Risk Factors for White Matter Changes Detected by Magnetic Resonance Imaging in the Elderly

Patrick Sullivan, MD, Robert Pary, MD, Frank Telang, MD, A. Hind Rifai, MD, and George S. Zubenko, MD, PhD

We found increased age (p=0.001) and history or evidence of stroke (p=0.016) to be significant independent multivariate predictors of the presence and severity of leukoencephalopathy on magnetic resonance imaging brain scans in a mixed population of 35 elderly psychiatric patients and 25 neurologically healthy elderly volunteers. These results suggest that subcortical ischemia, as well as age-related changes that may not be vascular in origin, contribute to the emergence of periventricular and other deep white matter hyperintensities that are commonly seen on the magnetic resonance imaging brain scans of older adults. (Stroke 1990;21:1424-1428)

Abnormal findings on magnetic resonance imaging (MRI) are relatively common in the brains of the elderly1-5 and are apparently more common in the brains of patients who develop mental disorders in late life.1-10 Several uncontrolled reports have suggested that the periventricular hyperintensities (PVHs) and other deep white matter hyperintensities (DWMHs) detected on T2-weighted (resonance time [TR]=2,500 msec; echo time [TE]=25–100 msec) MRI head scans are especially common in elderly patients with major depression.9-11 This suggestion has been confirmed in a recent study of the MRI head scans of 128 elderly psychiatric inpatients and 44 neurologically healthy volunteers.5 Controlling for the independent effects of age and sex, both subcortical white matter hyperintensities and cortical infarcts were more common among the patients with major depression than among the volunteers. Moreover, these studies suggest that MRI may have a role in the differential diagnosis of late-life mental disorders and may carry prognostic significance and that structural brain changes may participate in the pathogenesis of idiopathic major depression in this age group.5,9-11

The terms leukoaraiosis,12 leukoencephalopathy,1,2,4,5,9-11 subacute arteriosclerotic encephalopathy,1,13 and Binswanger's disease1,12-14 have been used to refer to cases in which PVHs and other DWMHs are detected on MRI head scans. The first two terms do not imply a particular pathophysiology, while the latter two implicate cerebrovascular insufficiency in the etiology of these abnormal MRI findings. In part, this variety in nomenclature reflects existing controversy about the underlying changes in the brain that give rise to these neuroradiologic findings. The common presence of DWMHs on MRI head scans in elderly subjects without overt neurologic disease,1-2 as well as the absence of clear neurologic correlates of these findings in the context of dementing disorders,1-6 has led some investigators to suggest that the MRI findings have limited clinical significance,15 despite reports of their increased prevalence in patients with primary dementia,4 dementia of vascular origin,1,4,6,7 and major depression in late life.5,9-11 A more convincing case has been made from combined antemortem and autopsy evidence that leukoaraiosis,12 detected as patchy areas of decreased density on computed tomograms (CT scans), reflects vascular insufficiency in watershed areas supplied by perforating medullary arterioles.16-26 However, the relevance of this body of work to DWMHs detected by MRI remains uncertain because the two imaging methods do not provide equivalent information.2,5,7,27 This is not surprising since proton (water) density detected by MRI and tissue density measured by CT are not necessarily identical. In general, MRI is typically more sensitive at identifying brain parenchymal changes than CT.2,5,7,27

We determined whether established risk factors for atherothrombotic brain infarction28 predicted the pres-
ence and severity of leukoencephalopathy (PVH and DWMH) on the MRI brain scans of patients with mental disorders in late life and of neurologically healthy elderly volunteers. Our goal was to gain further insight into the nature of the brain changes that give rise to this neuroradiologic finding in the elderly.

### Subjects and Methods

The study population (n=60) consisted of a subset of subjects that had been included in a previous investigation (N=172) of brain imaging abnormalities in mental disorders of late life. The previous investigation included all 128 elderly patients admitted between 1985 and 1988 to two inpatient units of the Geriatric Health Services of the Western Psychiatric Institute and Clinic who typically met DSM-III-29 or DSM-III-R criteria for dementia or major depression; the patients were evaluated by board-certified psychiatrists and internists, with brain imaging included as a part of the usual diagnostic evaluation. The previous investigation also included 44 neurologically healthy elderly controls, chiefly caregivers and family members of patients with the clinical diagnosis of dementia, provided by the Alzheimer’s Disease Research Center of the University of Pittsburgh, where they had been evaluated by board-certified psychiatrists and neurologists. The study population included those subjects whose available clinical records were sufficiently detailed to include values for all putative risk factors for leukoencephalopathy evaluated in our retrospective analysis. No subject had a known history of multiple sclerosis, cerebral tumor, or human immunodeficiency virus–related disease.

The MRI studies were performed on a General Electric 1.5-T Signa system (Milwaukee). Spin–echo pulse sequences were used to generate both T1-weighted (TR=800 msec; TE=20 msec) and T2-weighted (TR=2,500 msec; TE=25–100 msec) coronal and axial brain images. Serial coronal sections were obtained at 5-mm thicknesses, without an interscan gap. Axial sections were also obtained at 5-mm thicknesses, with an interscan gap of 1.0–2.5 mm. Two excitations were performed to produce each image.

The presence and severity of leukoencephalopathy was determined by one of two raters who were blind to all other clinical and demographic data. Four-point scales were used to assess PVH (0, absent; 1, caps or thin lining; 2, smooth halo; and 3, irregular areas extending into the deep white matter) and DWMH (0, absent; 1, large punctate foci; 2, beginning confluence of foci; and 3, large confluent areas) according to the criteria of Fazekas and coworkers. The sum of the PVH and DWMH scores was the leukoencephalopathy score, which ranged from 0 (absent) to 6 (maximal severity). To dichotomize the leukoencephalopathy score for use in logistic regression modeling, leukoencephalopathy was defined a priori as present if the score was ≥4.

Using 17 and 10 MRI head scans selected to represent the entire range of leukoencephalopathy scores in the study population, interrater and intrarater (test–retest) reliabilities, respectively, were determined using the Pearson correlation coefficient and the intraclass correlation coefficient. The Pearson correlation coefficient reflecting intrarater reliability of the two raters was 0.91, while the intraclass correlation coefficients reflecting intrarater reliabilities were 0.97 and 0.76. To dichotomize the leukoencephalopathy score for use in logistic regression modeling, leukoencephalopathy was defined a priori as present if the score was ≥4. Using this cutoff, the kappa value reflecting intrarater reliability was 0.77, and the kappa values reflecting intrarater reliabilities were 0.78 and 0.75.

### Table 1. Putative Risk Factors for Leukoencephalopathy

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Definition</th>
<th>Risk hypothesized increased if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>At time of magnetic resonance imaging, in years</td>
<td>Older</td>
</tr>
<tr>
<td>Ischemic score(33)</td>
<td>Sum of 13 items by history, neurologic examination, or mental state examination; range 0–18</td>
<td>Higher</td>
</tr>
<tr>
<td>Stroke</td>
<td>By history or presence of infarct/lacune on magnetic resonance imaging scan</td>
<td>Present</td>
</tr>
<tr>
<td>Hypertension</td>
<td>By history, prescribed antihypertensive medication, or systolic blood pressure of &gt;140 mm Hg and diastolic blood pressure of &gt;95 mm Hg</td>
<td>Present</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>As diagnosed by neurologist</td>
<td>Present</td>
</tr>
<tr>
<td>Sex</td>
<td>Male, female</td>
<td>Male</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>History of congestive heart failure, myocardial infarction, angina, left ventricular hypertrophy, or atrial fibrillation; cardiomegaly on chest radiograph; electrocardiographic evidence of past myocardial infarction, left ventricular hypertrophy, or atrial fibrillation</td>
<td>Present</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>By history, prescribed hypoglycemic medication, or fasting serum glucose concentration of &gt;140 mg/dl</td>
<td>Present</td>
</tr>
</tbody>
</table>

Age and ischemic score were coded as continuous variables. The remainder were coded as discrete variables (present as 1 and absent as 0, male as 1 and female as 0).
The putative variables predicting leukoencephalopathy are defined in Table 1. Published studies have consistently found these variables to be risk factors for atherothrombotic brain infarction.28 Demographic, historical, physical, and laboratory data were abstracted from the subjects' charts close to the date of MRI. Demographic data consisted of date of birth, sex, and race. Historical data included history or evidence of stroke, transient ischemic attack (TIA), congestive heart failure, myocardial infarction, angina pectoris, left ventricular hypertrophy, atrial fibrillation, hypertension, and diabetes mellitus. Maximum systolic and diastolic blood pressures were abstracted from the results of physical examinations. Pertinent laboratory data included the highest fasting serum glucose concentration, the serum vitamin B12 level, hematocrit, presence of cardiomegaly on chest radiograph, predominant electrocardiographic rhythm, and electrocardiographic evidence of previous myocardial infarction or left ventricular hypertrophy or strain. The ischemic score of Hachinski and coworkers,33 which is a composite generated from 13 items obtained from the clinical history and physical examination, was also determined for each subject. Age and ischemic score were coded as continuous variables, and history or evidence of stroke, cardiac disease, TIA, hypertension, and diabetes mellitus were coded as discrete variables, present (1) or absent (0); male sex was coded as 1 and female sex as 0.

We used SAS34 for database management and statistical analysis. To make univariate comparisons of the leukoencephalopathy score with the putative predictor variables, we used the Pearson correlation coefficient for the continuous variables and Student’s t test for the discrete variables. We employed multiple linear regression to estimate the independent effects of the predictor variables on the leukoencephalopathy score. To explore possible associations among the putative predictor variables and the presence of leukoencephalopathy by calculating odds ratios, we used logistic regression with the leukoencephalopathy score dichotomized and coded as present (1) or absent (0). We also performed stepwise logistic regression including referral source and psychiatric diagnosis in addition to the putative predictor variables.

Results

The overall mean ± SD age of the study population was 69.4 ± 8.3 (range 51.1–91.8, median 68.4) years. Three subjects (5.0%) were black, and the remainder (95.0%) were Caucasian. Thirty-six subjects (60.0%) were female and the remaining 24 (40.0%) were male. The subjects' serum vitamin B12 levels ranged from 197 to 999 (normal > 175) ng/ml, and their hematocrits ranged from 32.8% to 50.7%. The frequency distribution of their leukoencephalopathy scores is presented in Figure 1.

The clinical and demographic characteristics of the patients and controls are described separately in Table 2. The controls were all outpatient referrals and were significantly younger (t = 4.98, df = 58, p < 0.0001) and more likely to be male (χ2 = 3.50, df = 1, p = 0.06) than the patients. In addition, the patients had significantly higher leukoencephalopathy scores (t = 4.75, df = 58, p < 0.0001).

Univariate associations between the putative predictor variables and the leukoencephalopathy score are presented in Table 3. Significant associations were found for age, ischemic score, and history or evidence of stroke.

The multiple linear regression model is shown in Table 4. Higher leukoencephalopathy scores were significantly associated with increased age and history or evidence of stroke. Using forward selection stepwise regression, age entered first (β = 0.088, SE = 0.022, p < 0.001), stroke second (β = 1.096, SE = 0.412, p = 0.010), and ischemic score third (β = 0.101, SE = 0.047, p = 0.034). No other variables entered the model.

Logistic regression modeling allowed us to calculate the odds ratios associated with significant predictors of the presence of leukoencephalopathy. Leukoencephalopathy was present on 17 MRI brain scans and absent from 43. Age (odds ratio = 1.16, 95% confidence interval = 1.02–1.32) was the only significant independent predictor of the presence of leukoencephalopathy in the logistic regression model that included all eight of the putative predictor variables listed in Table 1. The stepwise logistic regression procedure was used to select from among these eight variables along with referral source (inpatient service or ambulatory clinic) and psychiatric diagnosis (present or absent) for inclusion in the most parsimonious logistic regression model. The model that resulted from the stepwise procedure included age (odds ratio = 1.15, 95% confidence interval = 1.03–1.28) and stroke (odds ratio = 6.41, 95% confidence interval = 1.46–28.14) as the sole independent variables.
Transient ischemic attack

Diabetes mellitus

Cardiac disease

Sex (male)

Age

Variables and Leukoencephalopathy Score in 60 Elderly Subjects

Discussion

Both age and history or evidence of stroke were significant independent predictors of the presence and severity of leukoencephalopathy on MRI brain scans in a mixed population of elderly patients and controls. The ischemic score also was a significant independent predictor of the leukoencephalopathy score, although the magnitude of its contribution was smaller than that of either age or stroke. These data suggest that subcortical ischemia contributes to the emergence of PVHs and other DWMHs on T2-weighted MRI brain scans in the elderly.

Our findings are comparable to those of other investigators. Awad and coworkers found increased age, prior brain ischemia, and history of hypertension to be significant independent multivariate predictors of "incidental subcortical lesions." Inzitari and colleagues found history of stroke and the interaction between infarction and hypertension to be independent multivariate predictors of leukoaraiosis on CT scans. Finally, Hunt and associates determined that increased age significantly predicted the size, number, and severity of white matter hyperintensities on MRI brain scans in the elderly.

The consistent association between leukoencephalopathy and increased age is intriguing and implies the presence of some cumulative factor in its pathogenesis independent of factors associated with atherothrombotic brain infarction. One possible explanation is the additive deleterious effects of aging on cerebral perfusion. The subcortical watershed areas of the brain, supplied by penetrating striate vessels and roughly corresponding anatomically to the areas in which we identified leukoencephalopathy, are most vulnerable to these effects. Alternatively, the independent effect of age on leukoencephalopathy may result from nonvascular insults including primary degeneration, metabolic compromise, or accumulated exposure to environmental toxins.

The absence of significant univariate associations between the remaining major risk factors for stroke (hypertension, TIA, cardiac disease, diabetes mellitus, and sex) and leukoencephalopathy was surprising. The absence of significant associations between TIA or diabetes mellitus and leukoencephalopathy may have resulted from the small number of our subjects who exhibited these disorders (six and 11, respectively). However, the remaining risk factors for stroke were quite prevalent.

Several possibilities could explain the absence of univariate associations between the remaining risk factors for stroke and leukoencephalopathy. First, the associations between these clinical variables and stroke were established in population-based studies of both young and old adults, while our analyses were performed on a mixed population of elderly controls and patients with mental disorders who were referred from clinical settings. Second, the predictors of large-vessel disease leading to cerebral infarction may differ from those of small-vessel disease and the risk factors for stroke may differ from those for the subcortical ischemia that occurs without frank infarction. Our findings cannot distinguish between these hypotheses.

TABLE 2. Clinical and Demographic Characteristics of Study Population

<table>
<thead>
<tr>
<th>Psychiatric diagnosis</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Leukoencephalopathy score (mean±SD)</th>
<th>Referral source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Male</td>
<td>Female</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Absent</td>
<td>25</td>
<td>14</td>
<td>11</td>
<td>64.1±6.2</td>
</tr>
<tr>
<td>Present</td>
<td>35</td>
<td>10*</td>
<td>25*</td>
<td>73.2±7.5†</td>
</tr>
</tbody>
</table>

Psychiatric diagnosis, 16 patients with dementia and 19 patients with affective disorders as defined by DSM-III criteria.

*p=0.061, sex ratio different from absent by χ² test with continuity correction.

†p<0.0001 different from absent by Student’s t-test.

TABLE 3. Univariate Associations Between Putative Predictor Variables and Leukoencephalopathy Score in 60 Elderly Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD</th>
<th>% No.</th>
<th>Test statistic</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>69.4±8.3</td>
<td>4.1±4.0</td>
<td>r=0.60</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ischemic score 33</td>
<td>4.2±4.0</td>
<td>0.49</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Stroke (yes)</td>
<td>36.7</td>
<td>22</td>
<td>t=5.34</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48.3</td>
<td>13.0</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic</td>
<td>10.0</td>
<td>6.8</td>
<td>1.68</td>
<td>0.10</td>
</tr>
<tr>
<td>attack (yes)</td>
<td>40.0</td>
<td>24</td>
<td>1.09</td>
<td>0.28</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>43.3</td>
<td>26</td>
<td>1.55</td>
<td>0.13</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18.3</td>
<td>11</td>
<td>1.18</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Putative predictor variables defined in Table 1.

TABLE 4. Multiple Linear Regression Model: Putative Predictor Variables and Leukoencephalopathy Scores in 60 Elderly Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SEE</th>
<th>F</th>
<th>p</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.091</td>
<td>0.025</td>
<td>13.38</td>
<td>0.001</td>
<td>0.36</td>
</tr>
<tr>
<td>Stroke (yes)</td>
<td>1.905</td>
<td>0.441</td>
<td>6.17</td>
<td>0.016</td>
<td>0.12</td>
</tr>
<tr>
<td>Hypertension (yes)</td>
<td>0.079</td>
<td>0.056</td>
<td>2.00</td>
<td>0.16</td>
<td>0.04</td>
</tr>
<tr>
<td>Transient ischemic</td>
<td>0.567</td>
<td>0.655</td>
<td>0.75</td>
<td>0.39</td>
<td>0.01</td>
</tr>
<tr>
<td>attack (yes)</td>
<td>0.175</td>
<td>0.365</td>
<td>0.23</td>
<td>0.63</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardiac disease (yes)</td>
<td>-0.095</td>
<td>0.390</td>
<td>0.06</td>
<td>0.81</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus (yes)</td>
<td>0.062</td>
<td>0.469</td>
<td>0.02</td>
<td>0.90</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>-0.041</td>
<td>0.369</td>
<td>0.01</td>
<td>0.91</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Intercept</td>
<td>-4.600</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall F_{all}=7.22, R²=0.53, p<0.0001.
In summary, our results suggest that the subcortical hyperintensities commonly detected on T2-weighted MRI brain scans of elderly patients with mental disorders reflect ischemic leukoencephalopathy in the brain parenchyma along with an important independent contribution from age-related insults that may not be vascular in origin. Further studies seem warranted to evaluate the relations of these radiologic findings to treatment response and prognosis in this population.

Acknowledgment
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References
39. Key Words • leukoencephalopathy • magnetic resonance imaging • risk factors
Risk factors for white matter changes detected by magnetic resonance imaging in the elderly.

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