White Matter Signal Abnormalities in Normal Individuals: Correlation With Carotid Ultrasonography, Cerebral Blood Flow Measurements, and Cerebrovascular Risk Factors

Franz Fazekas, MD, Kurt Niederkorn, MD, Reinhold Schmidt, MD, Hans Offenbacher, MD, Susanne Horner, MD, Götz Bertha, MD, and Helmuth Lechner, MD

We studied 52 asymptomatic subjects using magnetic resonance imaging, and we compared age-matched groups (51-70 years old) with and without white matter lesions with respect to carotid ultrasonography, cerebral blood flow (xenon-133 injection), and cerebrovascular risk factors. In the group with white matter signal abnormalities, we noted a higher frequency of extracranial carotid artery disease, a lower mean gray matter blood flow (F1), and a significant reduction (p<0.05) in blood flow of the slow-flowing (F2) compartment. Hypertension, diabetes mellitus, and cardiac diseases (p<0.002) were found more often in this group. Our results indicate that a higher incidence of changes known to be associated with an increased risk for stroke exists in the presence of white matter lesions in normal elderly individuals. (Stroke 1988;19:1285-1288)

Magnetic resonance signal abnormalities in the white matter have been an incidental finding in various clinical conditions of elderly patients as well as in normal aging. The frequency of these hyperintense white matter foci on T2-weighted images increases with advancing age and with the number of cerebrovascular risk factors. A correlation between the presence of white matter lesions (WMLs) and cerebrovascular disease has therefore been suggested, implying that magnetic resonance signal abnormalities in asymptomatic subjects may provide evidence of "silent" cerebrovascular disease.

To test further the significance of WMLs, we investigated their association with factors known to increase the risk for stroke in a population of symptom-free individuals. To our knowledge, ours is the first study to evaluate normal subjects with respect to cerebrovascular changes using magnetic resonance imaging (MRI), the xenon-133 injection method of cerebral blood flow (CBF) measurement, and carotid ultrasonography simultaneously.

Subjects and Methods

The 52 subjects (mean age 58, range 31-78 years) used are a sample of volunteers participating in a prospective field study on the incidence of cerebrovascular risk factors in the population of Graz, Austria, and the surrounding region. Subjects were eligible for the study if they had no evidence of cerebrovascular disease on history or neurologic examination and after exclusion of other neurologic or psychiatric disorders. Subjects were free of symptoms of systemic diseases and had not come to medical attention for cerebrovascular risk factors.

MRI and extracranial Doppler ultrasonography were performed in all subjects, and CBF was measured in 32 subjects; these tests were carried out within 1 day. Evidence of hypertension (blood pressure of >160 mm Hg systolic), diabetes mellitus (fasting blood sugar concentration of >160 mg/dl), and cardiac diseases (coronary heart disease, cardiomyopathy, arrhythmias, etc.) was based on appropriate findings on two independent visits.

All subjects were studied with a superconducting magnet at a field strength of 1.5 T (Gyroscan S15, Philips, Eindhoven, The Netherlands) and the spin-
FIGURE 1. Types of white matter hyperintensities present on mixed-intensity magnetic resonance images in asymptomatic subjects. Top left: punctate, top right: early confluent, bottom: confluent.

echo technique. A repetition time of 1800–2500 msec and two echo times of 30 and 60 msec were used to generate mixed-intensity and T2-weighted images in the axial plane. Slices were 5 mm thick in most instances. The images were evaluated for the presence and extent of hyperintense lesions in the deep and subcortical white matter. Minimal periventricular signal hyperintensities in the form of caps and/or "pencil-thin" lining around the lateral ventricles were not considered for analysis as available data do not point to their association with cerebrovascular disease.11,12

Continuous-wave Doppler examination of the extracranial cerebral arteries and duplex scanning of the extracranial carotid arteries were performed in all subjects. We used a 4-MHz probe (MX 300, Montagex, France) for continuous-wave Doppler and a duplex sector scanner with frequencies of 7.5
MHz for imaging and 5 MHz for pulsed Doppler (Mark 500, ATL, Seattle, Washington). The severity of extracranial carotid artery disease was graded as 0, no lesion; 1, unilateral plaque with <20% stenosis; 2, bilateral plaques with <20% stenosis or unilateral stenosis of 20–50%; and 3, bilateral stenoses of 20–50% or unilateral stenosis of >50–70%. More severe vessel wall damage was not observed in this study.

In 32 subjects, CBF was measured using a xenon-133 injection method modified from the originally described technique of Obrist et al. We used measurements from 23 of the 32 subjects (group means 59.6±5.2 and 57.6±5.1 years; not significantly different, Mann-Whitney U test) revealed carotid lesions in 14 of 23 subjects (61%) with WMLs and in six of 16 subjects (38%) without WMLs.

In the same five groups, hypertension and diabetes mellitus were present more frequently in subjects who had signal abnormalities in the white matter. A significantly higher incidence of cardiac disorders (p<0.002) was detected in the 51–70-year-old group with WMLs (Table 1).

We used measurements from 23 of the 32 subjects for age-matched statistical comparison. In 51–70-year-old subjects with WMLs, all blood flow parameters were slightly lower and F2 CBF was significantly lower than for subjects without WMLs (Table 2). This fact could not be accounted for by different mean PCO₂ in the groups; rather, correction for PCO₂ would have further enhanced the CBF differences.

### Table 1. Doppler Ultrasonographic Findings, Cerebrovascular Risk Factors, and White Matter Signal Abnormalities on Magnetic Resonance Imaging by Age

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Extracranial carotid artery disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤50</td>
<td>8</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>51–70</td>
<td>16</td>
<td>10</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt;70</td>
<td>23</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cerebrovascular risk factor</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>0</td>
</tr>
</tbody>
</table>

- - no white matter signal abnormalities on magnetic resonance imaging; +, abnormalities.

*p<0.002, Fisher's exact test (comparison of subjects 51–70 years of age).

### Results

We observed MRI signal abnormalities in 27 subjects; WMLs were present as punctate foci of hyperintensity in 23 subjects (85%). Early confluent foci were seen in three subjects (11%), and confluent areas of hyperintensity were present in only one subject (4%) (Figure 1). No WMLs were seen in the eight subjects younger than 50 years, whereas such lesions were noted in four of the five subjects (80%) over the age of 70 years.

Abnormalities in the extracranial division of the carotid arteries were detected using ultrasonogra-

### Table 2. Cerebral Blood Flow in Subjects 51–70 Years Old With and Without White Matter Lesions on Magnetic Resonance Imaging

<table>
<thead>
<tr>
<th>White matter lesions</th>
<th>With</th>
<th>Without</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>58.8±5.3</td>
<td>58.2±2.8</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>39.6±2.6</td>
<td>38.8±1.8</td>
</tr>
<tr>
<td>F1 (ml/100 g/min)</td>
<td>59.9±8.3</td>
<td>63.5±5.3</td>
</tr>
<tr>
<td>F2 (ml/100 g/min)</td>
<td>15.4±2.5*</td>
<td>17.3±1.1</td>
</tr>
<tr>
<td>CBF-15 (ml/100 g/min)</td>
<td>39.7±4.4</td>
<td>42.7±3.1</td>
</tr>
</tbody>
</table>

F1, fast compartment; F2, slow compartment; CBF-15, mean blood flow in fast and slow compartments.

*p<0.05, Mann-Whitney U test.
Discussion

Our results confirm the high incidence of white matter signal abnormalities detected by MRI in normal individuals older than 50 years of age.\textsuperscript{3,4} In our study, WMLs appeared predominantly as punctate foci of hyperintensity on T2-weighted images. Doppler ultrasonography revealed extracranial cerebral artery disease, ranging from unilateral plaques to bilateral stenoses of up to 50% of the vessel diameter, more frequently in subjects with WMLs than in those without. Higher-grade stenoses, however, were not detected in subjects with or in subjects without MRI signal abnormalities. Obstructive extracranial carotid artery disease therefore does not seem to play a role in the development of MRI white matter hyperintensities with aging. Recently, Heindel et al.\textsuperscript{15} also reported no correlation between angiographically documented stenoses with occlusions of the brachiocephalic arteries and small areas of white matter hyperintensity on MRI in subjects with overt cerebrovascular disease. The association between WMLs and extracranial vascular disease in our asymptomatic subjects nevertheless signifies a higher risk for stroke in people with this MRI finding because minor vessel wall lesions suffice to promote a cerebrovascular event.\textsuperscript{7} A further contributing factor is the higher incidence of well documented cerebrovascular risk factors such as hypertension, diabetes mellitus, and cardiac disorders\textsuperscript{8,10} in people with WMLs. As might be expected with a normal clinical condition and no high-grade carotid artery stenosis, gray matter blood flow of age-matched groups was only slightly reduced in the presence of WMLs. Measurements of glucose metabolism by positron emission tomography in another set of normal individuals also failed to reveal hypometabolism of cortical areas adjacent to white matter hyperintensities.\textsuperscript{16} In contrast, F2 CBF was significantly lower for subjects with WMLs. Although it has been demonstrated that F2 underestimates true white matter blood flow because of the admixture of extracranial components,\textsuperscript{17} the difference in mean F2 CBF between the groups with and without WMLs can be interpreted as further evidence of microcirculatory disturbances associated with WMLs and is in accordance with histopathologic data.\textsuperscript{6,18}

References

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Key Words • cerebral blood flow • magnetic resonance imaging • risk factors • ultrasonics
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