Leukoaraiosis, Intracerebral Hemorrhage, and Arterial Hypertension

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To investigate whether the observed association of leukoaraiosis with intracerebral hemorrhage is direct or mediated by risk factors, we compared 116 patients with intracerebral hemorrhage confirmed by computed tomography and 155 controls without intracerebral hemorrhage, evaluating the prevalence of leukoaraiosis and vascular risk factors. Leukoaraiosis was observed in 21 (18%) of the 116 patients and in 12 (8%) of the 155 controls \((p<0.01)\). Only two (6%) of the 31 patients with lobar hemorrhage had leukoaraiosis on computed tomograms, compared with 17 (24%) of the 71 patients with basal ganglionic hemorrhage \((p<0.05)\).

Leukoaraiosis was significantly correlated with intracerebral hemorrhage after controlling for age and sex by using multiple logistic regression analysis, while the correlation disappeared after controlling for hypertension. Our results indicate that leukoaraiosis is not an independent risk factor for intracerebral hemorrhage. \((Stroke\ 1990;21:1419-1423)\)

The term "leukoaraiosis" was introduced by Hachinski et al\(^1\) to describe computed tomographic (CT) images of symmetric patchy or diffuse areas of low density in the hemispheric white matter. Although leukoaraiosis has been reported in association with intracerebral hemorrhage (ICH),\(^2\) it is not yet clear whether leukoaraiosis itself is a risk factor for ICH or whether this association is related to the presence of shared vascular risk factors. It is known that leukoaraiosis shares with ICH arterial hypertension as a possible risk factor\(^3\,^4\) and that the parenchymal vasculopathy (hypertensive or amyloid) present in ICH has also been reported in leukoaraiosis.\(^3\) We sought to determine whether vascular risk factors, in particular arterial hypertension, explain the presence of leukoaraiosis on cranial CT scans of patients with ICH.

Subjects and Methods

All cranial CT scans were carried out by the Careggi Hospital Neuroradiology Service, the only city emergency neuroradiology service during the study period. From January 1, 1985, to December 31, 1986, a CT diagnosis of spontaneous ICH was made in 172 patients aged \(\geq40\) years. Of these 172 patients, 41 were excluded from the study because of the presence of movement artifacts, large lesions with a mass effect, previous neurosurgery, or other aspects interfering with a proper evaluation of leukoaraiosis on CT pictures and a further 15 were excluded because of insufficient data on the risk factors to be evaluated. This selection produced the 116 patients with ICH involved in this study. We randomly selected 224 from among 7,304 cranial CT studies with no evidence of ICH performed during the same period in patients aged \(\geq40\) years. Among these 224 patients, the 155 who met the criteria for proper definition of study variables were chosen as controls.

All CT scans were performed using a CGR ND 8000 (Paris, France) with 9-mm-thick slices, a 256×256-pixel matrix, and sections in the axial plane oriented in the orbitomeatal line. All CT scans were reviewed by one observer who was blinded to the clinical risk factor variables. Definitions of the main CT variables were preliminarily validated by interobserver agreement (\(\kappa\) values calculated according to Fleiss\(^5\) and Landis and Koch\(^6\)) for four observers of 40 CT scans. Leukoaraiosis was defined as white matter changes presenting as patchy or diffuse symmetric areas of low attenuation (density between that
of normal white matter and that of intraventricular cerebrospinal fluid [CSF]) with ill-defined margins, located in the subcortical regions, and involving both the periventricular zones and the centrum semiovale; \( \kappa \) value was 0.67. Lacunar infarcts were defined as deeply seated, small (<2 cm in diameter), sharply demarcated round or oval hypodense areas; \( \kappa \) value was 0.51. Nonlacunar infarcts were defined as sharply demarcated, cortically extended, wedge-shaped hypodense areas with or without associated local ventricular or sulcal enlargement or subcortical hypodense areas >2 cm in diameter; \( \kappa \) value was 0.62. The \( \kappa \) value for ICH was 0.94. We also examined the ICH variables site (lobar, basal ganglionic, or subcortical) and size (small, medium, or large) of the hemorrhage and the presence of ventricular or subarachnoid inundation in the patients.

Clinical risk factor data were retrospectively collected from hospital charts by one of the authors who was blinded to the CT findings. Arterial hypertension was defined by its previous diagnosis or previous or intercurrent treatment. Diabetes mellitus was defined by its previous diagnosis or previous or intercurrent treatment; patients presenting with only impairment on glucose tolerance tests were not considered to have diabetes mellitus. Heart disease (angina or myocardial infarction, rhythm disturbances, valvulopathy) was assessed by history and laboratory investigations; patients with only left ventricular hypertrophy were not considered to have heart disease.

To compare the two groups, univariate analysis of the categorical variables' frequencies was carried out using the \( \chi^2 \) test; the continuous variable age was analyzed using Student's two-tailed \( t \) test. Multiple logistic regression analysis was used to evaluate the relative contributions of the demographic, CT, and risk factor variables in discriminating the patients from the controls. Multiple regression models were used to determine the net predictive value of leukoaraiosis after controlling (in succession) for age and sex, risk factors, and CT variables. Further regression models examined whether interactions between variables were stronger predictors than single variables.

The level of statistical significance was established on the basis of the regression coefficient/standard error ratio, assuming a standardized normal distribution. Goodness-of-fit for each regression model was determined by Pearson's \( \chi^2 \) test. Statistical analysis was carried out using SPSS version 2.2.

### Results

The two groups are compared in Table 1. No significant difference in age or sex distribution was present. As expected, hypertension was more than twice as frequent in the patients as in the controls \( (p<0.001) \). The prevalence of heart disease was significantly higher in the controls than in the patients \( (p<0.05) \). The possible pathogenetic factors for ICH in our patients are reported in Table 2. Blood dyscrasia or the use of antplatelet drugs or anticoagulants were involved alone \( (i.e., \) without hypertension) in 10% of the patients.

Leukoaraiosis was present in 21 patients \( (18.1\%) \) and in 12 controls \( (7.7\%) \) \( (p<0.01, \) Table 1). Lacunar infarcts were also significantly more frequent in the patients \( (p<0.001) \). The prevalence of nonlacunar infarcts did not differ significantly between groups. Of the 21 patients with leukoaraiosis, 13 \( (62\%) \) were hypertensive and 19 \( (90\%) \) had hypertension, lacunar infarcts, or both.

The proportion of patients with leukoaraiosis varied significantly by site of the hemorrhage. Only two \( (6\%) \) of the 31 patients with lobar ICH had leukoaraiosis compared with 17 \( (24\%) \) of the 71 patients with basal ganglionic ICH \( (p<0.05) \) and two \( (14\%) \) patients with only left ventricular hypertrophy were not considered to have heart disease.

### Table 1. Demographic, Computed Tomographic and Risk Factor Variables of Patients With Intracerebral Hemorrhage and Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients ( (n=116) )</th>
<th>Controls ( (n=155) )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years) (mean±SD)</td>
<td>62.6±10.2</td>
<td>61.0±10.6</td>
</tr>
<tr>
<td>Sex (males)</td>
<td>61</td>
<td>72</td>
</tr>
<tr>
<td><strong>Computed tomographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukoaraiosis</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Lacunar infarct</td>
<td>43</td>
<td>22</td>
</tr>
<tr>
<td>Nonlacunar infarct</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td><strong>Risk factor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>59</td>
<td>36</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Heart disease</td>
<td>3</td>
<td>16</td>
</tr>
</tbody>
</table>

\( *p<0.01, 0.001, 0.05, \) respectively, different from control by \( \chi^2 \) test.

### Table 2. Possible Pathogenetic Factors for Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Pathogenetic factor</th>
<th>Lobar (n=31)</th>
<th>Basal ganglionic (n=71)</th>
<th>Subtentorial (n=14)</th>
<th>All sites (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>4</td>
<td>32</td>
<td>7</td>
<td>43</td>
</tr>
<tr>
<td>Blood dyscrasia and coagulopathy</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Hypertension plus blood dyscrasia</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension plus anticoagulants</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension plus aneurysm</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>12</td>
<td>22</td>
<td>2</td>
<td>36</td>
</tr>
</tbody>
</table>

Data are number of patients.
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of the 14 patients with subtentorial ICH. Of the two patients with lobar ICH and leukoaraiosis, one was hypertensive and both had CT evidence of lacunes. Of the 17 patients with basal ganglionic ICH and leukoaraiosis, six had hypertension and CT-documented lacunes, five had lacunes without hypertension, five had only hypertension, and one had neither hypertension nor lacunes. Of the two patients with subtentorial ICH and leukoaraiosis, one was hypertensive and had lacunes. No patient with ICH and leukoaraiosis had diabetes mellitus or heart disease.

Although we preliminarily excluded patients with overt hydrocephalus, it is possible that in patients with ventricular inundation (in whom obstacles to CSF drainage could lead to transpendymal CSF reabsorption) the resultant periventricular edema could have produced images similar to leukoaraiosis on CT. The negative association of lobar hemorrhage with the dependent variable leukoaraiosis could therefore be biased by the fact that this site of hemorrhage is less prone to produce ventricular inundation. Univariate analysis of the distribution of leukoaraiosis in subgroups of patients with or without ventricular or subarachnoid inundation and with different sized hemorrhages did not reveal any significant differences. Multiple logistic regression analysis of the effect of the ICH variables on the dependent variable leukoaraiosis confirmed the negative association of lobar hemorrhage with leukoaraiosis and the lack of a significant association of the other variables with leukoaraiosis.

The association of leukoaraiosis with the dependent variable ICH was then analyzed by multiple logistic regression models (Table 3, Equations 1–6). After controlling for age and sex (Table 3, Equation 1), leukoaraiosis was significantly correlated with ICH. When hypertension was added to the model (Table 3, Equation 2), leukoaraiosis was no longer significantly associated with ICH, while hypertension showed a strong predictive effect. Other risk factor variables (Table 3, Equation 3) did not modify the relative effects of leukoaraiosis and hypertension, although heart disease was negatively correlated with ICH. In a further model (Table 3, Equation 4) the other two CT variables were added to the demographic and risk factor variables. Both hypertension and lacunar infarcts were significantly and independently predictive of ICH, while the absence of a predictive effect of leukoaraiosis was further confirmed. No interaction between variables showed a predictive effect stronger than the single variables.

**Discussion**

The prevalence of leukoaraiosis among our patients (18%) was slightly higher than that reported by others2 (12%) in a smaller series of patients with ICH. Our results indicate that the association between leukoaraiosis and ICH is due mainly to hypertension. The presence of hypertension or lacunes almost fully explains the correlation of leukoaraiosis with ICH.

Although there was no difference between our patients and controls in demographic characteristics, the patients who had been excluded from the study due to difficulties in the CT definition of leukoaraiosis were on the whole in poorer physical and neurologic condition than the patients included. This could have led us to underestimate the roles of some risk factors. However, the prevalence of the considered risk factors among the patients included in the study were consistent with those reported in other studies of similar clinical series.

Definition of the CT variables, of leukoaraiosis and lacunes in particular, was expected to be difficult in our setting, that is, CT scans of patients during an acute stage of ICH. Hypodense images of a different origin (e.g., edema) could be incorrectly classified as leukoaraiosis. Therefore, we adopted certain expedients to reduce errors: we excluded cases with very large lesions, a mass effect, and hydrocephalus; we defined leukoaraiosis based predominantly on the observation of areas at a distance from the site of the hemorrhagic lesion; and we chose a strict definition of leukoaraiosis, (i.e., hypodense areas extending into the white matter of the centrum semiovale). The resulting κ value for leukoaraiosis was reasonable, and, although worse, the κ value for lacunes (0.51, corresponding to approximately 75% agreement) was similar to that reported in other studies.9

The pathogenesis of and risk factors for leukoaraiosis remain open to discussion. Pathology studies10-14 on brain specimens of patients with leukoaraiosis and the clinical features of Binswanger's disease indicate that hypertensive changes are frequent in small penetrating vessels. The severity of these changes has been related to both the size of the areas of leukoaraiosis and to the severity of the clinical findings. Okeda15 considers these hypertensive changes to be the typical lesion of Binswanger's disease. Information on the pathology of leukoaraiosis in cases not strictly fulfilling the clinical criteria for Binswanger's disease is scarce. One study16 tended to exclude the role of penetrating vessels' vasculopathy in relation

TABLE 3. Logistic Regression Analysis of Variables Predicting Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Variables</th>
<th>Equations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Age</td>
<td>0.57</td>
</tr>
<tr>
<td>Sex</td>
<td>1.13</td>
</tr>
<tr>
<td>Leukoaraiosis</td>
<td>2.31*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.44†</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
</tr>
<tr>
<td>Lacunar infarct</td>
<td></td>
</tr>
<tr>
<td>Nonlacunar infarct</td>
<td></td>
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</tbody>
</table>

Each value is the ratio between the regression coefficient and its standard error. Goodness of fit: Equation 1: χ²=269, df=265, p=0.42; Equation 2: χ²=270, df=264, p=0.38; Equation 3: χ²=269, df=263, p=0.38; Equation 4: χ²=270, df=262, p=0.39.

*†p<0.05, 0.001, 0.01, respectively.
to leukoaraiosis in such cases. On examination of 12 cases of hemorrhagic amyloid angiopathy, Dubas et al.\(^1\) reported a diffuse bilateral loss of myelin in the hemispheric white matter in eight patients, all of whom had lobar ICH. In three of these eight patients, white matter abnormalities had been documented in vivo by CT as leukoaraiosis.\(^18\) The coexistence of amyloid angiopathy and leukoaraiosis has also been reported in a few patients with Alzheimer's disease.\(^19,20\) Therefore, the causative role of amyloid angiopathy in relation to leukoaraiosis is still unproved.\(^20\)

A high incidence of hypertension was reported in early studies of the clinical correlates of leukoaraiosis in uncontrolled series of patients with cranial CT scans.\(^21-24\) Controlled studies of leukoaraiosis in clinically selected series have revealed the limited importance of hypertension. One study,\(^25\) carried out in a series of demented patients, showed that hypertension is less predictive of leukoaraiosis than a history of stroke. In that study, however, stroke associated with hypertension was more important in relation to leukoaraiosis than stroke without hypertension. The association between lacunes and leukoaraiosis has repeatedly been reported in both pathologic\(^11-14\) and CT\(^22-25\) studies. Although lacunes may be indicative of hypertension, the relative roles of lacunes and hypertension with respect to leukoaraiosis have not yet been clarified. The pathogenesis of lacunar infarction\(^26\) is not yet clear, although hypertensive angiopathy of the penetrating vessels is classically held to play a major role in it.

Traditionally, spontaneous ICH has been attributed to the rupture of arteries previously damaged by chronic hypertension.\(^4\) Pathologic changes in ICH include microaneurysms,\(^27\) fibrinoid degeneration,\(^28\) and lipohyalinosis.\(^29\) The same alterations have been found in subjects with chronic hypertension, lacunes, and leukoaraiosis. In recent CT series the prevalence of hypertension ranges from 45\% to 80\%\(^30-35\) depending on definition criteria, race, and patient selection. The role played by hypertension may vary in relation to the site of hemorrhage. The frequency of hypertension varies from 43\% to 81\%\(^30-35\) among patients with basal ganglionic hemorrhage and from 31\% to 45\%\(^30-37\) among patients with lobar hemorrhage. According to the same studies, other risk factors such as diabetes or cardiopathies (other than hypertensive cardiopathy) are irrelevant. The prevalences of hypertension in our study are consistent with those of the above studies (51\% in the entire patient group and 59\% and 26\% in the basal ganglionic and lobar ICH subgroups, respectively).

Kase and Mohr\(^28\) have reviewed the evidence on etiologic factors relevant to lobar ICH: arteriovenous malformations, tumors, blood dyscrasias, anticoagulation, and amyloid angiopathy. Hemorrhages due to cerebral amyloid angiopathy have a strong tendency to occur in the lobar subcortical white matter. Our observation of the rarity of leukoaraiosis in patients with lobar ICH is in contrast with the hypothesis of a relevant role of amyloid angiopathy in relation to leukoaraiosis.

Based only on radiologic and clinical data, our study is unable to explain the relations among the pathology of cerebral vessels, ICH, and leukoaraiosis. Neither can our study contribute answers to the many open questions regarding the pathogenesis of leukoaraiosis. However, by retrospective evaluation of leukoaraiosis and risk factors in relation to ICH, our study excludes that leukoaraiosis is an independent risk factor for ICH. Prospective studies may further support this conclusion.

References

KEY WORDS • cerebral hemorrhage • small-vessel disease • hypertension
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