Cerebrovascular and Brain Morphologic Correlates of Mild Cognitive Impairment in the National Heart, Lung, and Blood Institute Twin Study

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Objective: To evaluate the relative risk (RR) of mild cognitive impairment (MCI) associated with cerebrovascular risk factors and cerebrovascular-related brain changes.

Design: Mild cognitive impairment was determined for the subjects of the prospective National Heart, Lung, and Blood Institute Twin Study. Quantitative measures of brain, white matter hyperintensity, cerebral infarction, apolipoprotein E genotype, and psychometric testing were obtained.

Results: Subjects with MCI were older (73.5±3.0 vs 72.1±2.8 years), consumed less alcohol (3.7±5.8 vs 7.0±10.7 drinks per week), had greater white matter hyperintensity volumes (0.56%±0.82% vs 0.25%±0.34% of cranial volume), and had an increased prevalence of apolipoprotein E4 genotype (31.4% vs 19.2%) than normal subjects. White matter hyperintensity and the presence of the apolipoprotein E4 genotype were associated with a significantly increased risk for MCI. When all subjects were included in the analysis, alcohol consumption was associated with a reduced risk for MCI (RR=0.93, P<.05). When subjects with a history of symptomatic cerebrovascular disease were excluded from the analysis, elevated midlife diastolic blood pressure was associated with an increased risk for MCI (RR=1.70, P<.05).

Conclusions: Elevated midlife blood pressures, and the resulting increased white matter hyperintensities, increase the risk for MCI in a group of community-dwelling older men to at least the same degree as apolipoprotein E4 genotype. Given the common occurrence of elevations in midlife blood pressure, early and effective treatment may be warranted to prevent late-life brain abnormalities and MCI. Moreover, since many individuals with MCI progress to clinical dementia, longitudinal evaluations of this cohort will be important.

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Several longitudinal studies show an association between middle-age elevations in blood pressure (BP) and impaired later-life cognition. The mechanisms underlying these long-term associations are unclear, but several processes, including disturbed cerebral perfusion or reduced metabolism, abnormalities of cerebral white matter, and cerebral atrophy, have been implicated.

Elevated BP, especially elevated systolic BP and hypertension, are associated with an increased prevalence and extent of white matter hyperintensity (WMHI) as well as cerebral atrophy. Although the impact of WMHI on memory impairment in the elderly remains uncertain, considerable evidence suggests that large volumes of WMHI are associated with other impairments in cognitive performance. The extent of brain atrophy and WMHI that accompany middle-age elevations of systolic BP also correlate with the rate of cognitive decline during 10 years. While these results support the notion that brain injury in response to long-standing BP elevation can result in mild impairment in various cognitive domains, the clinical significance of these effects remains unclear.

Mild cognitive impairment (MCI) has become increasingly recognized as common in later life. Usually defined as isolated memory impairment in an otherwise healthy individual, MCI is associated with a yearly risk for Alzheimer disease (AD) that varies from 1% to 25% per year. Given that cerebrovascular risk factors, such as hypertension, are often associated with late-life brain abnormalities and cognitive impairment, we sought to examine the relationship between cerebrovascular risk factors, brain morphologic characteristics, and MCI in a group of 369 nondemented, community-dwelling older men who participated in the National Heart, Lung, and Blood Institute (NHLBI) Twin Study.
SUBJECTS AND METHODS

STUDY POPULATION

The NHLBI Twin Study is a longitudinal study of cardiovascular disease and associated cardiovascular disease risk factors in 514 pairs of male twins born between 1917 and 1927, who were 42 to 56 years old when first examined in 1969 to 1972. Three follow-up examinations after 10, 16, and 25 years assessed cardiovascular disease status and collected repeated measurements of physiological, biochemical, and psychosocial risk factors. In the most recent follow-up examination (1995-1997), brain magnetic resonance (MR) imaging was added to the sequence of tests previously given to these subjects. Analyses in the present study were limited to a subset of 369 individual twins who participated in the fourth examination of this cohort and for whom MR volumetric data and neuropsychological testing were available.

BP DETERMINATION AND DEFINITIONS OF CARDIOVASCULAR DISEASE AND RISK FACTORS

Complete details regarding BP assessment and determination of cerebrovascular risk factors are available elsewhere. In brief, however, sitting BP was measured at each examination by 2 independent examiners. Diastolic BP was recorded as the fifth phase. The slope of BP change was determined by linear regression of each individual across the 4 measurements, as described by DeCarli et al.

Cardiovascular disease and risk factors were determined through medical interviews and physical examination. Subjects’ self-report of cardiovascular events and medical procedures were confirmed with medical and hospital records. The final diagnoses of clinical stroke, transient ischemic attack, myocardial infarction, coronary insufficiency, and angina pectoris were determined by trained medical staff who reviewed the medical records and physical examination data and uniformly coded these according to standard protocols. Prevalent coronary heart disease was ascertained on the basis of the surveillance data and electrocardiographic data. Data on medication use were collected at each examination by presentation of medication vials. The ankle-brachial BP ratio, in combination with patient medical and hospital records, was used as a measure of prevalent peripheral vascular atherosclerosis. All subjects were free of cardiovascular disease at the first examination.

Alcohol consumption and smoking behavior were assessed at each examination. Alcohol consumption was defined as number of drinks per week and cigarette use as pack-years. History of current or past cigarette use was also determined.

CEREBRAL MR IMAGES AND IMAGE ANALYSIS

The MR (1.5-T) imaging was performed at 4 study sites by means of a conventional spin-echo, double-echo sequence in the axial orientation with repetition time of 2000 milliseconds, echo time of 20/100 milliseconds, 24-cm field of view, and 3-mm contiguous slices from the vertex to the foramen magnum imaged in a 256 × 192 matrix and interpolated to 256 × 256 with 1 excitation. The MR imaging information was transferred to a central location for processing and analysis without knowledge of age, zygosity, and medical history of the subjects. Image evaluation was based on a semiautomated segmentation analysis that involves operator-guided removal of nonbrain elements as previously described.

The presence of cerebral infarction on MR imaging was determined from the size, location, and imaging characteristics of the lesion. Only lesions 3 mm or larger qualified.

RESULTS

The distribution of scores on CVLT delayed free recall are displayed in the Figure. Since MCI was a priori defined as the lower 10th percentile or 1.4 SDs or more below the group mean, 37 subjects with a CVLT score of 4.0 or less were identified as having MCI. The average performance on the delayed free recall of the CVLT across all subjects was 8.18 ± 2.92. The mean performance for the MCI group was 2.97 ± 1.26, and for the normal memory group, 8.77 ± 2.44. Performance on CVLT delayed free recall of the normal group was 2.97 ± 1.26, and for the normal memory group, 8.77 ± 2.44. Performance on CVLT delayed free recall for all subjects was 8.18 ± 2.92. The mean performance for all subjects in the MCI group was 2.97 ± 1.26, and for the normal memory group, 8.77 ± 2.44. Performance on CVLT delayed free recall for the normal memory group was 8.77 ± 2.44.

Between-group comparisons are summarized in Table 1. Subjects with MCI were significantly older (73.5 ± 3.0 years vs 72.1 ± 2.8 years), consumed significantly less alcohol (3.7 ± 5.8 drinks per week vs 7.0 ± 10.7 drinks per week), and had significantly greater WMHI volumes (0.56% ± 0.82% of cranial volume vs 0.29% ± 0.34% of cranial volume) than subjects with normal delayed free recall.

Results of stepwise logistic regression are summarized in Table 2. Since symptomatic stroke is associated with a significant increase in risk for dementia, we also examined significant risk factors for MCI for the entire subject group (model 1) and then repeated the analysis excluding subjects with a history of any symptomatic cerebrovascular disease (model 2). This excluded 6 subjects in the MCI group and 37 control subjects from the model 2 analysis. Age, WMHI, and the presence of the ApoE4 genotype were associated with a significantly increased risk of MCI in both analytical models. Relative risk was calculated for each year of age and percentage change in WMHI volume as a proportion of cranial volume (eg, subjects with 1% WMHI volume were 2.31 times more likely to have MCI than those with minimal volumes of WMHI). When all subjects were included in the analysis (model 1), alcohol consumption (risk calculated as drinks per day) was additionally associated with a significant risk reduction for MCI. When subjects with a history of symptomatic cerebrovascular disease were excluded from the analysis (model 2), diastolic BP at examination 1 (calculated as 1 SD of the mean or 12.5 mm Hg) was additionally associated with a significantly increased risk of MCI.

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for consideration as cerebral infarcts. Other necessary imaging characteristics included (1) cerebrospinal fluid density on the subtraction image and (2) if the cerebral infarct was in the basal ganglia area, distinct separation from the circle of Willis vessels.

Intrarater and interrater reliabilities for this method have been published.37,28

**APOLIPOPROTEIN E GENOTYPING**

Since previous reports suggest that apolipoprotein E ε4 (ApoE4) is a risk factor for MCI and incipient AD,30,31 ApoE genotype status categorized as a dichotomized variable (E4 present or absent) was included in this analysis. For ApoE structural locus genotyping, the polymerase chain reaction was used to amplify 244–base pair fragments that contain variant amino acid residues 112 (cystine → arginine=ε4 allele) and 158 (arginine → cystine=ε2 allele). Polymerase chain reaction products were then digested with the restriction enzyme HhaI and underwent electrophoresis on an 8% polyacrylamide nondenaturing gel.32 In this procedure, the most common ε3 allele is cut by HhaI at position 158; the ε4 allele is cut twice by the addition of a second restriction site at position 112; and the less frequent ε2 allele lacks either recognition site. Genotyping by using this technique was completed on 589 individual twins of this cohort, showing allele frequencies of ε2=0.09, ε3=0.76, and ε4=0.15, consistent with expected frequencies in other white populations.33 The ApoE genotypes were available on 359 (97%) of the individuals in the subset of 369 of NHLBI twins used in the present analysis.

**DEFINITION OF MCI**

*Mild cognitive impairment* is commonly defined as the presence of clinically significant memory impairment in the absence of a clinical dementia.22 Various measures of memory performance can be used.22 For the purpose of this analysis, we defined MCI on the basis of delayed free-recall performance on the California Verbal Learning Test (CVLT). The CVLT34 quantifies numerous components of verbal learning and memory and has demonstrated validity in persons with AD.35 While performance on the CVLT is affected by both age and sex,36 few normative studies have been performed on older individuals since its publication.37 Therefore, MCI was defined as a score of 4 or less, corresponding to the lower 10th percentile of the distribution of scores or 1.4 SDs below the mean, consistent with MCI as defined by other memory tests.22 In addition, to exclude the presence of frank dementia, subjects with a score of 24 or less on the Mini-Mental State Examination were excluded from the analysis (n=45).

**STATISTICAL ANALYSIS**

To assess validity of designating MCI on the basis of performance within the NHLBI cohort, initial statistical analysis examined the distribution of scores from the long-term delayed recall portion of the CVLT by means of the SAS univariate procedure and the Kolomogorov D statistic.37 Between-group comparisons on a variety of demographic, genotypic, and cerebrovascular risk factors were performed by means of the t test. Forward stepwise logistic regression analysis was used to evaluate the relative risk and 95% confidence intervals for variables significantly associated with the presence of MCI. Because of missing ApoE data for 3% of the cohort, the number of subjects differed slightly between the univariate analysis, which included 369 individuals, and the logistic regression analyses, which included 339 individuals. All analyses were conducted with the SAS statistical package (version 6.08; SAS Institute Inc, Cary, NC). Data are given as mean±SD unless otherwise indicated.

**COMMENT**

Our results show that elevations in midlife diastolic BP and WMHI volumes are significant risk factors for MCI in a large group of community-dwelling older men. Moreover, the relative risk for MCI related to WMHI is at least as great as, if not greater than, the relative risk for MCI attributable to the presence of the ApoE4 genotype. Importantly, however, the pathophysiology of MCI caused by brain vascular disease is likely to differ substantially from that of the more common “neurodegenerative” type22,23 that often progresses to AD. Since our data suggest that MCI is a heterogeneous condition, future work will be necessary to determine the actual likelihood that MCI of the “vascular” type might progress to clinical dementia and, if so, the type of dementia expressed (ie, AD vs vascular dementia).

In addition to identifying factors that increase the risk for MCI, we also found that alcohol consumption was slightly protective. This finding supports previous data showing a positive correlation between alcohol consumption and cognitive performance.38 This effect appeared significant only for individuals with cerebrovascular disease, as it was not present in model 2. How alcohol consumption might reduce the risk of later-life MCI is presently unclear.39 Recent evidence suggests that moderate alcohol consumption can reduce the risk of both vascular disease and AD.40-41 Unfortunately, the current study was not designed to test potential causes of MCI.

![Histogram distribution of delayed free-recall scores on the California Verbal Learning Test for all subjects participating in this study. The heights of the bars indicate the number of subjects at each value with that score. The arrow indicates the cutoff score used to determine the presence of mild cognitive impairment.](http://www.archneurol.com/links/645.png)
Risk reduction due to alcohol consumption, and further research in this area is clearly necessary. Fortunately, another clinical evaluation of this group is ongoing. Assessing dementia incidence and type of dementia in this cohort may give some clues to the protective effect of alcohol consumption for these individuals.

We have previously shown that midlife diastolic BP is a significant predictor of later-life WMHI volume. However, we also have shown that extensive WMHI volumes are significantly associated with an increased rate of decline on measures of attention, memory, and verbal fluency. We believe these cognitive changes result from the effect of elevated BP on the brain. Unfortunately, the magnitude of cognitive impairment related to WMHI noted in previous studies has been relatively small. The results of this study suggest that the impact of elevated BP and increased WMHI may be clinically relevant in that they both increase the risk of MCI in subjects without a history of symptomatic cerebrovascular disease.

Our data also confirm that MCI is likely to be a pathologically heterogeneous disorder. Previous studies suggest that MCI is part of the continuum that ranges from healthy aging to AD. The ApoE4 genotype increases both the lifetime risk of AD and the risk of conversion of MCI to AD, presumably through enhanced amyloid deposition or increased neuronal vulnerability. Our finding that ApoE4 genotype status independently increased subject risk for MCI is consistent with these previously published reports. The fact that both ApoE4 genotype status and WMHI volume independently increased risk of MCI suggests the possibility of 2 independent processes leading to MCI, supporting the notion of MCI as a pathologically as well as clinically heterogeneous disorder. Importantly, there are no data yet available regarding the potential impact of WMHI volume on the progression from MCI to clinically probable AD or other dementia. Current ongoing work with the subjects of the NHLBI Twin Study may allow us to directly examine the relationship between WMHI volume, current MCI status, and dementia incidence.

It is likely that vascular risk factors, such as hypertension, cause MCI through mechanisms different from AD. Chronic essential hypertension is associated with age-related differences in brain structure and function, which in the presence of WMHI are associated with reduced cerebral metabolism of glucose in the frontal lobes of otherwise healthy individuals. This may reflect preferential impairment of frontal-subcortical circuits by WMHI. While frontal-subcortical circuits generally are not considered involved with memory encoding, they may underlie working memory function. It is possible that the CVLT is a type of task that uses these frontal circuits. Alternatively, recent evidence suggests that cerebrovascular disease may interact significantly with pathologic changes of AD to enhance the expression of clinical dementia. It is possible that a similar phenomenon could occur with WMHI. Future work in this area of research may help to define the potential interaction between these 2 very common age-related diseases.

Two important limitations to this study also should be mentioned. For all these analyses, twin subjects were treated as individuals. First, although we found no evidence that ApoE4 genotype status and WMHI could occur with WMHI. Future work in this area of research may help to define the potential interaction between these 2 very common age-related diseases.

Table 1. Univariate Comparisons of Age, Education, CVD Risk Factors, Medical Histories, and Brain Volumes on MR Imaging in Subjects With and Without Mild Cognitive Impairment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mild Cognitive Impairment (n = 37)</th>
<th>No Cognitive Impairment (n = 332)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>73.5 (3.0)</td>
<td>72.1 (2.8)</td>
<td>.005</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.5 (3.8)</td>
<td>13.7 (3.1)</td>
<td>.52</td>
</tr>
<tr>
<td>Long-delay free recall</td>
<td>2.97 (1.25)</td>
<td>8.76 (2.44)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SBP at examination 1, mm Hg</td>
<td>123.5 (14.7)</td>
<td>123.9 (14.3)</td>
<td>.56</td>
</tr>
<tr>
<td>DBP at examination 1, mm Hg</td>
<td>79.2 (12.5)</td>
<td>79.4 (9.7)</td>
<td>.86</td>
</tr>
<tr>
<td>Slope SBP, mm Hg/y</td>
<td>0.84 (0.85)</td>
<td>0.59 (0.81)</td>
<td>.08</td>
</tr>
<tr>
<td>Slope DBP, mm Hg/y</td>
<td>−0.15 (0.58)</td>
<td>−0.17 (0.50)</td>
<td>.18</td>
</tr>
<tr>
<td>Glucose tolerance at</td>
<td>157.6 (40.0)</td>
<td>154.8 (40.5)</td>
<td>.60</td>
</tr>
<tr>
<td>examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pack-years smoked</td>
<td>24.6 (27.3)</td>
<td>23.8 (30.4)</td>
<td>.22</td>
</tr>
<tr>
<td>Alcohol, drinks/wk</td>
<td>3.7 (5.8)</td>
<td>7.0 (10.7)</td>
<td>.005</td>
</tr>
<tr>
<td>History of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking history, %</td>
<td>Never</td>
<td>38</td>
<td>.37</td>
</tr>
<tr>
<td></td>
<td>Former</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Alcohol, drinks/d</td>
<td>46</td>
<td>33</td>
<td>.08</td>
</tr>
<tr>
<td>ApoE4 genotype, %</td>
<td>16</td>
<td>11</td>
<td>.08</td>
</tr>
<tr>
<td>WMHI, % of cranial volume</td>
<td>75.1 (3.2)</td>
<td>75.4 (2.5)</td>
<td>.20</td>
</tr>
<tr>
<td>MR imaging infarct, %</td>
<td>33.3</td>
<td>20.7</td>
<td></td>
</tr>
</tbody>
</table>

* CVD indicates cardiovascular disease; MR, magnetic resonance; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; CVA, cerebrovascular accident; PAD, peripheral vascular atherosclerosis; ApoE4, apolipoprotein E 4; WMHI, white matter hyperintensity; and TCB, total cranial brain volume. Data are given as mean (SD) unless otherwise specified.

† Boldface type indicates significant or near-significant values.

Table 2. Adjusted RR Ratios and 95% CIs From Stepwise Logistic Regression Analyses That Include (Model 1) and Exclude (Model 2) Subjects With Clinical CVA

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of MCI/healthy subjects</td>
<td>37/332</td>
<td>31/295</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.17 (1.03-1.33)</td>
<td>1.18 (1.03-1.35)</td>
</tr>
<tr>
<td>WMHI, % of cranial volume</td>
<td>2.31 (1.27-4.21)</td>
<td>5.34 (1.80-15.9)</td>
</tr>
<tr>
<td>ApoE4 genotype</td>
<td>2.68 (1.00-6.19)</td>
<td>3.54 (1.45-8.78)</td>
</tr>
<tr>
<td>Alcohol, drinks/d</td>
<td>0.93 (0.88-0.99)</td>
<td>NA</td>
</tr>
<tr>
<td>DBP at examination 1, mm Hg</td>
<td>NA</td>
<td>1.70 (1.97-2.71)</td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval; CVA, cerebrovascular accident; MCI, mild cognitive impairment; WMHI, white matter hyperintensity; ApoE4, apolipoprotein E 4; DBP, diastolic blood pressure; and NA, not applicable. Data are given as adjusted RR (95% CI) unless otherwise indicated.
ability to generalize these findings. However, there is important evidence that WMHI volumes are increased in women and African Americans, suggesting that the impact of WMHI on MCI may be greater than that observed with this cohort. Replication of these findings in a more representative population, therefore, will be important to understanding the full significance of these observations.

Finally, these observations may have therapeutic implications. If midlife elevations of diastolic BP lead to later-life MCI and potentially cause WMHI, then greater awareness and treatment of midlife BP elevations may lower the risk of later-life MCI. Our finding that the effect of midlife diastolic BP and WMHI volumes on later-life cognition is at least as great as that of ApoE genotype also suggests that the clinical impact of this risk reduction could be considerable. Further research into the issues of midlife BP control as it relates to later-life cognitive function is clearly needed.

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