Magnetic Resonance Imaging White Matter Hyperintensities and Mechanism of Ischemic Stroke

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Background and Purpose—We sought to determine the relations between infarct subtype and white matter hyperintensities (WMHIs) on MRI.

Materials and Methods—We studied 395 ischemic stroke patients with 1.0-T MRI. The number of lacunar, border-zone, and cortical infarcts was registered. WMHIs were analyzed in 6 areas. Univariate and multivariate statistical analyses were used to find the risk factors for different infarct subtypes and to study the connections between WMHIs and brain infarcts.

Results—Lacunar infarcts were associated with hypertension (odds ratio [OR], 1.79; 95% CI, 1.17 to 2.73), alcohol consumption (OR, 1.96; 95% CI, 1.17 to 3.28), and age (OR, 1.03; 95% CI, 1.00 to 1.06). Border-zone infarcts were associated with carotid atherosclerosis (OR, 2.20; 95% CI, 1.15 to 4.19). Atrial fibrillation (OR, 3.02; 95% CI, 1.66 to 5.50) and carotid atherosclerosis (OR, 1.94; 95% CI, 1.12 to 3.36) were independent positive predictors, and history of hyperlipidemia (OR, 0.44; 95% CI, 0.26 to 0.75) and migraine (OR, 0.48; 95% CI, 0.25 to 0.93) were negative predictors for cortical infarcts. Patients with lacunar infarcts had more severe WMHIs than patients with nonlacunar infarcts in all WM areas (P<0.001). Patients with border-zone infarcts showed severe periventricular lesions (P=0.002), especially around posterior horns (P=0.003). The extent of WMHIs in patients with cortical infarcts did not differ from that in those without cortical infarcts.

Conclusions—Various infarct subtypes have different risk profiles. The association between lacunar infarcts and WMHIs supports the concept of small-vessel disease underlying these 2 phenomena. The connection between border-zone infarcts and periventricular WMHIs again raises the question of the disputed periventricular vascular border zone. (Stroke. 1999;30:2053-2058.)

Key Words: cerebral ischemia ■ lacunar infarction ■ leukoencephalopathy ■ magnetic resonance imaging ■ white matter

Ischemic stroke may be due to large-artery atherosclerosis, cardioembolism, or small-vessel occlusion.1 Large-artery occlusion typically gives rise to an infarct affecting cortical parts of the cerebrum, whereas occlusion of the small penetrating branches of cerebral arteries is thought to be the source of small deep infarcts termed lacunes.2,3

Lacunar infarcts are generally the consequence of hypertensive cerebral small-vessel vasculopathy,2,3 but cardiac embolism,2,4 intracranial large-artery disease,5 and carotid stenosis5,6 have also been proposed as possible etiologic factors. It has also been postulated that single and multiple lacunar infarcts might form distinct entities with different pathogenesis and risk factors.7–9

Diffuse white matter (WM) low attenuation on CT (CT leukoaraiosis) and lacunar infarcts have been associated in several studies.10–14 MRI is superior to CT in detecting both lacunar infarcts15 and WM changes.16,17 However, only a few studies have investigated the relationship between white matter hyperintensities (WMHIs) on MRI and different infarct subtypes, and the results have been contradictory.18,19

We performed this study to clarify the basic mechanisms behind different stroke subtypes by comparing the risk factor profiles in patients with and without different types of brain infarcts on MRI and to study the relations between different stroke mechanisms and the extent and distribution of WMHIs in a large poststroke cohort.

Subjects and Methods

The study group consisted of 395 patients from the Helsinki Stroke Aging Memory Study (SAM Study), a prospective cross-sectional study of consecutive persons with ischemic stroke aged 55 to 85 years. The detailed clinical20–22 and imaging procedures23,24 have been previously described. The mean age of the patients was 70.8

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years (SD, 7.7; range, 55 to 85 years), and there were 191 men (mean age, 68.9 years; SD, 7.3; range, 55 to 84 years) and 204 women (mean age, 72.6 years; SD, 7.6; range, 55 to 85 years).

Risk Factors
In each patient, the case history was obtained regarding arterial hypertension, heart failure, atrial fibrillation, history of angina pectoris, myocardial infarction, diabetes, migraine (with or without aura),

Total cholesterol was considered high at >6.5 mmol/L and total triglycerides at >2.0 mmol/L. Peripheral atherosclerosis was considered present if the patient had claudication, >2 peripheral pulsations missing, or history of amputation or operations for circulatory reasons. Carotid atherosclerosis was considered present if there was occlusion, clear stenosis, or other atherosclerotic plaque, including ulceration of a major extracranial or intracranial artery, demonstrated on carotid ultrasound or angiogram.

Magnetic Resonance Imaging
MRI was performed 3 months after stroke with a superconducting kT (Siemens Magnetom). The imaging protocol included transaxial T2-weighted (repetition time [TR], 3000 ms; echo time [TE], 90 ms; number of excitations [NEX], 1), proton density (PD)–weighted (TR, 3000 ms; TE, 15 ms; NEX, 1), and T1-weighted (TR, 400 ms; TE, 15 ms; NEX, 2) images with conventional spin-echo technique. The angulation of slices was bicommissural, with slice thickness 5 mm, gap 0, field of view 230 mm, matrix size 256 x 256 pixels, and number of slices 26 on every pulse sequence. In addition, a 3-dimensional gradient-echo TR/TE/alpha/NEX 30/5/40/1 sequence with 64 3-mm-thick coronal sections was used.

Infarct Subtypes
All MR images were reviewed by the same neuroradiologist (R.M.) blinded to the clinical data. The number, location, and size of focal lesions were recorded. Lesions equivalent to the signal characteristics of cerebrospinal fluid on T1-weighted images and measuring >3 mm in diameter, as well as wedge-shaped corticospinal subcortical lesions, were regarded as brain infarcts. Small 3- to 9-mm lesions located inferior to the lateral putamen were regarded as large Virchow-Robin spaces and were not counted as infarcts.

Different infarct subtypes were determined by MRI findings. Lacunar infarcts were defined as lesions 3 to 9 mm in diameter on T1-weighted images, located in the deep WM or basal ganglia and supplied by the deep branches of anterior (ACA), middle (MCA), or posterior (PCA) cerebral arteries or internal carotid artery (ICA).

Border-zone infarcts were located in the vascular border zone between ACA, MCA, or PCA or between the superficial and deep branches of cerebral arteries. Infarcts affecting the corticospinal layers of cerebral hemispheres in the territories of superficial branches of ACA, MCA, and PCA were classified as cortical.

White Matter Hyperintensities
WMHIs were rated on PD-weighted images in 6 WM areas: around the frontal and posterior horns, along the bodies of lateral ventricles, and in deep, watershed, and subcortical WM areas.

Periventricular hyperintensities (PVHs) around the frontal and posterior horns were classified on the basis of size and shape into small cap (≤5 mm), large cap (>10 mm), and extending cap (>20 mm). PVHs along the bodies of lateral ventricles were classified on the basis of thickness and shape into thin lining (≤5 mm), smooth halo (6 to 10 mm), and irregular halo (>10 mm). WMHs in the subcortical, deep, and watershed areas were classified on the basis of size (greatest diameter) and shape into small focal (≤5 mm), large focal (6 to 10 mm), focal confluent (11 to 25 mm), diffusely confluent (>25 mm), and extensive WM change (diffuse hyperintensity [HI] without distinct focal lesions affecting the majority of WM area). The number of each type of HI was counted, and extensive WM change was rated as absent or present.

The extent of WMHIs was graded 2 ways. First, PVHIs were graded into 4 categories: 0, absence of PVH; 1, small caps or thin lining; 2, large caps or smooth halo; and 3, extending caps or irregular halo. The side more affected was taken into account. WMHIs were graded separately in watershed, deep, and subcortical WM into 6 grades: 0, absence of WMHI; 1, only small focal lesions; 2, at least 1 large focal, no confluent lesions; 3, at least 1 focal confluent, no diffusely confluent lesions; 4, at least 1 diffusely confluent lesion; and 5, extensive WMHI.

Second, WMHIs were rated according to the 4-point scale proposed by Fazekas et al:

- grade 0, absence of PVHs; 1, small or large caps or thin lining; 2, smooth halo; and 3, extending caps or irregular halo. Deep WMHIs were classified as follows: grade 0, absence of WMHIs; 1, small or large focal lesions only; 2, at least 1 focal confluent lesion, no diffusely confluent lesions or extensive WM change; and 3, at least 1 diffusely confluent lesion or extensive WM change.

The reliability of rating was tested and was found to be good (intraobserver agreement, weighted k=0.90 to 0.95; interobserver agreement, weighted k=0.72 to 0.84).

Statistical Analysis
Differences in the risk factor profiles and in the WMHI grades between patients with and without different infarct subtypes were assessed by the Mann-Whitney U test. Multiple logistic regression analysis in a forward stepwise manner was used to estimate the significant independent predictors of different brain infarcts.

The statistical tests were performed with BMDP New System 1.1, BMDP Classic 7.0, and SPSS for Windows 7.0. A level of P<0.05 was regarded as statistically significant.

Results
Risk Factors and Infarct Subtype
Three months after clinical ischemic stroke, 378 patients (95.7%) had at least 1 infarct on T1-weighted images. At least 1 cortical infarct was found in 221 patients (55.9%), lacunar infarct in 228 patients (57.7%), and border-zone infarct in 54 patients (13.7%). Multiple lesions were found in 55.3% of the lacunar patients (range, 2 to 7), 16.7% of the border-zone patients (range, 2 to 4), and 35.7% of the patients with cortical infarct (range, 2 to 8).

Patients with lacunar infarcts (n=228) differed from patients with nonlacunar infarcts (n=167) in the frequency of arterial hypertension (P=0.005) (Table 1). They were also more likely to use alcohol weekly or daily (P=0.032) than patients with nonlacunar infarcts. The risk factors of patients with a single lacunar infarct (n=102) did not differ from those with multiple lesions (n=126) (data not shown).

Patients with border-zone infarcts more frequently had carotid atherosclerosis (P=0.017) than patients without this type of infarct, but no other risk factor differences were detected (Table 1).

Cortical infarcts related positively to heart disease, especially atrial fibrillation (P<0.001), and negatively to hyperlipidemia (P=0.009) and history of migraine (P=0.034) (Table 1).
WMHIs and Infarct Subtype

Patients with lacunar infarcts had the highest relative frequency of moderate and severe WM changes in the subcortical WM, deep WM, and watershed area. Advanced PVHIs were most often found in patients with border-zone infarcts (Table 2).

The extent of WMHIs (all grades included) was more severe in all analyzed WM areas in patients with lacunar infarcts than in those without (P < 0.001). Patients with multiple lacunae showed even more severe changes than patients with a single lacunar infarct in all other WM areas, except the subcortical region, where the difference was not significant (P = 0.650). Patients with border-zone infarcts differed from those without border-zone infarcts in the size of caps around posterior horns (P = 0.003) and in the extent of PVHIs assessed by the Fazekas scale (P = 0.002). The extent of WMHIs among patients with cortical infarcts did not differ from those without.

To determine the independent predictors for different infarct subtypes, we used a multivariate logistic regression analysis (Table 3). All clinical risk factors were set in model A and WMHIs on MRI in model B. In model A, hypertension (odds ratio [OR], 1.786; 95% CI, 1.170 to 2.725), alcohol consumption (OR, 1.958; 95% CI, 1.170 to 3.280), and age (OR, 1.030; 95% CI, 1.002 to 1.059) were independent predictors for lacunar infarcts. Carotid atherosclerosis (OR, 2.198; 95% CI, 1.154 to 4.187) was the predictor for border-zone infarcts. Atrial fibrillation (OR, 3.018; 95% CI, 3.018; 95% CI, 1.301 to 6.977) was the predictor for cortical infarcts.

### Table 1. Risk Factors Among 395 Subjects Without and With Different Types of Brain Infarct

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Lacunar Infarct</th>
<th></th>
<th>Border-Zone Infarct</th>
<th></th>
<th>Cortical Infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent (n=167)</td>
<td>Present (n=228)</td>
<td></td>
<td>Absent (n=341)</td>
<td>Present (n=54)</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>70.2±8.1</td>
<td>71.2±7.3</td>
<td></td>
<td>70.8±7.5</td>
<td>71.0±8.4</td>
</tr>
<tr>
<td>Sex, male</td>
<td>47.9</td>
<td>48.7</td>
<td></td>
<td>46.6</td>
<td>59.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40.1</td>
<td>45.4</td>
<td>0.005</td>
<td>48.7</td>
<td>46.3</td>
</tr>
<tr>
<td>Myocardial infarct</td>
<td>19.8</td>
<td>17.1</td>
<td>0.500</td>
<td>18.8</td>
<td>14.8</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>24.5</td>
<td>26.7</td>
<td>0.621</td>
<td>26.4</td>
<td>22.2</td>
</tr>
<tr>
<td>Heart failure</td>
<td>25.7</td>
<td>18.9</td>
<td>0.107</td>
<td>21.8</td>
<td>22.2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>22.7</td>
<td>16.7</td>
<td>0.135</td>
<td>20.0</td>
<td>14.8</td>
</tr>
<tr>
<td>Peripheral atherosclerosis</td>
<td>12.6</td>
<td>10.5</td>
<td>0.527</td>
<td>12.0</td>
<td>7.4</td>
</tr>
<tr>
<td>Carotid atherosclerosis</td>
<td>22.7</td>
<td>17.1</td>
<td>0.162</td>
<td>17.6</td>
<td>31.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25.1</td>
<td>22.8</td>
<td>0.590</td>
<td>24.6</td>
<td>18.5</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>23.5</td>
<td>18.4</td>
<td>0.219</td>
<td>21.5</td>
<td>14.8</td>
</tr>
<tr>
<td>Migraine</td>
<td>15.0</td>
<td>9.2</td>
<td>0.078</td>
<td>12.3</td>
<td>7.4</td>
</tr>
<tr>
<td>Ever smoking</td>
<td>44.8</td>
<td>52.2</td>
<td>0.151</td>
<td>48.1</td>
<td>55.6</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>18.3</td>
<td>27.6</td>
<td>0.032</td>
<td>22.8</td>
<td>29.6</td>
</tr>
<tr>
<td>Snoring</td>
<td>26.7</td>
<td>29.9</td>
<td>0.501</td>
<td>27.9</td>
<td>32.7</td>
</tr>
</tbody>
</table>

S indicates significance (P<0.05). *Mann-Whitney U test.

### Table 2. Relative Frequency (%) of Moderate and Severe White Matter Changes* in Different Infarct Subtypes

<table>
<thead>
<tr>
<th>White Matter Area</th>
<th>Lacunar Infarct</th>
<th></th>
<th>Border-Zone Infarct</th>
<th></th>
<th>Cortical Infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent (n=167)</td>
<td>Present (n=228)</td>
<td></td>
<td>Absent (n=341)</td>
<td>Present (n=54)</td>
</tr>
<tr>
<td>Frontal horns</td>
<td>33.5</td>
<td>54.8</td>
<td>&lt;0.001</td>
<td>44.3</td>
<td>55.6</td>
</tr>
<tr>
<td>Body of lateral ventricles</td>
<td>26.3</td>
<td>47.8</td>
<td>&lt;0.001</td>
<td>37.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Posterior horns</td>
<td>49.7</td>
<td>65.8</td>
<td>&lt;0.001</td>
<td>56.0</td>
<td>77.8</td>
</tr>
<tr>
<td>Subcortical</td>
<td>6.0</td>
<td>9.2</td>
<td>&lt;0.001</td>
<td>8.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Deep</td>
<td>10.8</td>
<td>35.5</td>
<td>&lt;0.001</td>
<td>25.5</td>
<td>22.2</td>
</tr>
<tr>
<td>Watershed</td>
<td>25.2</td>
<td>43.4</td>
<td>&lt;0.001</td>
<td>34.6</td>
<td>42.6</td>
</tr>
<tr>
<td>Periventricular by Fazekas scale</td>
<td>48.5</td>
<td>65.8</td>
<td>0.001 S</td>
<td>55.4</td>
<td>77.8</td>
</tr>
<tr>
<td>Deep by Fazekas scale</td>
<td>28.8</td>
<td>52.6</td>
<td>&lt;0.001</td>
<td>41.9</td>
<td>46.3</td>
</tr>
</tbody>
</table>

S indicates significance (P<0.05). *Periventricular hyperintensity >5 mm, in other areas hyperintensity >10 mm; Fazekas grade 2 or 3. †Mann-Whitney U test; all white matter grades included.
TABLE 3. Multivariate Logistic Regression Analysis: Independent Predictors of Different Infarct Subtypes Among 395 Subjects

<table>
<thead>
<tr>
<th>Subtype</th>
<th>BS</th>
<th>SE</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacunar infarct</td>
<td>0.580</td>
<td>0.216</td>
<td>0.007</td>
<td>1.786</td>
<td>1.170–2.725</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.672</td>
<td>0.263</td>
<td>0.011</td>
<td>1.958</td>
<td>1.170–3.280</td>
</tr>
<tr>
<td>Age</td>
<td>0.030</td>
<td>0.014</td>
<td>0.039</td>
<td>1.030</td>
<td>1.002–1.059</td>
</tr>
<tr>
<td>Border-zone infarct</td>
<td>0.788</td>
<td>0.329</td>
<td>0.017</td>
<td>2.198</td>
<td>1.154–4.187</td>
</tr>
<tr>
<td>Carotid atherosclerosis</td>
<td>1.105</td>
<td>0.306</td>
<td>&lt;0.001</td>
<td>3.018</td>
<td>1.657–5.498</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>−0.828</td>
<td>0.272</td>
<td>0.002</td>
<td>0.437</td>
<td>0.256–0.745</td>
</tr>
<tr>
<td>Carotid atherosclerosis</td>
<td>0.664</td>
<td>0.280</td>
<td>0.018</td>
<td>1.941</td>
<td>1.122–3.361</td>
</tr>
<tr>
<td>Migraine</td>
<td>−0.726</td>
<td>0.335</td>
<td>0.030</td>
<td>0.484</td>
<td>0.251–0.933</td>
</tr>
<tr>
<td>Cortical infarct</td>
<td>Deep WMHIs</td>
<td>0.588</td>
<td>0.098</td>
<td>&lt;0.001</td>
<td>1.800</td>
</tr>
<tr>
<td>Border-zone infarct</td>
<td>PVHIs by Fazekas scale</td>
<td>0.515</td>
<td>0.170</td>
<td>0.002</td>
<td>1.673</td>
</tr>
</tbody>
</table>

Discussion
The etiology of ischemic stroke affects the prognosis, outcome, and management of the patient.1 The basic mechanisms for brain infarction are thrombotic, embolic, and hemodynamic.34 The recognition of the predisposing factors for different types of brain infarct on CT or MRI reflects the mechanisms behind infarct subtypes and forms the basis for prevention and management of ischemic stroke.

Risk Factors and Infarct Subtype
In this large poststroke cohort, history of arterial hypertension was the most important risk factor for lacunar infarcts. This is in accordance with some previous works35–37 and with the original concept of lacunar lesions being mainly caused by hypertension-induced small-vessel arteriopathy.2 In contrast to some previous studies,4,6 we did not find any association between lacunar lesions and history of myocardial infarct, heart failure, atrial fibrillation, or carotid atherosclerosis.

This may be due to the strict inclusion criteria for lacunar lesions in our study; only small lacunae (diameter, 3 to 9 mm on T1-weighted images) were included. We therefore tested whether embolism might be a more frequent etiologic factor in larger lacunes. Larger infarcts (10 to 29 mm in diameter), located in the deep white or gray matter in the vascular territories of deep arteries from ACA, MCA, PCA, and ICA, were included in lacunar lesions. Still, hypertension (P=0.006) and weekly or daily consumption of alcohol (P=0.030) were significant correlates for deep infarcts, and heart disease (atrial fibrillation, angina pectoris, heart failure, or history of myocardial infarction) was negatively associated (P=0.003, Mann-Whitney U test). Carotid atherosclerosis did not reach significance (P=0.092).

We conclude that cardiogenic embolism or embolism from a carotid bifurcation is not a frequent source for deep infarcts among elderly stroke patients and is far less significant than hypertension in the genesis of lacunar lesions.

On the other hand, the high frequency of heart disease (60.2%) among patients with cortical infarcts suggests cardiac embolism to be a major etiologic factor in cortical infarcts. This result encourages the search for potential heart disease in elderly stroke patients with a cortical infarct and stresses the importance of anticoagulative therapy in this patient group.38

The main risk factor for border-zone infarcts was carotid atherosclerosis (OR, 2.20; 95% CI, 1.15 to 4.19). There are 2 possible explanations: (1) ulcerated plaques may serve as a source of embolism, and these emboli may end in the periphery of vascular territories, resulting in border-zone lesions, or (2) border-zone infarcts may be hemodynamically determined. In hemodynamically determined infarcts, severe stenosis in carotid arteries causes hemodynamic alterations in the brain tissue, and an infarction takes place when global cerebral perfusion is critically decreased.34 Although cerebral perfusion may also decrease because of heart disease, no significant connection between heart disease and border-zone infarcts could be seen.

The role of alcohol as a risk factor for stroke is interesting. In our study, weekly or daily consumption of alcohol was significantly associated with lacunar infarcts (OR, 1.96; 95% CI, 1.17 to 3.28). Epidemiological studies have suggested that the relation between alcohol consumption and ischemic stroke might be dose dependent, following a J-shaped curve.39 Moderate drinking may reduce the risk for stroke,
whereas heavy consumption may increase the risk for stroke. Since the consumption of alcohol has in our country been traditionally related to hard liquors,40,41 weekly or daily drinking is more likely to be related to heavy than to moderate alcohol consumption in this group. The connection between lacunar infarcts and alcohol raises the question of whether it is alcohol as such that increases the risk for lacunar infarcts or whether the increased risk is related to the consumption of alcoholic beverages known to increase blood pressure,42 which could explain why the connection was seen especially with lacunar infarcts.

The negative relations between cortical infarcts and migraine, as well as hyperlipidemia, are rather surprising, since recent studies have proposed a positive association between migraine and ischemic stroke,48,49 and occipital infarction causing homonymous hemianopia is a well-defined clinical syndrome in young migrainous women.44 The relation between migraine and cortical infarcts in our study could relate to the fact that despite positive associations seen in certain study cohorts, migraine is probably not a risk factor for ischemic stroke in general.44

The role of hyperlipidemia in the development of stroke is still uncertain, although most studies seem to support a positive association between stroke and dyslipidemia,39 and a recent study has shown statins to reduce the risk of stroke in patients with coronary disease.45 If the same holds true in patients with transient ischemic attack or stroke, the negative association between cortical infarcts and hyperlipidemia in our study might be explained by selection. Hyperlipidemia is an established risk factor for coronary heart disease, causes earlier morbidity, and may exclude patients from elderly study cohorts.

Unlike some previous reports,8,35 we did not manage to find a significant difference in the prevalence of diabetes in different infarct groups, nor did we find evidence for the hypothesis of 2 different lacunar syndromes (single versus multiple).7–9

**WMHIs and Infarct Subtype**

WMHIs have been related to aging and cerebrovascular risk factors.46,47 Histopathologically, they represent areas of gliosis,48–52 demyelination,49,53 and loss of axons.51–53 It has been suggested that small-vessel alterations and hypoperfusion might play a central role in the pathogenesis of WMHIs.47,54 However, direct demonstration for the ischemic origin of these lesions is still lacking.47

On CT, a connection has been found between WM changes and lacunar infarction,10–14 but on MRI the topic has not been widely investigated or the results have been contradictory.18,19 If some types of WMHIs represent ischemic damage due to small-vessel changes, one would expect to find a positive connection between lacunar infarcts and WMHIs on MRI studies as well.

In our study, patients with lacunar infarcts more often had moderate or severe WM changes than patients with cortical infarcts. The difference in the extent of WMHIs in lacunar compared with nonlacunar patients was highly significant \( (P<0.001) \) in all WM areas and by both rating scales. The greatest difference was noticed in the deep WM. These results are consistent with the previous CT works and support the concept that small-vessel vasculopathy is the common underlying pathology behind lacunar lesions and WMHIs.

Patients with border-zone infarcts had a tendency toward more severe PVHIs. Caps around posterior horns \( (P=0.003) \) or PVHI assessed by the Fazekas scale \( (P=0.002) \) were in our study more severe in patients with border-zone lesions compared with other infarct types. Similar results have been reported by Adachi et al,18 who found PVHIs to be more severe in lacunar infarction and infarction of the deep border zone.

The connection between PVHIs and border-zone infarcts again raises the question of the vascular vulnerability of the periventricular WM. De Reuck55 has suggested that the periventricular WM represents a vascular border zone and is selectively vulnerable to changes in blood pressure. However, this was later questioned.56 Our results support de Reuck’s view and may warrant further studies in this field.

The extent of WMHIs was unrelated to cortical infarcts. This supports the concept that cortical infarcts in elderly subjects are mainly related to embolism and large-artery disease. It also provides further evidence for the view that WMHIs are primarily related to small-vessel rather than large-artery disease.

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**References**

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