Cerebral Lesions on Magnetic Resonance Imaging, Heart Disease, and Vascular Risk Factors in Subjects Without Stroke

A Population-Based Study

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Background and Purpose To assess the prevalence of asymptomatic abnormalities on magnetic resonance imaging of the brain and their possible relation to hypertension, heart disease, and carotid artery disease, we studied 77 randomly selected subjects (mean age, 65.1 years; range, 36 to 95 years) with no history of focal brain lesions.

Methods The study protocol included magnetic resonance imaging of the brain, transthoracic and transesophageal echocardiography, ultrasonography of the carotid arteries, and electrocardiographic recording. Deep and periventricular white matter hyperintensities on magnetic resonance imaging were assessed both separately and together.

Results On magnetic resonance imaging of the brain 62.3% (95% confidence interval [CI], 51.5% to 73.2%) of the subjects had white matter hyperintensities. These abnormalities increased significantly with age (χ² test; P = 0.001), from 13.6% (95% CI, 0% to 28.0%) of subjects aged younger than 55 years to 85.2% (95% CI, 71.8% to 98.6%) of subjects aged 75 years or older. Six subjects had deep gray matter hyperintensities localized in the basal ganglia, and one had a cerebellar infarction. Stepwise logistic regression analysis identified age and a history of heart disease (but not echocardiographic findings) to be independently associated with deep and periventricular white matter hyperintensities. Hypertension was only independently associated with periventricular white matter hyperintensities. Of the 68 subjects examined with both transthoracic and transesophageal echocardiography, potential cardioembolic sources were detected in 38.2% (95% CI, 26.7% to 49.8%) of the subjects with transthoracic echocardiography and in 47.1% (95% CI, 35.2% to 58.9%) of those with transthoracic and transesophageal echocardiography combined. In subjects aged 75 years or older, a possible cardiac embolic source was detected in 64.0% on transthoracic echocardiography and in 72.0% on transthoracic and transesophageal echocardiography combined, compared with 5.3% and 15.8%, respectively, in subjects aged younger than 55 years.

Conclusions White matter hyperintensities and potential cardioembolic sources are frequently present in asymptomatic individuals, stressing the need for age-matched control subjects in studies of patients with stroke or dementia. (Stroke. 1994;25:929-934.)

Key Words • magnetic resonance imaging • white matter • echocardiography • epidemiology • risk factors

Brain magnetic resonance imaging (MRI) and transesophageal echocardiography (TEE) are more sensitive to detect abnormalities of the brain and heart than previous methods. However, the relevance of common findings such as cerebral white matter hyperintensities (WMH) on MRI of the brain and possible cardiac embolic sources such as atrial septal aneurysm and patent foramen ovale is unclear. Therefore, such observations in patients with stroke or dementia need to be related to findings in a randomly selected population. The frequency of WMH on MRI of the brain and abnormalities on transthoracic echocardiography (TTE) and TEE varies, presumably because of selection of examined persons or geographic differences in risk factors. The aim of our study was to determine the prevalence of WMH and cardiac abnormalities on TTE and TEE and their possible correlation in a large group of individuals without stroke.

To this aim, we examined a randomly selected group of subjects, intended to later be compared with an epidemiologic study of first-ever stroke patients from the catchment area of the University Hospital, Lund. The possible correlation between WMH and echocardiographic findings (on TTE and TEE), carotid stenosis, electrocardiographic (ECG) abnormalities, and vascular risk factors including age, hypertension, history of heart disease, and smoking was analyzed.

Subjects and Methods

Subjects

The population register of the local catchment area (158 000 inhabitants) of the University Hospital, Lund, supplied a list with 177 randomly selected subjects aged 35 years or older who were invited to participate in this study. Of those subjects, 6.2% could not be contacted, 36.2% declined to participate, 9.6% were not able to participate, and 1.7% died before they were included in the study. In each age group the proportion of subjects participating was as follows: 35 to 44 years, 52.6%; 45 to 54 years, 76.5%; 55 to 64 years, 58.8%; 65 to 74 years, 51.4%; 75 to 84 years, 48.9%; 85 years or older, 19.0%. One...
were divided into major and minor cardioembolic sources similar to those described by Hart. Major sources included prosthetic valve, mitral stenosis, recent myocardial infarction, left atrial or ventricular thrombus, atrial myxoma, infective or marantic endocarditis, and dilated cardiomyopathy. Minor sources included mitral valve prolapse, severe mitral annulus calcification, patent foramen ovale, atrial septal aneurysm, calcific aortic stenosis, slight dysfunction of the left ventricle, and spontaneous contrast in the left atrium.

The same division of major and minor sources was made for TTE and TEE, although some of the abnormalities are detectable with one of the methods only. Because TEE was performed in addition to TTE, the findings on TEE are presented together with the TTE findings and not separately. Atrial fibrillation was not included among the ultrasonographic findings because this condition is normally diagnosed with ECG. A more detailed account of the cardiac findings will be reported separately (A.R., unpublished data, 1993).

Ultrasoundography of the Carotid Arteries

Ultrasoundography of the carotid arteries with continuous-wave technique was performed with SC 6100 continuous-wave equipment (Carolina Medical Electronics Inc). A 5-MHz probe was used to investigate the carotid arteries, and a Doppler shift greater than 4.5 kHz over the common or internal carotid artery was considered to represent a stenosis of 50% or more. Absence of Doppler signal from the internal carotid artery was considered to represent an occlusion.

Ultrasoundography of the carotid arteries was also performed with duplex technique (Diasonic CV400 or Acuson 128XP). A stenosis of 50% or greater was considered to be present if two or more of the following criteria were met: (1) peak flow velocity greater than 1.7 m/s at the stenosis; (2) ratio of peak flow velocities in internal and common carotid arteries greater than 1.5; (3) frequency of the Doppler shift of 5.5 kHz or greater at peak flow, with a pulsed-Doppler frequency of 5 MHz; (4) diameter reduction of 50% or more of internal or common carotid artery observed on the real-time image; and (5) area reduction of 75% or more of internal or common carotid artery measured on the real-time image.

A carotid stenosis of 50% or greater was considered to be present if the criteria for a stenosis of 50% or greater were fulfilled on either of the ultrasound examinations.

Statistical Analysis

Means and 95% confidence intervals (CI) were calculated when appropriate. Univariate analysis for comparing deep and periventricular WMH with various vascular risk factors and findings on TTE and TEE was performed with the χ2 test (except for age, in which case ANOVA was used). Stepwise logistic regression analysis was performed to reveal a possible correlation of WMH (deep, periventricular, or both) with the summarized scale) with age, hypertension, heart disease, and smoking (earlier smokers were classified as nonsmokers) and findings on TTE and TEE of the heart, ultrasonography of the carotid arteries, and ECG. Kappa statistics were used to evaluate interobserver reliability for the two neuroradiologists for deep and periventricular WMH and for WMH according to the three-grade summarized classification.

Results

Demographic data and some risk factors of the 77 persons participating in the study are shown in Table 1. Twenty-six subjects had a systolic blood pressure of 160 mm Hg or greater, and 9 subjects had a diastolic blood pressure of 95 mm Hg or greater. The mean age of the subjects was 65.1 years (range, 36 to 95 years).

MRI findings of WMH in different age groups are shown in Table 2. WMH increased significantly with age (χ2; P=0.0001). The proportions of subjects with WMH (grades 0 to 2) in the different age groups are shown in Fig 1. The mean ages were 53.2 years for grade 0, 68.8 years for grade 1, and 78.1 years for grade 2. The
frequency of deep and periventricular WMH is shown in Table 3. A significant correlation between deep and periventricular WMH was seen \( (x^2; P = .0001) \). In a stepwise logistic regression model in which age was included, the correlation between deep and periventricular WMH remained significant \( (x^2; P = .0001) \).

Interobserver agreement showed a \( \kappa \) value of 0.88 (95% CI, 0.71 to 1.00) for deep WMH and 0.85 (95% CI, 0.68 to 1.00) for periventricular WMH when rated according to Fazekas et al. For the three-grade summarized scale the \( \kappa \) value was 0.86 (95% CI, 0.70 to 1.00).

Three subjects had asymmetrical white matter abnormalities; 2 of these subjects had low signal on proton density images. Six subjects had deep gray matter hyperintensities, and 1 subject had a cerebellar infarction. Only two of these abnormalities were larger than 1 mL (the largest was 2 mL). No subject had a finding of cortical infarction on MRI.

The main findings on ultrasound examination of the carotid arteries, ECG, TTE, and TEE are given in Table 4. The frequency of carotid stenosis of 50% or greater, atrial fibrillation, and left ventricular hypertrophy on ECG increased with age. No additional potential major cardioembolic source was detected when TEE was considered together with TTE. When comparing patients examined with both TTE and TEE (n=68), the frequency of potential cardioembolic sources increased markedly with age: of the persons aged 75 years or older, 64.0% (95% CI, 45.2% to 82.8%) had a possible major or minor cardioembolic source on TTE and 72.0% (95% CI, 54.4% to 89.6%) on TTE and TEE combined compared with 5.3% on TTE and 15.8% on TTE and TEE in subjects aged younger than 55 years.

The presence of WMH is related to demographic data, hypertension, and findings on examination of the heart and carotid arteries in Table 5. The proportions of subjects with hypertension related to the degree of WMH are shown in Fig 2.

Stepwise logistic regression analysis showed a significant correlation between deep WMH on MRI and age \( (x^2; P = .0001) \) and heart disease \( (P = .045) \). In a similar model, periventricular WMH correlated significantly with age \( (P = .02) \), left ventricular hypertrophy on ECG \( (P = .002) \), history of heart disease \( (P = .02) \), and hypertension (defined as systolic blood pressure \( \geq 160 \text{ mm Hg} \) or history of hypertension) \( (P = .03) \). Deep and periventricular WMH combined on the summarized scale correlated significantly with age \( (P = .0001) \) and history of heart disease \( (P = .02) \). With earlier smokers classified as smokers, smoking was not an independent variable.

### Discussion

#### Selection of Control Population and Statistical Methods

In studies of randomly selected populations it is difficult to obtain the participation of all invited sub-

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**TABLE 1. Demographic Features and Risk Factors of the 77 Subjects**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>35-54</th>
<th>55-74</th>
<th>≥75</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>22</td>
<td>28</td>
<td>27</td>
<td>77</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>11/11</td>
<td>15/13</td>
<td>13/14</td>
<td>39/38</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>3</td>
<td>11</td>
<td>17</td>
<td>31</td>
</tr>
<tr>
<td>Diabetes mellitus§</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>History of heart disease¶</td>
<td>0</td>
<td>5</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Smoking, no/yes/earlier</td>
<td>7/7/8</td>
<td>10/9/9</td>
<td>18/4/4</td>
<td>36/20/21</td>
</tr>
</tbody>
</table>

*Defined as receiving medical treatment for hypertension.
†Defined as receiving medical treatment for hypertension or systolic blood pressure \( \geq 160 \text{ mm Hg} \).
§Defined as receiving medical treatment for diabetes mellitus.
¶Defined as receiving medical treatment for heart disease now or previously.

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**TABLE 2. Brain Magnetic Resonance Imaging Abnormalities In Relation to Age**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>35-54</th>
<th>55-74</th>
<th>≥75</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>22</td>
<td>28</td>
<td>27</td>
<td>77</td>
</tr>
<tr>
<td>White matter hyperintensities*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>19</td>
<td>6</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>16</td>
<td>11</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Asymmetrical white matter abnormalties or DGMH</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

DGMH indicates deep gray matter hyperintensities.
*Deep and periventricular hyperintensities according to a summarized 3-grade scale (see text).
†Defined as focal asymmetrical abnormalities on T2-weighted images and if <1 mL with low signal on proton density-weighted images.
Subjects. Many reports have not clearly stated how the subjects have been enrolled and what proportion of invited persons actually participated. In some studies control subjects have been spouses of hypertensive patients, relatives of demented patients, or members of the authors' families. In our study of a randomly selected group from the general population, 43.5% of those invited participated in the study. The proportion of participants was higher in the younger age groups (eg, 52.6% in the group aged 35 to 44 years and 76.5% in the group aged 45 to 54 years). In the group aged older than 85 years, in which only 19.0% of the invited subjects participated, it is uncertain if the examined subjects are representative of the population.

It is essential to use appropriate statistical methods in studies correlating WMH with clinical findings. The gradings of WMH are ordinal scale, and not continuous, variables. Univariate analysis alone is not sufficient because covariation between different risk indicators may occur. In other studies, analysis of subjects in different age groups, multivariate linear regression analysis, or analysis of some possible markers only for WMH have been performed. Stepwise logistic regression is suitable for variables that are not continuous and has been used by Sullivan et al.

Brain MRI Findings

The classification of WMH on MRI may vary between examiners. In the present study the interobserver agreement was good for deep ($k=0.88$) and periventricular WMH according to Fazekas et al and the summarized three-grade scale for grouping WMH ($k=0.86$). van Swieten et al found interobserver agreement with a $k$ value of 0.6 (0.78 weighted $k$) for their scale of grading white matter lesions on MRI. The proportion of subjects with WMH and the severity of WMH increased with age in our study. Age was the most important predictor for WMH in our stepwise logistic regression analysis, in agreement with earlier studies.

Correlation Between WMH and Heart and Carotid Disease

Univariate analysis showed a significant correlation between WMH and a history of heart disease as well as abnormal findings on echocardiography (TTE or TEE and TEE combined). History of heart disease (but not findings on TTE and TEE) was found to be an independent predictor for WMH after stepwise logistic regression analysis had been performed. One explanation for this finding could be that the echocardiographic examinations were only used to identify possible cardiac embolic sources, whereas the history of heart disease also included several other heart conditions, eg, history of ischemic heart disease and arrhythmia. A relation between heart disease and WMH has been seen in some but not all previous studies. We did not find carotid stenosis of 50% or greater to be independently related to WMH. This is in accordance with earlier studies.

Correlation Between WMH and Hypertension

With univariate analysis both deep and periventricular WMH significantly correlated with hypertension (defined as medical treatment for hypertension or systolic blood pressure $\geq 160$ mm Hg), but the significance only remained for periventricular WMH after stepwise logistic regression analysis. Because blood pressure increases with age, hypertension may not have been detected as an independent variable in a stepwise logistic statistical model for deep WMH. The fact that we only measured blood pressure once is a limitation, and it is also possible that our study included too few subjects to obtain a significant correlation between deep WMH and hypertension. A relation between WMH and hypertension has been found in some studies but not in others.

What Is the Anatomic/Pathological Correlate to WMH?

The significance of WMH is debated. Overall, 62.3% of the subjects in our study had WMH on MRI of the brain, with the highest proportion among the older subjects. Because of the frequent observation of minor WMH, we used a summarized three-grade scale in which minor WMH were placed in a separate group and deep and periventricular WMH were considered together. We consider this justified because there was a significant correlation between the grade of deep and periventricular WMH. WMH have been correlated with several histopathologic findings in autopsy studies and found to represent dilated perivascular spaces (Virchow-Robin spaces), arteriosclerosis, and vascular ectasia. Gliosis, infarctions, and areas of demyelination were also found to be correlated with WMH in these studies.

TABLE 3. Deep and Periventricular White Matter Hyperintensities, Classified According to Fazekas et al

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
</tr>
</tbody>
</table>
TABLE 4. Electrocardiography and Ultrasound Examination of Carotid Arteries and Heart

<table>
<thead>
<tr>
<th>Age, y</th>
<th>35-54</th>
<th>55-74</th>
<th>≥75</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>22</td>
<td>28</td>
<td>27</td>
<td>77</td>
</tr>
<tr>
<td>Carotid stenosis ≥50%</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

Electrocardiography

- Atrial fibrillation: 0/19
- Infarction: 0/19
- Left ventricular hypertrophy: 0/19

Possible major embolic source on TTE: 0/19
Possible minor embolic source on TTE: 1/19
Possible major embolic source on TTE or TEE*: 0/19
Possible minor embolic source on TTE or TEE*: 1/19

TTE indicates transthoracic echocardiography; TEE, transesophageal echocardiography. Atrial fibrillation was not included as a possible embolic source on echocardiographic examination. Possible embolic sources found on TTE were also detected on TEE, unless otherwise noted.

* Nine individuals were not examined with TEE.
† Two of these subjects were not examined with TEE.

Brain Infarctions and Their Relation to WMH

Deep gray matter hyperintensities should be separated from WMH. In our study we found deep gray matter hyperintensities in 6 individuals. It is possible that these gray matter abnormalities are of the same origin as WMH, but the proportion of small, deep “lacunar” infarctions and enlarged Virchow-Robin spaces may be different in the gray matter. We also found asymmetrical deep white matter changes that in other aspects resembled symmetrical WMH on T2-weighted MRI images.

TABLE 5. Relation Between White Matter Hyperintensities and Cardiovascular Risk Indicators by Univariate Analysis

<table>
<thead>
<tr>
<th>Risk Indicator</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>P (χ²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.0001†</td>
<td>.0001†</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Hypertension†</td>
<td>.006</td>
<td>.004</td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>.004</td>
<td>.0005</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Carotid stenosis ≥50%</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>ECG abnormal‡</td>
<td>.004</td>
<td>.0003</td>
<td></td>
</tr>
<tr>
<td>Possible cardiac embolic source</td>
<td>.003</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>TTE</td>
<td>.003</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>TTE or TEE</td>
<td>.02</td>
<td>.03</td>
<td></td>
</tr>
</tbody>
</table>

WMH indicates white matter hyperintensities; SBP, systolic blood pressure; DBP, diastolic blood pressure; ECG, electrocardiogram; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; and NS, not significant (P > .05).

† Medical treatment for hypertension or SBP ≥ 160 mm Hg.
‡ Medical treatment for heart disease now or previously.
§ Atrial fibrillation, myocardial infarction, or left ventricular hypertrophy.
| ANOVA. |
Clinical Relevance of Minor Cardioembolic Sources

The fact that minor potential cardioembolic sources were common in older subjects without stroke or transient ischemic attack raises the question of how cardiac abnormalities should be interpreted in patients with stroke. Even if present in studies of ischemic stroke patients, they may not be the explanation of the cause of stroke. It is therefore essential to compare findings of a minor potential cardiac embolic source in patients with stroke or vascular dementia with findings in a representative control group.

Acknowledgments

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