Progression of white matter hyperintensities in elderly individuals over 3 years

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Abstract—
Objective: The aims of this study were to examine white matter hyperintensities (WMHs) in the brains of elderly individuals, the rate of progression, the anatomic regions most vulnerable, and the predictors of change.

Methods: We examined 51 healthy volunteers (mean age 71 years) with T2-weighted brain MRI on the same scanner 3 years apart. WMH volumes were determined by an automated method, and the anatomic location of change was determined for both deep WMHs (DWMHs) and periventricular WMHs (PVWMHs).

Results: The total brain WMH volume increased by 39.6%, i.e., 13.2% per year, with the change in DWMH being 43.8% and 29.7% in PVWMH. The increase was significant in all regions except the occipital lobe and cerebellum. Age, sex, and cerebrovascular risk factors were not significant predictors of WMH progression. The main predictor of progression was baseline level of WMH. The number of WMH lesions increased by a mean of 1.78, and the progression was mainly accounted for by an increase in very large (>16 mm) lesions. Eight subjects showed a slight decrease in WMH.

Conclusions: White matter hyperintensities are progressive in most elderly individuals with an increasing rate of progression as the burden of lesions increases. The rate of progression is greater in deep white matter and in the anterior brain regions. Risk factors for progression are not well understood, and genetic and other environmental factors must be examined. Quantitation of white matter hyperintensities may serve as a surrogate marker of the progression of small vessel disease.

The data published so far suggest that WMHs do progress with time, but not in every individual. In the Austrian Stroke Prevention Study5 with mean age of the participants of 60 years, 17.9% showed progression over 3 years. In an older group (mean age 79 years), the volumes of WMHs increased by 1.1 mL over 4 years.6 Somewhat similar progression was noted in the PROSPER study9 also over 3 years, with progression notably greater in women. Many risk factors for such progression have been examined, but the results have not been consistent. Suggested risk factors include age, female sex, baseline level of WMHs, hypertension, systolic or diastolic blood pressure level, and genetic factors.10

We examined a cohort of elderly individuals for progression of WMHs and the determinants of such progression using quantitative measures of WMHs. We also investigated the possible regression of these lesions in some subjects.

Methods. Sample. Subjects were community-dwelling volunteers who participated in the control limb of the Sydney Stroke...
Study. They were aged 58 to 85 years, had no history of a neurol-
logic or psychiatric disorder, and were living independently in the
community. Eighty subjects received a brain MRI scan at base-
line. Three years later, 55 subjects were scanned on the same MRI
scanner before a change in scanner occurred. Four of these sub-
jects were excluded because of an interval history of stroke (n =
2) or TIA or transient global amnesia. Excluded subjects were com-
pared with the included subjects on demographic, clinical, and
brain imaging variables. No significant difference was found (p <
0.05) (see table E-1 on the Neurology Web site at www.neurology.
org). All subjects gave written informed consent, and the study
was approved by the Research Ethics Committee of the South-
Eastern Sydney and Illawarra Area Health Service, Sydney,
Australia.

Assessment procedure. The detailed procedures for this study
have previously been published. The baseline assessment in-
cluded a detailed medical history and examination, history of pa-
tative risk factors for cerebrovascular disease (hypertension,
diabetes, smoking, coronary artery disease, atrial fibrillation, hy-
percholesterolemia, and hypertriglyceridemia), a detailed neuro-
psychological assessment, the Mini-Mental State Examination,
a functional assessment (activities of daily living [ADL], instru-
mental ADL, and Informant Questionnaire on Cognitive Decline
in the Elderly, and laboratory investigations including fasting
blood glucose, total and high-density lipoprotein cholesterol, and
triglycerides. A subject was considered hypertensive if he or she
had been treated for hypertension or the mean current blood pres-
sure was high (systolic ≥160 or diastolic ≥95 mm Hg). Diabetes
was scored positive if the subject had previously been diagnosed
as having diabetes or a fasting blood sugar was ≥10 mM/L. The
reference normal values for cholesterol are 3.0 to 5.5 mM/L and
<2.0 mM/L for triglycerides.

MRI scans. MRI was performed on a 1.5-T Signa GE scanner
(GE Systems, Milwaukee, WI) using the following protocol: A scout
mid-sagittal cut (two-dimensional, TR 300 msec, TE 14
msec; 5 mm thickness, number of excitations 1.5); 1.5 mm thick T1-
weighted contiguous coronal sections through whole brain using a
FSPGR sequence and three-dimensional acquisition (TR [repeti-
tion time] 14.3 msec, TE [echo time] 5.4 msec); 4 mm thick (0 skip)
T2-weighted fluid-attenuated inversion recovery (FLAIR) coronal
slices through whole brain (TR 8,900, TE 145, TI [inversion time]
2200, FOV [field of view] 25, 256 × 192).

Image analysis. MRI scans were transferred to an indepen-
dent Windows NT workstation and analyzed using the software
packages ANALYZE (Mayo Foundation, Rochester MI), SPMM99
(Cognitive Neuroscience Group, National Hospital for Nervous
Diseases, London, UK), and other in-house programs. There were
two main components to image analysis. The first was the auto-
mated detection, delineation, severity rating, and volumetric mea-
surements of WMHs from FLAIR images. Because the abnormal
white matter signal varied in its intensity, we categorized it into
mild (signal intensity 3 to 6 SD greater than mean intensity for
white matter) and severe (signal intensity >6 SD). The former
usually appears as a milky fuzziness, whereas the latter is a white
opacity to the naked eye. The details of the algorithm and its
validation have been described previously.

In brief, we constructed an age-specific FLAIR template in
Montreal Neurologic Institute (MNI)-space. Spatial normaliza-
tion of the coregistered FLAIR and T1-weighted MRIs was then
performed using the FLAIR template as the target. Detection and
grading of WMH from each normalized FLAIR image with T1-
weighted image as reference were then carried out. We visually
inspected each WMH map and manually removed false classifi-
cation of WMH from the map. WMH maps thus generated were
two binary images, the voxel values of which indicated either
the presence or absence of WMH at that location. Linear and nonlin-
ear transforms were applied onto each individual MRI in warping
them into MNI-space. Therefore, WMH volume measured in MNI-
space for a subject is an absolute volume only if the subject’s intracranial volume (ICV) is the same as the ICV of the template
brain. Because this is usually not the case, the measured WMH
volume is multiplied by a scaling factor that is the ratio of the
subject’s ICV and the ICV of the template brain. The WMH
volume thus measured is a corrected volume that accounts for the
variation in ICV.

The second component of the analysis was a comparison of
baseline and follow-up scans on WMHs using two methods: i)
change of WMH volumes in brain regions of interest (ROI) and ii)
a voxel-wise analysis of 102 WMH brain maps (two scans for each
subject at baseline and 3-year follow-up scans). Both methods
were automated. In the first method, the reference brain was
partitioned into lobes or regions (table 1) using a standard atlas, and
WMH volumes in particular brain regions were calculated
from brain warped into the reference space. Details of the method,
including the maps of brain regions, have been previously pub-
lished. The WMH volume differences between the baseline and
3-year follow-up scans were then compared (table 1). In the second
method, voxel-wise analysis was performed to generate statistical
parametric maps in detecting anatomic regions with significant
differences between the scans at two time points. To prepare the
images, we applied a gaussian smoothing kernel (full width at half
maximum 10 mm) on the individual WMH map to increase the
signal-to-noise ratio. The resulting blurred WMH map can be
thought of as an estimate of the probability that the subject has a

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Baseline (mean, SD)</th>
<th>3 y (mean, SD)</th>
<th>t Value</th>
<th>Change, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWMHs</td>
<td>11.32 (11.12)</td>
<td>16.27 (15.15)</td>
<td>5.375*</td>
<td>4.96 (6.58)</td>
</tr>
<tr>
<td>FrONTAL</td>
<td>2.22 (3.89)</td>
<td>3.39 (4.66)</td>
<td>4.963*</td>
<td>1.17 (1.68)</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.22 (0.30)</td>
<td>0.33 (0.41)</td>
<td>4.158*</td>
<td>0.11 (0.19)</td>
</tr>
<tr>
<td>Parietal</td>
<td>6.33 (7.06)</td>
<td>9.74 (10.08)</td>
<td>5.156*</td>
<td>3.41 (4.72)</td>
</tr>
<tr>
<td>Occipital</td>
<td>2.54 (1.52)</td>
<td>2.81 (1.38)</td>
<td>1.847</td>
<td>0.27 (1.04)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.01 (0.02)</td>
<td>0.03 (0.09)</td>
<td>1.578</td>
<td>0.02 (0.09)</td>
</tr>
<tr>
<td>PVWMHs</td>
<td>5.05 (3.32)</td>
<td>6.56 (3.85)</td>
<td>6.085*</td>
<td>1.50 (1.76)</td>
</tr>
<tr>
<td>Anterior horn</td>
<td>1.73 (1.16)</td>
<td>2.05 (1.18)</td>
<td>5.880*</td>
<td>0.32 (0.39)</td>
</tr>
<tr>
<td>Posterior horn</td>
<td>1.42 (1.15)</td>
<td>1.94 (1.43)</td>
<td>5.272*</td>
<td>0.52 (0.71)</td>
</tr>
<tr>
<td>Periventricular body</td>
<td>1.91 (1.35)</td>
<td>2.57 (1.64)</td>
<td>5.592*</td>
<td>0.66 (0.84)</td>
</tr>
<tr>
<td>Total WMH volume</td>
<td>16.38 (13.79)</td>
<td>22.86 (18.02)</td>
<td>6.057*</td>
<td>6.48 (7.64)</td>
</tr>
<tr>
<td>Severe WMH volume</td>
<td>4.11 (5.78)</td>
<td>5.54 (7.33)</td>
<td>4.537*</td>
<td>1.43 (2.25)</td>
</tr>
</tbody>
</table>

Volumes are in cubic centimeters.

*p < 0.001.

DWMHs = deep white matter hyperintensities; PVWMHs = periventricular white matter hyperintensities.
WMH at that location. The comparison of time 1 with time 2 is a voxel-by-voxel comparison using SPM99, with figure 1 showing significant ($p < 0.001$) increases in WMH in different brain regions. The number of nonoverlapping (discrete) WMHs was calculated automatically by a computer program that also estimated the diameter of each WMH, assuming it to be a sphere. The scans were also rated visually by a trained rater with good interrater (intraclass correlation coefficients from 0.7 to 0.86 various measures) and intrarater (intraclass correlation coefficients 0.8 to 0.9) reliability determined on 10 scans each. Periventricular white matter hyperintensity (PVWMH) and deep WMH (DWMH) hyperintensity were rated on a 0 to 3 modified scale with the images displayed on a computer console. There ratings correlated well with the automated measures of WMH volumes, thereby validating the technique (intraclass correlation coefficients for DWMH (0.63) and for PVWMH (0.59), both with $p < 0.001$).

Statistical analysis. A repeated-measures analysis of variance was conducted to determine the change in WMH volume from the baseline scan to the 3-year scan. Changes in total brain WMH volumes and DWMH and PVWMH volumes were examined. Post hoc analyses were performed to examine changes in four anatomic regions in the deep white matter and three regions in the periventricular white matter. We also examined whether any individuals had experienced a decrease in WMH volume over this period. To examine the determinants of the change in WMH volume, we performed an exploratory single-variable analysis using correlations with change scores and subgroup comparisons. We finally performed a regression analysis on the variables approaching significance ($p < 0.01$).

Results. Subject characteristics. The demographic and clinical characteristics of the subjects are summarized in table 2. The mean (SD) age of the subjects was 70.96 (5.9) years and 51% were men. (table E-2).

Progression of WMH. There was a significant increase in volume of WMH in both the deep and periventricular white matter (table 1). Total brain WMH volume increased by 39.6%, i.e., 13.2% per year. The DWMH increased by 43.8%, whereas the PVWMH increased by 29.7% in the same period. An increase was seen in 47 (92.2%) subjects. When brain regions were examined, the increase was significant in all regions except in the occipital lobe and cerebellum. The percentage change ranged from 10.6% (occipital lobe) to 52.5% (frontal lobe) (figures E-1 and E-2).

Figure 1. Voxel-by-voxel longitudinal comparison (3 years apart) of white matter hyperintensities using paired t test with SPM99. Significant increases were detected in the color-coded areas. Axial view of the t map, with voxels showing increase at $p < 0.001$ (uncorrected for multiple observations, $t > 3.13$) highlighted, is registered with the average brain (mni-152 brain). The first slice is at $z = -10$ mm and the last slice is at $z = 54$ mm with 2 mm apart in the $z$ direction.
When subjects were subdivided based on the baseline WMH volume, age was a determinant of progression of WMH \((F = 2.088, \text{Wilks } \lambda = 0.635, p = 0.011)\), but not sex \((F = 1.163, \text{Wilks } \lambda = 0.808, p = 0.342)\). However, age was not a determinant of progression, with its correlation with change in volume of WMH being 0.18 \((p = 0.21)\). Similarly, there was no sex difference in the rate of progression. Of the cerebrovascular risk factors, only the presence of hypertension reached significance (table 3), but the direction of effect was opposite to what was expected, with participants with normal cholesterol showing greater increase in WMHs. Because we used a single measure of cholesterol level for the categorization, which could have been influenced by the current use of statins, we repeated the analysis with statin categorization, which could have been influenced by the current use of statins.

### Determinants of progression

When the baseline WMH volumes were examined, age was a determinant \((F = 2.088, \text{Wilks } \lambda = 0.635, p = 0.011)\), but not sex \((F = 1.163, \text{Wilks } \lambda = 0.808, p = 0.342)\). However, age was not a determinant of progression, with its correlation with change in volume of WMH being 0.18 \((p = 0.21)\). Similarly, there was no sex difference in the rate of progression. Of the cerebrovascular risk factors, only the presence of hypertension reached significance (table 3), but the direction of effect was opposite to what was expected, with participants with normal cholesterol showing greater increase in WMHs. Because we used a single measure of cholesterol level for the categorization, which could have been influenced by the current use of statins, we repeated the analysis with statin categorization, which could have been influenced by the current use of statins.

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### Discrete WMH

In size, WMHs may vary from small punctate to large confluent areas. The total numbers, mean (SD), of discrete WMHs increased from 20.69 (9.67) at baseline to 22.47 (7.96) at 3-year follow-up. On average, there were 1.78 more hyperintensities in the white matter on follow-up. It is not certain that these were new lesions as the increase represented a combination of the emergence of new and the possible resolution and disappearance of old lesions. The changes in the number of WMH of different sizes are presented in table 4. Four subjects who did not have large or very large WMHs at the baseline scan continued to be free of large lesions on follow-up. The number of punctate (diameter <3 mm) WMHs for baseline and 3-year follow-up scans were 12.14 (6.73) and 13.12 (5.93), focal (3 mm < diameter < 12 mm) WMHs 4.47 (3.41) and 4.82 (2.96) and large (>12 mm) WMHs 2.71 (0.90) and 2.78 (1.06). None of the above showed any significant difference in numbers (table 4). The change in total WMH volume over the 3 years was mainly accounted for by an increase in very large (>16-mm diameter) WMH from a mean of 1.33 to a mean of 1.75 lesions per scan (paired t test: \(t = 4.050, df = 50, p < 0.001\)). The number of subjects with very large lesions increased from 38 to 40 over the 3 years.

### Regression of WMH

Seven subjects had a decrease in PVWMH (mean 0.57 mL, range 0.08 to 2.04 mL) whereas only one subject showed a decrease in DWMH volume.
Discussion. We examined 51 elderly subjects, who had no previous neurologic or psychiatric disorders, with repeat MRI brain scans after an interval of 3 years. An increase in the extent of WMH of 39.6% over baseline levels was found in this period. The mean volume of increase in total brain WMH was 6.48 mL, on a baseline of 16.38 mL. This is not inconsistent with previous studies that have examined WMH with serial MRI scans5-9 and is to be expected based on the well-documented relationship of WMH with age.2 A number of previous reports relied on visual ratings of MRI lesions5,7 and therefore were

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**Table 3 Effects of demographic factors on change in total white matter hyperintensity (WMH) volume (single variable analysis, uncorrected)**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Sample size</th>
<th>Mean change in total WMHs (SD)</th>
<th>t†/Pearson correlation‡</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51</td>
<td>6.48 (7.64)</td>
<td>0.179‡</td>
<td>—</td>
<td>0.21</td>
</tr>
<tr>
<td>Education</td>
<td>51</td>
<td>6.48 (7.64)</td>
<td>−0.011‡</td>
<td>—</td>
<td>0.94</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>26</td>
<td>6.84 (8.42)</td>
<td>0.337†</td>
<td>49</td>
<td>0.74</td>
</tr>
<tr>
<td>Women</td>
<td>25</td>
<td>6.11 (6.89)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>19</td>
<td>6.10 (8.47)</td>
<td>0.274†</td>
<td>49</td>
<td>0.79</td>
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<tr>
<td>No</td>
<td>32</td>
<td>6.71 (7.24)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Smoking§</td>
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</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>5.22 (7.30)</td>
<td>1.010†</td>
<td>48</td>
<td>0.32</td>
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<tr>
<td>No</td>
<td>29</td>
<td>7.45 (8.00)</td>
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<td>Coronary arterial disease</td>
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<tr>
<td>Yes</td>
<td>8</td>
<td>4.52 (5.06)</td>
<td>0.790†</td>
<td>49</td>
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<tr>
<td>No</td>
<td>43</td>
<td>6.85 (8.02)</td>
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<tr>
<td>Hypercholesterolemia¶</td>
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<tr>
<td>Yes</td>
<td>12</td>
<td>3.86 (3.78)</td>
<td>2.021†</td>
<td>42.26</td>
<td>0.05*</td>
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<tr>
<td>No</td>
<td>35</td>
<td>7.57 (8.72)</td>
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</table>

<table>
<thead>
<tr>
<th>Factor</th>
<th>Sample size</th>
<th>Mean of increased total WMH change (SD)</th>
<th>t†</th>
<th>df</th>
<th>p</th>
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<tr>
<td>Diabetes</td>
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<td>Yes</td>
<td>3</td>
<td>1.29 (2.02)</td>
<td>1.218†</td>
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<td>No</td>
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<td>6.81 (7.75)</td>
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<td>Atrial fibrillation</td>
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<td>Yes</td>
<td>2</td>
<td>0.53 (0.41)</td>
<td>1.132†</td>
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<tr>
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<td>48</td>
<td>6.81 (7.76)</td>
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<tr>
<td>Taking antihypertensive medication</td>
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<tr>
<td>Yes</td>
<td>17</td>
<td>6.36 (7.96)</td>
<td>0.108†</td>
<td>45</td>
<td>0.92</td>
</tr>
<tr>
<td>No</td>
<td>30</td>
<td>6.10 (7.98)</td>
<td></td>
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<td>Taking antioxidant</td>
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<tr>
<td>Yes at baseline</td>
<td>8</td>
<td>9.53 (8.66)</td>
<td>−1.235†</td>
<td>49</td>
<td>0.22</td>
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<td>No at baseline</td>
<td>43</td>
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<tr>
<td>Yes at 12 mo</td>
<td>5</td>
<td>7.86 (5.40)</td>
<td>−0.423†</td>
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<td>0.67</td>
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<tr>
<td>No at 12 mo</td>
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<td>6.33 (7.88)</td>
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<td></td>
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<tr>
<td>Yes at 3 y</td>
<td>8</td>
<td>5.20 (4.19)</td>
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<td>0.61</td>
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<tr>
<td>No at 3 y</td>
<td>43</td>
<td>6.72 (8.14)</td>
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</tbody>
</table>

Volumes are in cubic centimeters.

* When covaried for use of statins, F = 1.503, p = 0.22.
§ Missing data for one subject.
¶ Missing data for four subjects.
unable to quantify the change. One study\(^6\) reported a mean volume increase of 1.1 ± 1.8 mL over 4 years in individuals 79 ± 4 years old, which is much lower than that seen in our study. This may be due to the fact that these authors used only three brain slices for the estimation of WMH volume, whereas our study used a volumetric acquisition of the whole brain. Another study\(^8\) reported a change of 26.7% in WMH volume over 2 years, suggesting an annual increase of about 13.4%, which is similar to our result. The volumetric increase was 1.51 mL on a baseline value of 4.91 mL in this study. The increase in WMH occurred in a majority (92.2%) of the subjects in our study. In an Austrian study,\(^5\) 17.9% of individuals aged 60 ± 6 years showed progression over 3 years. In a further report,\(^20\) subjects were followed over 6 years, and a further increase was reported. This was most marked in those with early confluent and confluent lesions. Those with confluent lesions at baseline had a median increase of 9.3 mL over the 6 years. In one small study,\(^7\) eight of 14 subjects showed progression.

Although the increase in WMH was quite widespread in the brain, there were some regional variations. The increase in DWMH was greater than that seen in PVWMH, similar to that reported in one study.\(^9\) There has been some debate in the literature whether DWMH and PVWMH represent distinct subcategories of lesions or should be considered on a continuum.\(^21\) It has been suggested that the pathogenesis of these two kinds of lesions is different even though they share some commonalities.\(^4,22\) The functional consequences of DWMH and PVWMH may also be different.\(^23\) The different rates of progression of the two types further support maintaining a distinction between them. In the deep white matter, the frontal WMH progressed the most and the occipital WMH the least. This explains the functional consequences of WMHs, which generally lead to slowing of information-processing speed and the dysexecutive syndrome.\(^3,5,24\) A few new WMHs were seen as having formed in the period of follow-up, but most of the change was explained on the basis of an increase in size of relatively large WMH. Similar results were seen in the somewhat younger cohort of the Austrian Stroke Prevention Study,\(^20\) in which there was no or negligible progression in subjects with no or punctate WMH, whereas those with confluent lesions showed significant increase in volume of WMH.

Even though there has been much discussion of the pathogenesis of WMH, predictors of the progress-

![Figure 2. Correlation of baseline white matter hyperintensity (WMH) volumes and change in WMH volumes over 3 years in elderly subjects.](image)

Table 4 Change in white matter hyperintensities (WMHs) over 3 years according to size, measured with the assumptions of WMHs as small spheres: Only the very large WMHs increased in number, suggesting an increase in size from large to very large

<table>
<thead>
<tr>
<th>Size of discrete WMH clusters</th>
<th>No. of discrete WMH clusters</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Punctuate, &lt;3 mm (3–10 voxels)</td>
<td>Baseline</td>
<td>2</td>
<td>34</td>
<td>12.14</td>
<td>1.520</td>
<td>50</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>3</td>
<td>29</td>
<td>13.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal, 3–12 mm (11–115 voxels)</td>
<td>Baseline</td>
<td>0</td>
<td>19</td>
<td>4.47</td>
<td>0.953</td>
<td>50</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>0</td>
<td>13</td>
<td>4.82</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confluent large, 12–16 mm (116–268 voxels)</td>
<td>Baseline</td>
<td>1</td>
<td>5</td>
<td>2.71</td>
<td>0.481</td>
<td>50</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>1</td>
<td>6</td>
<td>2.78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very large, &gt;16 mm (&gt;268 voxels)</td>
<td>Baseline</td>
<td>0</td>
<td>3</td>
<td>1.33</td>
<td>4.050</td>
<td>50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>0</td>
<td>4</td>
<td>1.75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Baseline</td>
<td>8</td>
<td>50</td>
<td>20.96</td>
<td>2.144</td>
<td>50</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>9</td>
<td>51</td>
<td>22.47</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
sion of these lesions have been difficult to determine.\textsuperscript{25} Age is the most consistent risk factor for WMH, but age did not increase the rate of progression of the lesions in our study. In only one study was age found to be a risk factor for an increase in the rate of progression.\textsuperscript{8} In the Austrian study,\textsuperscript{20} the number of subjects with progression was lower than in some other studies,\textsuperscript{6,7} including our own, and this could be accounted for by a lower age of the sample in that study. However, those with large lesions at baseline did demonstrate a major change, suggesting that proportionate increase may well be independent of age. A factor such as age may be related to baseline values but not the rate of subsequent change if age has a linear relationship with WMH volume. We must point out, however, that the statistical power for the different relationships varies, with that for examining the determinants of change being much lower, and this may account for the findings.

Hypertension has been another important factor implicated in the pathogenesis of WMH. Two studies\textsuperscript{5,7} implicated a high diastolic blood pressure as a risk factor for progression, but this was not seen in our study nor in others.\textsuperscript{6,8,9} In our study, hypertensive patients taking regular medication did not have lower rates of progression than those with a diagnosis of hypertension but who were not taking medication, although the numbers in the latter group were small. Another factor implicated is diabetes,\textsuperscript{8} but our sample had too few participants with diabetes to examine this. We did not find sex differences in the rate of progression, but a higher rate in women has been reported in one study.\textsuperscript{8} A caveat in the acceptance of these results is the low power of our study as mentioned above, which increases the risk of falsely accepting the null hypothesis.

As has been reported in a number of studies,\textsuperscript{5,6,8,9,20} the main predictor of progression is the extent of WMH at baseline. In our study, the change in DWMH volume was mainly accounted for by an increase in the size and number of large and very large lesions. In the Austrian study,\textsuperscript{20} the early confluent and confluent lesions demonstrated a significant increase, but not the punctate and focal lesions. These findings suggest a worsening trajectory for these lesions, with a worsening rate of progression as their extent increases. It appears that much of this worsening is independent of putative risk factors for cerebrovascular disease.

It has been proposed that genetic factors may be important in the genesis of WMH and may explain the rate of its expression. The best study of the genetic factors is CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy), but this accounts for a very small minority of cases with extensive WMH.\textsuperscript{26} Some single nucleotide polymorphisms have been examined as risk factors of WMH progression. In the Austrian study,\textsuperscript{20} an association was noted for the angiotensinogen M235T polymorphism. Homozygosity for the T allele was related to a 3.19-fold increased likelihood of lesion progression when compared to the other genotypes, and this accounts for a very small minority of cases with extensive WMH.\textsuperscript{26} The possible mechanisms are not known. It could be a marker in linkage disequilibrium with a close-by etiologically important polymorphism, such as mutations in the promoter region of the angiotensinogen gene. Mutations in the promoter regions have been related to an eightfold increase in brain changes due to small vessel disease.\textsuperscript{10} The renin-angiotensin system may have an effect on small vessel disease and thereby WMH independent of hypertension. Arguably, other

### Table 5 Comparisons of age, sex, risk factors, and MRI measures between subjects with and without decreased white matter hyperintensity (WMH) volumes either in deep or periventricular white matter

<table>
<thead>
<tr>
<th>Subjects with decreased WMHs</th>
<th>Yes (n = 18)</th>
<th>No (n = 43)</th>
<th>df</th>
<th>t/χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, no. (%)</td>
<td>74.63 (4.75)</td>
<td>70.19 (6.01)</td>
<td>49</td>
<td>−1.972</td>
<td>0.05</td>
</tr>
<tr>
<td>Sex, male, no. (%)</td>
<td>7 (87.5)</td>
<td>19 (44.2)</td>
<td>1</td>
<td>3.479</td>
<td>0.06</td>
</tr>
<tr>
<td>Education, y, no. (%)</td>
<td>11.38 (2.20)</td>
<td>11.98 (3.92)</td>
<td>49</td>
<td>0.420</td>
<td>0.68</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>4 (50)</td>
<td>15 (34.9)</td>
<td>1</td>
<td>0.659</td>
<td>0.42</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>1 (12.5)</td>
<td>2 (4.7)</td>
<td>1</td>
<td>0.002</td>
<td>0.96</td>
</tr>
<tr>
<td>Coronary artery disease, no. (%)</td>
<td>2 (25)</td>
<td>6 (14)</td>
<td>1</td>
<td>0.622</td>
<td>0.43</td>
</tr>
<tr>
<td>Hypercholesterolemia, no. (%)</td>
<td>2 (25.0)</td>
<td>10 (25.6)</td>
<td>1</td>
<td>0.001</td>
<td>0.97</td>
</tr>
<tr>
<td>Smoking, no. (%)</td>
<td>5 (62.5)</td>
<td>16 (38.1)</td>
<td>1</td>
<td>0.794</td>
<td>0.37</td>
</tr>
<tr>
<td>Atrial fibrillation, no. (%)</td>
<td>0 (0)</td>
<td>2 (4.8)</td>
<td>1</td>
<td>0.000</td>
<td>1.00</td>
</tr>
<tr>
<td>Baseline WMHs, mL</td>
<td>22.74 (18.84)</td>
<td>15.20 (12.58)</td>
<td>49</td>
<td>−1.435</td>
<td>0.16</td>
</tr>
<tr>
<td>Baseline DWMHs, mL</td>
<td>16.33 (15.14)</td>
<td>10.38 (10.16)</td>
<td>49</td>
<td>−1.402</td>
<td>0.17</td>
</tr>
<tr>
<td>Baseline PVWMHs, mL</td>
<td>6.38 (3.93)</td>
<td>4.81 (3.18)</td>
<td>49</td>
<td>−1.236</td>
<td>0.22</td>
</tr>
</tbody>
</table>

DWMHs = deep white matter hyperintensities; PVWMHs = periventricular white matter hyperintensities.
even less well understood genetic factors may be relevant to the pathogenesis of WMH.

It is interesting that not all subjects showed a worsening of WMH, as has been reported by other authors. In our study, some subjects showed a reduction in the extent of WMH. It is conceded that these improvements were small in magnitude and may represent artifacts of measurement. However, because WMHs are not representative of irreversible pathology, as evidenced by the partial reversibility of MS lesions, it is conceivable that some of the WMH seen in elderly brains may be reversible. The study shows that the majority of these lesions are persistent.

Some limitations of our study should be highlighted. First, the sample comprised volunteers who had responded to advertisements. Therefore, they cannot be deemed truly representative of the community, even though they were screened for the absence of neuropsychiatric disorders. Second, a number of subjects in the original cohort did not receive a follow-up scan as our scanner was replaced with a Philips scanner due to reasons extraneous to this study. Even though the subjects were imaged on the new scanner, the results of WMHs were significantly different between the two scanners for the data to be useful. A comparison of those who were excluded from the study for this reason with those included showed that this did not unduly bias the sample. Third, the sample size was relatively small compared to some of the larger studies such as the Austrian study and the PROSPER study. The study had sufficient power to examine the main determinants of WMHs at baseline, but the power for examining the various determinants of progression was low. The smaller size of the study, however, permitted us to do a more detailed analysis of WMH. Fourth, we did not investigate genetic and some other risk factors, but this is the subject of future work. Fifth, we did not investigate the functional consequences of change in WMH volumes for this report. Sixth, a methodological issue is noteworthy. Our image analyses were carried out in “standard” space, which meant that both our ROI- and voxel-based approaches could only achieve an approximation of the variability of each individual’s anatomy. A clear example is that of the ventricles. Although nonlinear warping was used, effects of individual differences in the sizes and shapes of ventricles were still present, and within a standard template of periventricular area, a WMH cluster could be defined as either PVWMH or DWMH based on these individual differences. Furthermore, the ROI approach sometimes led to an arbitrary grouping. A confluent WMH could, for instance, be categorized as being both frontal and temporal if it crossed the boundary between the two regions. These spatial limitations must be considered in the interpretation of the results.

The rapid increase in WMH in our subjects supports the potential use of WMH volume as a surrogate marker for small vessel disease progression in elderly individuals. Because WMHs are known to have functional consequences and the volumetric estimation of these lesions is now possible, they can provide an objective measure of outcome of preventive trials. Based on the Austrian study data of an increase of 5.2 mL in WMH volume over 3 years, it has been suggested that 195 subjects with confluent lesions would be required per treatment arm to demonstrate a 20% reduction in the rate of disease progression over a 3-year period. An increase of 6.46 mL over 3 years in our study is consistent with this estimation. The baseline level of WMHs was higher in our sample, which may be due to the older age of our sample.

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References


January 16, 2007 NEUROLOGY 68 221

VIDEO  Ocular dipping and ping-pong gaze in hypoxic encephalopathy
Young-Mi Oh, MD; Seong-Hae Jeong, MD; and Ji Soo Kim, MD, Seoul, Korea

A 16-year-old girl with fever of unknown origin was found comatose in the morning. Examination disclosed periodic eye movements with an initial downward deviation followed by rapid upward correction (dipping), which lasted 10 to 15 seconds (figure, A; video E-1, on the Neurology Web site at www.neurology.org). Intermittently, these movements were followed by slow to-and-fro horizontal eye motion (ping-pong gaze) immediately or with a latency of several seconds (figure, A, arrow; video E-1). During the dipping and roving eye motion, EEG showed irregular mixed slowings in all the leads. MRI revealed lesions consistent with anoxic brain damage (figure, B). The ocular dipping and ping-pong gaze resolved over the following several weeks. However, she remained in vegetative state without recovery for the past 6 months since the initial event.

While ocular bobbing is commonly observed in intrinsic pontine lesions, ocular dipping and ping-pong gaze rarely occur in metabolic or hypoxic encephalopathies.1 However, the occurrence of ocular dipping and ping-pong gaze in our patient suggests a common pathophysiology such as hypoxia at several sites in the nervous system.2

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Disclosure: The authors report no conflicts of interest.

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Figure. (A) Video-oculographic recording demonstrates initial downward ocular deviation followed by rapid upward correction (ocular dipping), which is associated with disjunctive horizontal eye motion in the left eye (slow rightward deviation). The recording also shows slow to-and-fro horizontal eye motion (arrow), consistent with ocular roving (ping-pong gaze). LH = horizontal position of the left eye; LV = vertical position of the left eye; RH = horizontal position of the right eye; RV = vertical position of the right eye. (B) T1-weighted MRIs, 20 days after initial event, show high signal intensities in bilateral basal ganglia and cortices, and diffuse brain atrophy, which are consistent with hypoxic brain damage. (Video) Patient shows periodic eye movements with an initial downward deviation followed by rapid upward correction (ocular dipping), and slow to-and-fro horizontal eye motion (ocular roving, ping-pong gaze). Also, rightward deviation is shown in the left eye during the slow downward movements.
Ocular dipping and ping-pong gaze in hypoxic encephalopathy
Young-Mi Oh, Seong-Hae Jeong and Ji Soo Kim

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