matter was graded as 1 when only the region adjoining the ventricles was abnormal and as 2 when the entire region from the ventricle to the cortex was abnormal. Separate scores were given for the frontal and parietal regions, and when both hemispheres were not equally affected, the score of the more abnormal side was used. Both scores were added so that leukoaraiosis could be graded from 0 to 4. In a separate study the interobserver variation with this grading method proved to be low (average weighted K of 0.63). In patients with hemorrhages, AVMs were only considered present or absent when angiography or autopsy had been performed.

To analyze differences between proportions we used Fisher's exact test, and to analyze differences between mean ages we used the two-sample t test. To explore the relative weight of each variable we performed stepwise logistic regression (with forward selection of independent variables),* with leukoaraiosis (scored as 0 [absent] or 1 [present]) as the dependent variable. In the first analysis we entered only the clinical variables age (full range of values), sex, hypertension, diabetes mellitus, and vascular disease (the last three scored as 0 [absent] or 1 [present]). In the second analysis we added the GT variables intracerebral hemorrhage, cortical infarct, subcortical infarct, and lacunar infarct (all scored as 0 [absent] or 1 [present]).

Results

Of the 367 patients, 141 (38%) had leukoaraiosis of some grade. The prevalence of this condition in several subgroups is presented in Tables 1 and 2. Patients with leukoaraiosis were significantly older than patients with normal white matter (t=9.28, df=365, p<0.0001), and they were significantly more likely to have hypertension (t=0.001), diabetes mellitus (p=0.023), or vascular disease (p=0.002) (Table 1). They also were significantly more likely to have lacunar (p<0.0001) and less likely to have cortical (p=0.001) infarcts (Table 2). These differences were not greater in patients with higher leukoaraiosis grades, and for further analyses we therefore considered leukoaraiosis to be present or absent. The importance of age may be appreciated better from Table 3.

TABLE 2. Prevalence of Leukoaraiosis According to Lesion Type in 256 Patients With Single Lesion Type

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>Absent (n=174)</th>
<th>Total (A=82)</th>
<th>Grade 1 (n=22)</th>
<th>Grade 2 (n=29)</th>
<th>Grade 3 (n=18)</th>
<th>Grade 4 (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>91</td>
<td>52</td>
<td>37</td>
<td>45</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>Cortical infarct</td>
<td>46</td>
<td>26</td>
<td>7</td>
<td>9*</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Subcortical infarct</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lacunar infarct</td>
<td>30</td>
<td>17</td>
<td>37</td>
<td>45t</td>
<td>11</td>
<td>50</td>
</tr>
</tbody>
</table>

*p<0.001 and 0.0001, respectively, different from absent by Fisher's exact test.
Discussion

In this population of hospitalized patients with various types of stroke we demonstrated that increasing age and hypertension are important determinants of leukoaraiosis. When the type of cerebral pathology as demonstrated by CT was also taken into account, increasing age, lacunar infarcts, and, to a lesser extent, hemorrhage are its main determinants, while cortical infarcts are negatively correlated with leukoaraiosis.

The importance of increasing age in the prevalence of leukoaraiosis has been repeatedly demonstrated. With our analysis we can add that this effect is independent of the effects of hypertension and certain types of cerebrovascular pathology.

Hypertension has also been found by other investigators to be an important variable. We found it not to be independent when the type of cerebral pathology was also taken into account. We may have underestimated the prevalence of hypertension in our study population by our pragmatic definition (need for treatment, as judged by the attending physician). An alternative explanation for our finding is that hypertension leads to leukoaraiosis only when it has caused small-vessel disease to such a degree that lacunar infarcts are present, and then the correlation of leukoaraiosis with lacunar infarcts is stronger than that with hypertension alone.

Apart from increasing age, the presence of lacunar infarcts is the most important determinant of leukoaraiosis. This may be taken as a confirmation of our hypothesis that leukoaraiosis is predominantly associated with small-vessel disease. An alternative explanation (not necessarily leading to a different conclusion) is that lacunar infarcts and leukoaraiosis are not easily differentiated on a CT scan. By CT, and more often by magnetic resonance imaging, periventricular lucency may appear as a conglomerate of separate small white matter lesions. In such cases we may have scored both lacunar infarcts and leukoaraiosis as two appearances of a pathologic spectrum. This may be the case with occasional paraventricular lacunar infarcts, but most such lesions are located in the basal ganglia region, were leukoaraiosis is not present. A similar explanation is that small, sharply defined hypodense lesions in the basal ganglia region are not always lacunar infarcts but may be widened perivascular spaces. Therefore, a number of 'lacunes' may actually represent this recognized pathologic correlate of leukoaraiosis. Thus, the correlation between 'lacunes' and leukoaraiosis may be no more than giving different names to different aspects of the same phenomenon. But, of course, this is what our hypothesis was all about.

The association of leukoaraiosis with hemorrhages is less strong than that with lacunar infarcts. When patients with macrovascular lesions (aneurysms and AVMs) are removed from the analysis, the association is stronger. In elderly patients with hemorrhage, AVMs may have been missed because angiography was less frequently performed. This, however, under-
estimates rather than overestimates the prevalence of leukoaraiosis in elderly patients with hemorrhage due to small-vessel disease. The combination of hemorrhage and lacunar infarcts was strongly associated with leukoaraiosis, but the logistic regression analysis shows that hemorrhage independently adds to the risk of leukoaraiosis.

Whether our findings really support our small-vessel disease hypothesis rests upon the evidence linking 'lacunes' and spontaneous intracerebral hemorrhage with arteriolar disease. For small deep infarcts (diameter of <2 cm), microatheromata and lipohyalinosis of small perforators have been demonstrated as the most important underlying vascular lesions in a number of pathologic studies (summarized and discussed in References 19–21). Not all small holes deep in the brain are infarcts; some are caused by small hemorrhages or by dilatation of the perivascular spaces. For both types of lesions, however, changes in the small vessels (microaneurysms and arteriolosclerosis with increased tortuosity, respectively) have been shown to be responsible. Large hemorrhages in the absence of berry aneurysms or AVMs are also caused by the rupture of arteriolar microaneurysms.22,23 Larger subcortical infarcts have a more diverse etiology and may also be caused by vessel-to-vessel or cardiac emboli.24,25 We have therefore deliberately excluded subcortical lesions with a largest diameter of >2 cm from the definition of lacunar infarcts. Conversely, only a small proportion of patients with demonstrated middle cerebral artery occlusion or severe internal carotid artery disease had small deep infarcts.26,27 In conclusion, the evidence linking arteriolar rather than large-vessel disease with 'lacunes' and spontaneous intracerebral hemorrhage is strong and supports our small-vessel disease hypothesis. Additional support is derived from our finding that, as expected, isolated cortical infarcts (which are generally caused by cardiac or vessel-to-vessel emboli or by large-vessel thrombosis) were significantly less associated with leukoaraiosis than were the other types of lesions, to such an extent that cortical infarct appears as a negative variable in the regression equation. Furthermore, our conclusion is confirmed by pathologic evidence of an association between arteriolosclerosis and periventricular white matter changes.10–16

The CT scans were assessed by observers who were aware of the hypothesis underlying our investigation. This may have led to decisions favoring the hypothesis in cases with equivocal leukoaraiosis, but this seems unlikely for two reasons. First, we found significant differences between patients with and without leukoaraiosis and for variables to which the observers were blinded during their assessments of the CT scans (Table 1). Second, we repeated the logistic regression analysis for patients with severe leukoaraiosis (grade 2 in either the anterior or posterior region, when no doubt is possible about the presence of leukoaraiosis), and this led to essentially the same results (not shown) as those presented in Table 6.

The logistic regression approach to analysis was not intended to lead to a prediction rule for leukoaraiosis but was used as a method to analyze the complex relations between the clinical and CT variables thought to contribute to leukoaraiosis. One should also be careful in the extrapolation of our results to other populations because our population was selected; we considered only hospitalized patients with cerebrovascular disease, with (from an epidemiologic point of view) overrepresentation of patients with hemorrhages. For instance, leukoaraiosis has also been demonstrated in elderly subjects without apparent disease,28 in whom a "pure" age effect may have been present, but the quantitative contribution of increasing age to the presence of leukoaraiosis in those subjects may be very different from that suggested by our observations.

Our results allow no conclusions to be drawn about the clinical significance of leukoaraiosis in patients with cerebrovascular disease. However, since patients with leukoaraiosis (even those without apparent disease) may have neuropsychologic impairments,10,20,29 leukoaraiosis may be an important contributor to whether a patient with (multiple) infarcts will be demented. Fur-

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**TABLE 5. Prevalence of Leukoaraiosis in 30 Patients Age ≥50 Years With Hemorrhages According to Presence of AVM**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Leukoaraiosis</th>
<th>N.</th>
<th>%</th>
<th>N.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent</td>
<td></td>
<td></td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age ≤59.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age ≥60.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td></td>
<td></td>
<td>No.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td>%</td>
<td></td>
</tr>
</tbody>
</table>

| AVM, aneurysm or arteriovenous malformation proven by angiography or autopsy. Difference between ages is not significant (t=1.05, p=0.30) by two-sample t test.

*p = 0.014 different from AVM present by Fisher’s exact test.

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**Table 6. Logistic Regression Model for Chance of Leukoaraiosis in Patients With Cerebrovascular Disease**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Value</th>
<th>Coefficient</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0</td>
<td>-7.434</td>
<td>1.0372</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>0.009</td>
<td>0.0132</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Present=1, absent=0</td>
<td>0.811</td>
<td>0.3727</td>
</tr>
<tr>
<td>Lacunar infarct</td>
<td>Present=1, absent=0</td>
<td>1.545</td>
<td>0.3336</td>
</tr>
<tr>
<td>Cortical infarct</td>
<td>Present=1, absent=0</td>
<td>-0.902</td>
<td>0.3281</td>
</tr>
</tbody>
</table>

V(eulakoaraiosis)=e Y+(1+e Y), where Y=c 0+c 1xAge+c 2xHemorrhage+c 3xLacunar infarct+c 4xCortical infarct.
thermore, prognosis for stroke outcome in such patients may be worse than in those without leukoaraiosis. Both these hypotheses are subjects of our current research.

Acknowledgment

John van Swieten developed the grading method for leukoaraiosis; his comments on the manuscripts are gratefully acknowledged.

References

25. Santamaría J, Graus F, Rubio F, Aribau T, Peres J: Cerebral infarction of the basal ganglia due to embolism from the heart. Stroke 1983;14:911–914

Key Words • cerebrovascular disorders • leukoencephalopathy • small-vessel disease
Relation of leukoaraiosis to lesion type in stroke patients.
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Stroke. 1990;21:890-894
doi: 10.1161/01.STR.21.6.890
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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World Wide Web at:
http://stroke.ahajournals.org/content/21/6/890

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