Longitudinal Magnetic Resonance Imaging Vascular Changes, Apolipoprotein E Genotype, and Development of Dementia in the Neurocognitive Outcomes of Depression in the Elderly Study

David C. Steffens, M.D., Guy G. Potter, Ph.D., Douglas R. McQuoid, B.S., James R. MacFall, Ph.D., Martha E. Payne, Ph.D., James R. Burke, M.D., Brenda L. Plassman, Ph.D., Kathleen A. Welsh-Bohmer, Ph.D.

Objective: Several studies suggest that depression is a risk factor for development of dementia in the elderly. In a study of older depressed individuals, the authors examined both neuroimaging and genetic factors in development of dementia. The authors hypothesized that change in subcortical gray matter and white matter hyperintensity volumes would be associated with development of dementia, as would presence of an apolipoprotein E (APOE) epsilon 4 allele. Methods: The sample consisted of 161 older depressed subjects without dementia who had magnetic resonance imaging scans at baseline and at two years. Blood samples were also taken to determine APOE genotype. All participants were treated with antidepressants using a guideline-based treatment algorithm. Their cognitive status was evaluated annually. A consensus panel of experts evaluated each case to determine cognitive status and assign a diagnosis. Results: Twenty subjects became demented over the follow-up period (5.4 years on average). Change in white matter hyperintensity volume was significantly associated with development of dementia, especially among non-Alzheimer dementias. There was a trend for change in subcortical gray matter hyperintensity volume to be associated with incident dementia. APOE genotype was not associated with onset of dementia. Conclusion: Worsening cerebrovascular disease in older depressed adults is associated with cognitive decline and dementia, particularly of the non-Alzheimer disease type. The association of change in white matter lesion volume and incident dementia among depressed elders extends the vascular depression hypothesis of geriatric depression to include cognitive outcomes of depression in the elderly. (Am J Geriatr Psychiatry 2007; 15: 839–849)
Both epidemiological and clinical studies have provided evidence that geriatric depression is associated with higher risk of development of Alzheimer disease (AD) and other dementias.\textsuperscript{1–4} Research in the past decade suggests that late-life depression may be either a risk factor or a prodrome for dementia,\textsuperscript{5–7} but the biological basis of the link is not clear.

Neuroimaging studies may prove useful to explain the neurobiological relationship between depression and dementia. Vascular changes in subcortical gray and white matter on magnetic resonance imaging (MRI) brain scans are associated with poor affective and cognitive outcomes of depression in older adults.\textsuperscript{8} Subcortical vascular change also appears to affect cognition over time. For example, periventricular white matter hyperintensities were associated with cognitive decline in one three-month study of an elderly population.\textsuperscript{9} We previously reported an association between gray-matter hyperintensities and subsequent development of dementia in an older, depressed sample.\textsuperscript{10}

There have been few neuroimaging studies examining progression of vascular change and cognitive decline. One study found that change in lacunar infarct volume but not in white-matter hyperintensity (WMH) volume was associated with worsening in executive function in one study,\textsuperscript{11} whereas another found that increased WMH volume was associated with decline in verbal intelligence quotient.\textsuperscript{12} The aim of the present study was to examine the relationship between changes in subcortical vascular lesion burden and development of dementia among nondemented depressed patients. We hypothesized that increases in subcortical white and gray matter hyperintensity volumes would be associated with development of dementia, as would presence of the apolipoprotein E (APOE) epsilon 4 allele. Ultimately, our goal is to determine if MRI can be used to stratify depressed patients for risk of dementia.

METHODS

Subjects

Subjects were enrolled in the Neurocognitive Outcomes of Depression in the Elderly (NCODE) study, a longitudinal study of older adults with and without depression at Duke University Medical Center. In a previous report,\textsuperscript{13} we noted that 2 of 138 non-depressed controls had developed dementia; currently that number is 3, which precludes meaningful comparisons with depressed subjects. As a result, the present study focuses only on the depressed cohort (N = 161). Details of methods used in the NCODE study have been reported previously.\textsuperscript{13} Briefly, depressed subjects were enrolled in the study if they met criteria for a current episode of unipolar major depression and were age 60 and older. Subjects were referred to the study from the Duke inpatient and outpatient psychiatry services and from the Duke General Internal Medicine Clinic. Exclusion criteria included presence of another major psychiatric illness, including schizophrenia, schizoaffective disorder, bipolar disorder, lifetime alcohol or substance dependence, and dementia. Patients with psychotic depression or comorbid anxiety disorders were included, as long as major depression was deemed by the study psychiatrist to be the primary psychiatric disorder. Aside from dementia, other neurological illnesses that could affect structural brain MRI scans were excluded, including stroke, Parkinson disease, multiple sclerosis, and seizure disorder. Subjects with contraindications to brain MRI were also excluded. After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the Institutional Review Board at Duke University Medical Center.

Structured Interview and Depression Assessment

At baseline, a study geriatric psychiatrist interviewed each depressed subject and completed standardized clinical assessments, including the 17-item Hamilton Rating Scale for Depression,\textsuperscript{14} the Montgomery-Asberg Depression Rating Scale (MADRS),\textsuperscript{15} and the Clinical Global Impression scale. A trained interviewer administered the Duke Depression Evaluation Schedule (DDES,\textsuperscript{16}), which assesses depression using National Institute of Mental Health (NIMH) Diagnostic Interview Schedule,\textsuperscript{17} as well as cognitive status, physical health (two questions asking about diagnosis of “high blood pressure” and “heart trouble”), and the four measures that comprise the Duke Social Support Index (DSSI): instru-
mental social support, social interactions, subjective social support, and nonfamily social network. Clinical assessments were repeated when clinically indicated, but at least every three months. For the present study, the MADRS was the main depression outcome measure. All raters (N = 5) are trained on completion of the MADRS (using 10 patients), and high interrater reliability (κ > 0.9) was confirmed.

**Baseline Cognitive Screen**

Subjects were excluded if they had dementia or suspected dementia at baseline based on information available to the assigned Minnesota Child Response Center (MHCRC) geriatric psychiatrist, who examined the subject, reviewed medical records, and conferred with referring physicians for all patients. Regarding those more severely depressed subjects with initial Mini-Mental State Exam (MMSE) scores less than 25 (N = 11), MHCRC protocol is to follow such patients through an acute (eight-week) phase of treatment to determine if cognition improves. Subjects whose MMSE scores remain below 25 are not followed longitudinally in the MHCRC. Thus, in the clinical judgment of the study geriatric psychiatrist and by established MHCRC protocol, dementia was effectively excluded at or close to baseline in all elderly depressed MHCRC subjects.

**Clinical Follow-up of Depressed Subjects**

The NCODE study operated in a naturalistic treatment milieu using treatment guidelines established by the Duke Affective Disorders Program. Treatment modalities available included antidepressant medications, electroconvulsive therapy, and individual and group cognitive behavior psychotherapy. Treatment was monitored to ensure that clinical guidelines are followed appropriately. As indicated above, patients were evaluated when clinically indicated, and at least every three months while they were in the study. The protocol recommended that patients receive continuation treatment for at least one to two years (some indefinitely) once they achieve remission. Mean length of follow-up was 5.39 years.

**Neuropsychological Assessment**

The neuropsychological assessment consisted of a brief screening battery for dementia supplemented by additional measures to enhance sensitivity and specificity of the detection of early stage dementia. This battery was designed for efficient neuropsychological evaluation of geriatric patients and now has been successfully employed in a number of clinical and epidemiological settings. Composition of the tests in the battery has been reported previously. To summarize, the battery was comprised of the Consortium to Establish a Registry in Alzheimer Disease (CERAD) neuropsychological battery, supplemented by other common neuropsychological measures used in clinical practice for assessing: 1) immediate and delayed verbal memory (Logical Memory subtest of the Wechsler Memory Scale—Revised); 2) visual immediate memory (Benton Visual Retention Test); 3) verbal initiation/lexical fluency (Controlled Oral Word Association Test from the Multilingual Aphasia Examination); 4) attentional/executive functions (Trail Making Test, Symbol-Digit Modalities Test, Digit Span subtest of the WAIS–Revised, and a separate ascending Digit Span task modeled after the Digit Ordering Test); and 5) premorbid verbal ability (Shipley Vocabulary Test). In addition, at time of testing, a knowledgeable informant completed the Dementia Severity Rating Scale, a measure of cognitive and functional status. A licensed clinical neuropsychologist reviewed the results of testing to alert treatment providers to conditions that may require further evaluation, and to identify individuals with suspected cognitive impairment for evaluation at the consensus conference (see below).

**Referral of Subjects With Cognitive Impairment**

When subjects presented with cognitive complaints, if family members brought concerns to the study geriatric psychiatrist, or if the psychiatrist had a clinical suspicion of cognitive impairment or dementia, he or she had the option to refer the patient to the Memory Disorders Clinic at Duke University Medical Center. When this happened, the study obtained copies of those medical records.
Subjects are assigned to be reviewed by the consensus panel if they meet one of the following criteria: 1) the study geriatric psychiatrist suspects dementia or clinically significant cognitive decline; 2) a neuropsychological diagnosis consistent with dementia or cognitive impairment; or 3) neurological consultation resulting in a diagnosis of dementia or cognitive impairment. Therefore, the individuals who have not come to Consensus Diagnostic Conference are those subjects whose study geriatric psychiatrist has not identified a cognitive problem and/or those subjects with broadly normal neuropsychological testing.

Using a model developed in our epidemiological studies of dementia, we convened a panel of experts to review each case. The panel consisted of a core group of experts, including five geriatric psychiatrists (JLB, KRG, DCS, WDT, MET), a cognitive neuroscientist (BLP), two neuropsychologists specializing in memory disorders (KAW-B, GGP), and a neurologist specializing in memory disorders (JRB). For each study subject, panel members reviewed the following information: 1) initial evaluation and most recent clinical depression study notes, 2) neuropsychological testing profiles and provisional diagnoses for all subjects who underwent cognitive testing, and 3) neurological consultations when available. The treating study psychiatrist (JLB, KRG, DCS, WDT, or MET) briefly presented the case, and a neuropsychologist (KAW-B) reviewed the neuropsychological findings. The panel would discuss the case until a consensus cognitive diagnosis was reached.

Panel members chose among several clinical diagnoses (Table 1). We used published criteria for diagnoses of Probable and Possible Alzheimer disease and Probable and Possible Vascular Dementia. Clinical judgment was used to diagnose incident Parkinson dementia, Lewy body dementia, and alcoholic dementia. The category of “dementia of undetermined etiology” was used when a subject met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for dementia, but no clear diagnosis could be assigned based on the subject’s clinical evaluation. Thus, a diagnosis of “dementia of undetermined etiology” would not necessarily exclude Alzheimer disease or vascular dementia.

We also included several categories of nondementia diagnoses selected a priori based on our previous studies (Table 1). “Subsyndromal Alzheimer disease” was defined as early or prodromal stages of Alzheimer disease. This term is broader than amnestic “mild cognitive impairment,” in that it may include mild impairment in functional activities or in one or more cognitive domains (i.e., not just memory impairment) that is clinically suggestive of the early stages of Alzheimer disease. “Subsyndromal vascular dementia” was defined as cognitive or functional decline caused by progression of cerebrovascular disease, but not meeting dementia criteria. A diagnosis of “cognitive impairment, no dementia” was assigned to subjects with cognitive impairment by report or on neuropsychological testing accompanied by mild or no functional impairment (as evidenced by clinician report or report of knowledgeable informant on the Dementia Severity Rating Scale), and who did not present with syndromes consistent with subsyndromal Alzheimer disease or subsyndromal vascular dementia. We adopted this definition from criteria described previously. The final diagnostic category was normal/noncase.

Subjects were imaged with a 1.5-Tesla whole-body, research-dedicated MRI system (Signa, GE Medical Systems, Milwaukee, WI) using a standard head (volumetric) radiofrequency coil. A dual-echo fast spin-echo acquisition was obtained in the axial plane for morphometry. The pulse sequence parameters were as follows: repetition time, 4000 msec; echo time, 30, 135 msec, 32 kHz; full imaging bandwidth; echo train length, 16, 256 × 256 matrix, contiguous 3-mm section thickness, 1 excitation, and a 20-cm field of view.

Volume measurements were performed with a modified version of MRX software, which was created by GE Corporate Research and Development (Schenectady, NY) and originally modified by Brigham and Women’s Hospital for image segmentation (Boston, MA). The segmentation protocol used has been previously described along with illustrations demonstrating how image intensity is converted to segmented tissue types. This is a super-
### TABLE 1. Characteristics of the Sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incident Dementia</th>
<th>No Incident Dementia</th>
<th>Full Sample</th>
<th>Test Statistic (t-Test Unless Noted)</th>
<th>df</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>141</td>
<td>161</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>76.14 (1.20)</td>
<td>68.28 (0.57)</td>
<td>69.23 (7.09)</td>
<td>−4.80<a href="#fn1">^a</a></td>
<td>159</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female, % (N)</td>
<td>85.00 (17)</td>
<td>58.87 (83)</td>
<td>62.11 (100)</td>
<td>5.0837<a href="#fn1">^a</a></td>
<td>1</td>
<td>0.024</td>
</tr>
<tr>
<td>White, % (N)</td>
<td>80.00 (16)</td>
<td>94.33 (133)</td>
<td>92.6 (149)</td>
<td></td>
<td>159</td>
<td>0.045b</td>
</tr>
<tr>
<td>Education, years (SD)</td>
<td>12.90 (2.94)</td>
<td>14.28 (2.69)</td>
<td>14.11 (2.75)</td>
<td>2.12</td>
<td>159</td>
<td>0.056</td>
</tr>
<tr>
<td>MADRS total, baseline (SD)</td>
<td>28.25 (7.55)</td>
<td>26.83 (7.35)</td>
<td>27.00 (7.37)</td>
<td>−0.81</td>
<td>159</td>
<td>0.420</td>
</tr>
<tr>
<td>MADRS total, last visit (SD)</td>
<td>13.35 (9.67)</td>
<td>7.21 (7.77)</td>
<td>7.97 (8.25)</td>
<td>−3.21</td>
<td>159</td>
<td>0.002</td>
</tr>
<tr>
<td>MMSE total, baseline (SD)</td>
<td>26.70 (3.40)</td>
<td>28.44 (2.32)</td>
<td>28.22 (2.53)</td>
<td>2.46</td>
<td>229</td>
<td>0.022</td>
</tr>
<tr>
<td>MMSE total, last visit (SD)</td>
<td>28.25 (7.56)</td>
<td>26.83 (7.36)</td>
<td>27.01 (7.37)</td>
<td>−0.81</td>
<td>159</td>
<td>0.422</td>
</tr>
<tr>
<td>Reported hypertension, baseline, % (N)</td>
<td>55.00 (11)</td>
<td>38.73 (55)</td>
<td>40.74 (66)</td>
<td>1.9216<a href="#fn1">^a</a></td>
<td>1</td>
<td>0.166</td>
</tr>
<tr>
<td>Reported heart problems, baseline, % (N)</td>
<td>5.00 (1)</td>
<td>19.86 (28)</td>
<td>18.01 (29)</td>
<td></td>
<td>211</td>
<td>0.110</td>
</tr>
<tr>
<td>White matter lesion volume, baseline, mL (SD)</td>
<td>11.82 (15.80)</td>
<td>5.80 (9.72)</td>
<td>6.54 (10.78)</td>
<td>−1.66</td>
<td>212</td>
<td>0.056</td>
</tr>
<tr>
<td>White matter lesion volume, year 2, mL (SD)</td>
<td>16.34 (18.30)</td>
<td>6.90 (11.46)</td>
<td>8.07 (12.82)</td>
<td>−2.25</td>
<td>20.9</td>
<td>0.009</td>
</tr>
<tr>
<td>White matter lesion change, mL (SD)</td>
<td>4.52 (5.19)</td>
<td>1.10 (5.02)</td>
<td>1.55 (3.53)</td>
<td>−2.87</td>
<td>159</td>
<td>0.136</td>
</tr>
<tr>
<td>Gray matter lesion volume, baseline, mL (SD)</td>
<td>0.36 (0.49)</td>
<td>0.22 (0.39)</td>
<td>0.25 (0.40)</td>
<td>−1.50</td>
<td>159</td>
<td>0.004</td>
</tr>
<tr>
<td>Gray matter lesion volume, year 2, mL (SD)</td>
<td>0.55 (0.52)</td>
<td>0.25 (0.42)</td>
<td>0.291 (0.441)</td>
<td>−2.92</td>
<td>159</td>
<td>0.0056</td>
</tr>
<tr>
<td>Gray matter lesion change, mL (SD)</td>
<td>0.19 (0.38)</td>
<td>0.04 (0.27)</td>
<td>0.06 (0.29)</td>
<td>−1.75</td>
<td>21.7</td>
<td>0.093</td>
</tr>
<tr>
<td>Parenchymal volume change, ml (SD)</td>
<td>−49.95 (35.78)</td>
<td>−20.24 (39.30)</td>
<td>−23.92 (45.22)</td>
<td>2.81</td>
<td>159</td>
<td>0.0056</td>
</tr>
<tr>
<td>Any APOE ε4 allele, N (%)</td>
<td>4 (20.00)</td>
<td>33 (24.26)</td>
<td>37 (23.72)</td>
<td></td>
<td>785</td>
<td>0.785b</td>
</tr>
<tr>
<td>Time in study, days (SD)</td>
<td>1337.50 (1025.7)</td>
<td>2055.70 (803.27)</td>
<td>1966.45 (863.7)</td>
<td>3.61</td>
<td>159</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

[^a]: χ² test.
[^b]: Fisher’s exact test.
vised, semiautomated method that uses the multiple magnetic resonance contrasts available to identify different tissue classifications through a “seeding” process wherein a trained analyst manually selects pixels in each tissue type to be identified (such as gray matter, white matter, cerebrospinal fluid, lesions, or background). Our variable, “parenchymal volume” consisted of the sum of whole brain gray matter and whole brain white matter. Gray matter included gray matter lesions and white matter includes white matter lesions. Whole brain includes cerebrum, diencephalon, cerebellum, and brainstem. Meninges were not included.

Lesion areas were selected based upon a set of explicit rules. These rules were developed from neuroanatomical guidelines, consultation with a neuroradiologist, and knowledge of the neuropathology of lesions. Periventricular lesions were defined as regions that were contiguous with lateral ventricle and did not extend into the white matter tracts. They were classified as white matter lesions on the segmented image. Deep white matter lesions were located in the white matter tracts and may or may not have adjoined periventricular lesions. Subcortical gray matter lesions were defined as lesions within the caudate nucleus, putamen, globus pallidus or thalamus. Regions likely to be partially volumed cerebrospinal fluid rather than lesions were excluded. The final step was to run a summarizing program that calculated the volume of each tissue type within each cerebral hemisphere.

MRI Training and Reliability

All technicians received extensive training by experienced volumetric analysts. Reliability was established by repeated measurements by two raters on MRI scans from 16 subjects before raters processed study data. Intraclass correlation coefficients (ICCs) were as follows: left cerebral gray matter lesions, 0.995; right cerebral gray matter lesions, 0.996; left cerebral white matter lesions, 0.988; and right cerebral white matter lesions, 0.994.

Determination of APOE Genotype

All subjects were asked to donate a blood sample for APOE genotyping. White blood cells are processed using a method previously described.

Statistical Analyses

Variables were tested for differences between demented and nondemented patients on a bivariate level using t-test, χ² test, and Fisher’s exact test where appropriate. These tests were done to help determine which variables would be included in the full model, such as those significant at the p <0.1 level.

A survival analysis was performed using Cox proportional hazard models in SAS 8.2 for UNIX to determine if change in WMH volume predicts increased hazard of dementia. Specifically, the comparison is between average time to dementia for the group that became demented and average time to the last visit for the nondemented group. The full model included sex, age, baseline MMSE score, years of education, total baseline MADRS total score, and 2-year change in WMH volume. We assessed the assumption of proportion hazards.

We also examined change in WMH volumes using a log-rank test and developed Kaplan-Meier curves. Here we identified the median value for change in WMH volumes and compared incident dementia rates for individuals with low versus high WMH volume change, the latter defined as values below and above the median value.

RESULTS

The sample consisted of 161 depressed elderly subjects who had a mean age of 69.23 (SD: 7.09) and was 62.1% female (Table 1). Subjects were followed 5.39 (SD: 2.37) years on average, and all subjects had baseline and two-year MRI brain scans. Of the 20 subjects who became demented over the course of the study, five subjects had onset of dementia symptoms that occurred prior to the two-year brain scan (three by year 1, and two by 18 months). Among the total group of subjects with dementia, two were diagnosed with probable AD, eight with possible AD, seven with dementia of undetermined etiology, and three with possible vascular dementia.

We performed proportional hazards regression analyses examining baseline demographic and clinical variables associated with time to dementia onset that were individually associated (at p <0.1) with
incident dementia in the bivariate analyses from Table 1. The proportion hazards assumption was assessed and found to be met. Change scores for white-matter and gray-matter lesion volumes were also examined. In the first model containing variables significant at \( p < 0.1 \) from Table 1, only age (years), baseline MMSE score, and change in white matter lesion volume (mL) were significantly associated with time to dementia. In subsequent stepwise regression analysis (Table 2), age, MMSE score, and change in WMH volumes were significantly associated with time to onset of dementia. Presence of at least one \( APOE \varepsilon 4 \) was not associated with development of dementia in this sample. We also examined a model that contained baseline MRI values, and the change in WMH volumes remained significant. Finally, we note that individuals with incident dementia had higher MADRS scores at last visit than nondemented individuals (Table 1).

We also examined low versus high values for change in WMH volumes and development of dementia using the Log-Rank test. As shown in Figure 1, the Kaplan-Meier curves also demonstrate the significant relationship between WMH volume change and incident dementia.

We reexamined our analyses deleting the five subjects who became demented prior to the 2-year MRI brain scan. Here, only age remained significantly associated with time to dementia (\( \chi^2 = 14.052, \text{df} = 1, \ p = 0.0002 \)). In this three-variable model, neither baseline MMSE (\( \chi^2 = 2.330, \text{df} = 1, \ p = 0.127 \)) nor change in WMH volume (\( \chi^2 = 2.535, \text{df} = 1, \ p = 0.111 \)) were significantly associated with time to dementia. When we compared those with dementia onset before and after year 2 of the study, we found no significant differences in age at study entry (77.0 versus 75.7 years), baseline MMSE score (25.4 versus 27.1), or change in WMH volume (5.68 versus 4.13 mL).

We also examined the relationship between change in WMH volume and change in brain parenchymal volume. These two variables were moderately correlated (Pearson correlation coefficient = \(-0.303,\ N = 161, \ p < 0.0001 \)). Development of dementia was associated with greater change in brain parenchymal volume in univariate (21.55 \pm 44.93 mL in nondemented versus 54.64 \pm 47.21 mL in demented; \( t = -3.07, \text{df} = 160, \ p = 0.0026 \)) but not in proportional hazards regression model controlling for age and baseline MMSE score (\( \chi^2 = 1.319, \text{df} = 1, \ p = 0.251 \)). Further, in another proportional hazards regression model controlling for age and baseline MMSE score, with both MRI variables in the model, neither change in WMH volume (\( \chi^2 = 2.349, \text{df} = 1, \ p = 0.125 \)) nor change in brain parenchymal volume (\( \chi^2 = 0.356, \text{df} = 1, \ p = 0.551 \)) were associated with time to dementia. Hence, the only longitudinal MRI variable we chose to present in Table 2 was the change in WMH volume.

In post-hoc analyses, we examined the effect of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter Estimate</th>
<th>Standard Error of the Estimate</th>
<th>Hazard Ratio</th>
<th>( \chi^2 ) (df = 1)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.1579</td>
<td>0.0396</td>
<td>1.171</td>
<td>15.8707</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MMSE (score)</td>
<td>-0.1279</td>
<td>0.0610</td>
<td>1.136</td>
<td>4.3944</td>
<td>0.0361</td>
</tr>
<tr>
<td>Two-year change in white-matter lesion volume (mL)</td>
<td>0.0872</td>
<td>0.0415</td>
<td>1.091</td>
<td>4.4163</td>
<td>0.0356</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Individuals With Change in White Matter Hyperintensity Volumes Above (Circles) and Below (Asterisks) the Median

Dementia Event Stratified by Median Lesion Volume
change in lesion volume in the AD group (N = 10) relative to all other dementia diagnoses (N = 10). Mean (SD) for change in WMH volumes for the AD and non-AD-dementia groups were 2.28 (3.52) mL and 6.75 (5.78) mL, respectively (t = 2.09, df = 18, p = 0.0516). When we compared the effects of change in lesion volumes in a logistic model controlling for age and baseline MMSE, we did not find a significant association between change in WMH volume development of incident AD versus non-AD-dementias (odds ratio = 0.724, 95% confidence interval = 0.482–1.087).

DISCUSSION

This study examined demographic, clinical, and biological variables related to development of dementia among older nondemented depressed individuals. The major finding of this study is that change in WMH volume was independently associated with time to dementia, controlling for the effects of age and baseline MMSE score. Neither change in gray matter lesion volume nor APOE genotype was significantly associated with development of dementia in this cohort.

Our findings add to previous literature linking depression to incident dementia in the elderly by identifying the important role played by progression of vascular change on MRI in the development of cognitive decline and dementia in geriatric depression. We found an incidence of dementia among older depressed individuals three times higher than that reported among normal controls followed over five years. The presence of mild cognitive impairment among older depressed subjects may persist after depression has remitted, and such impairment has been shown to confer an especially high risk for later dementia. Incident depression among cognitively normal elderly has been shown to increase risk for subsequent cognitive impairment, particularly in the presence of an APOE ε4 allele. However, not all studies have found an association between geriatric depression and subsequent cognitive decline. A recent example is a large community-based study with a cohort followed up to 12 years that found that baseline depression symptoms had no effect on cognitive decline in either the dementia-free group or among those who eventually became demented. One difference may lie in the fact that the community-based study assessed depression based on self-reported depressive symptoms on a modified version of the Center for Epidemiological Studies–Depression Scale with a cutoff to define depression, whereas the current study included both structured interviews and psychiatric clinical interviews to establish major depression diagnosis. Thus, the present study may employ a more valid and reliable depression assessment.

We found that the group who became demented was older and tended to have a lower MMSE score at baseline. This should not be surprising, given that older age and cognitive impairment are known to be risk factors for incident dementia. These individuals may therefore be in early stages of Alzheimer disease or other dementias. Our method of excluding baseline dementia was based on clinical assessment by a study geriatric psychiatrist. Thus, although we conclude that our subjects did not meet clinical criteria for dementia at baseline, they may certainly have underlying pathology consistent with Alzheimer disease or other dementias.

Our finding that greater change in WMH volume was associated with later dementia among individuals with geriatric depression occurs in the context of mixed results in prior studies of nondepressed individuals. Although one large 3-year follow-up study found no relationship between WMH progression and cognitive decline, a positive association has been reported in the Cardiovascular Health Study. A more recent study found the detrimental effect of lesion progression on cognition could be explained by the overall loss of brain parenchymal volume. Similarly, we found that change in WMH volume and change in brain parenchymal volume were highly correlated.

Our WMH volume variable included both periventricular and deep white matter hyperintensities. As such, we are unable to identify possible differential effects of these two regional types of WMH on development of cognitive decline and dementia. Other studies examining WMH volume and cognitive decline have also combined periventricular and deep white matter hyperintensities. In a Japanese study of normal, cognitively impaired, and demented elderly, periventricular and deep white matter hyperintensities were separately assessed for
severity rather than volume; neither had a significant effect on cognitive decline. Thus, future studies are needed to separate the effects of the volumes of these hyperintensities.

Our finding that genotype at APOE was not associated with dementia may be considered surprising given that this gene has been associated with development of dementia, particularly Alzheimer disease. However, the finding is consistent with other findings suggesting little relationship between APOE and cognitive deficits among depressed older adults. Because AD did not predominate among dementia diagnoses in the current study, it is not surprising that presence of an APOE ε4 allele was not associated with incident dementia among the older depressed subjects in the sample. Moreover, the greater change in WMH volume would be expected to predict dementia among both atypical cases (i.e., dementia of undetermined etiology), and among cases of vascular dementia. It is also possible that some of our AD cases might be mixed AD and vascular dementia cases; we aimed for diagnostic precision using all available data by including information from MRI scans when assigning diagnoses. We did not assign probable AD in cases where there was extensive white matter change. However, the literature is not clear about when to assign mixed dementia diagnosis when the amount of MRI vascular change is not severe. In this study, when subjects had a mild to moderate degree, we were guided by clinical course in deciding whether to include a vascular dementia component.

Although gray matter hyperintensity volume change was not associated with development of dementia, there was a trend favoring the association such that our lack of a significant finding may reflect the relatively low number of demented individuals in the sample. Nevertheless, our findings linking WMH volume changes with incident dementia in depressed elders are important and serve to extend the vascular depression hypothesis of geriatric depression to include cognitive outcomes.

That our dementia cases were comprised of a large number of individuals in the diagnostic category “dementia of undetermined etiology” reflects the challenge facing clinicians who follow older depressed patients with cognitive decline. In the experience of our group, the cause for the dementia syndrome was not clear and did not appear to be due to the depression itself. The diagnostic complexity is magnified when it appears that individuals may have recently crossed into a dementia. For many such individuals, it is expected that the passage of time and ongoing assessment will clarify the diagnosis. Again, this process mirrors clinical practice; here, the consensus panel must make a clinically informed judgment regarding cause. In several cases, particularly in early stage dementia of undetermined etiology, such a definitive clinical adjudication has not proven possible.

There are some limitations to the present study. First, the sample of subjects is relatively small, as we were limited to 161 subjects with MRI data from both baseline and two years. Among those subjects only 20 developed incident dementia, with only 15 with dementia occurring after the second-year scan. Nevertheless, the incidence rate of dementia was high enough to allow statistical modeling of the data to examine MRI vascular changes. Another limitation of the study is that antidepressant treatment was not standardized, but rather administered by individual study psychiatrists using a guideline-based treatment algorithm. Most subjects were treated with selective serotonin reuptake inhibitors, but other agents including bupropion, mirtazapine, venlafaxine, and duloxetine were also prescribed. We cannot therefore rule out the possibility that depression treatment may have affected dementia outcome. Finally, we examined dementia, rather than cognitive decline, so we cannot exclude the possibility that some individuals may have been experiencing cognitive decline short of dementia.

In conclusion, in this sample of older depressed adults, about one-eighth of the sample became demented during the follow-up period. Half of the sample had probable or possible AD development of dementia that was associated with change in WMH volume but not with presence of the APOE ε4 allele. These results extend prior findings linking depression and later dementia. They also confirm previous literature highlighting the importance of MRI-confirmed vascular change in expression of AD and other dementias. Future studies that incorporate longitudinal neuroimaging that seek larger samples of individuals at risk for dementia (e.g., with mild cognitive impairment) should also include depressed...
patients because the relationship between mild cognitive impairment, depression, and cognitive decline is receiving increasing attention.\textsuperscript{54} It may be informative to evaluate white matter hyperintensities by location because some hyperintensities may better predict dementia. Finally, treatment studies among older depressed adults should be undertaken to examine whether clinical interventions to minimize worsening of cerebrovascular disease may prevent cognitive decline and dementia.

This study was supported by the National Institute of Mental Health (grants P50 MH60451, R01 MH54846, and K24 MH70027).

The authors thank Ms. Karee Powers and Ms. Julie Fleenor for their assistance in preparing information for the Consensus Diagnostic Conference; Ms. Denise Fetzer for performing the hyperintensity measurements; and Drs. John L. Beyer, Kenneth R. Gersing, Warren D. Taylor, and Mugdha E. Thakur for their valuable clinical assessments and participation in Consensus Diagnostic Conferences.

References

predicts age when prevalence of AD increases, then declines: the Cache County Study. Neurology 1999; 53:321–331
49. Terai S: A neuroradiological study on the influence of cerebral atrophy and white matter lesion on cognitive function in the elderly. Nippon Ronen Igakkai Zasshi 2004; 41:521–527