Magnetic Resonance Imaging Predictors of Cognition in Mild Cognitive Impairment

Laura A. van de Pol, MD; Esther S. C. Korf, MD; Wiesje M. van der Flier, PhD; H. Robert Brashear, MD; Nick C. Fox, MD, FRCP; Frederik Barkhof, MD, PhD; Philip Scheltens, MD, PhD

Objectives: To describe magnetic resonance imaging characteristics in a large sample of subjects with mild cognitive impairment (MCI) and to investigate associations between these characteristics and cognition.

Design: Cohort study.

Setting: Baseline data of a randomized, double-blind, placebo-controlled clinical trial of galantamine in MCI (Trial Registration: clinicaltrials.gov Identifier: NCT00236574).

Patients: Included in the study were 896 subjects with MCI (age [mean±SD], 70±9 years; 54% women) with available clinical and magnetic resonance imaging data.

Main Outcome Measures: Neuropsychology: Alzheimer Disease Assessment Scale, cognitive subscale, MCI version, assessing global cognition; delayed recall on the New York University Paragraph Recall Test, assessing episodic memory; and Digit Symbol Substitution Test, assessing executive function. Neuroimaging: Medial Temporal Lobe Atrophy (MTA) Rating Scale (0-4) and Age-Related White Matter Changes Scale (0-30), assessing white matter hyperintensities (WMHs); and lacune counts.

Results: Median MTA score was 2 (range, 0-4), and mean (±SD) Age-Related White Matter Changes Scale score 6.0 (±4.7). Lacunes were present in 33% of subjects. In unadjusted models, increasing MTA and WMHs were associated with poorer performance on all cognitive tests, and lacunes with poorer performance on the Alzheimer Disease Assessment Scale, cognitive subscale, MCI version, and the Digit Symbol Substitution Test. In multivariable models, including magnetic resonance imaging measures simultaneously, MTA remained a predictor of cognition, whereas WMH had no independent predictive value. There was an interaction between MTA and lacunes: the strength of the association with the Digit Symbol Substitution Test increased with decreasing MTA.

Conclusions: Medial temporal lobe atrophy seems to be a more important predictor of cognition than small-vessel disease in MCI. Lacunes were associated with performance on the Digit Symbol Substitution Test, especially in subjects with milder MTA. Although WMHs were prevalent and associated with cognition in unadjusted analyses, there was no discernible association between WMHs and the cognitive measures in this study after adjustment for age.

Arch Neurol. 2007;64(7):1023-1028
well.12,13-18 Our purpose was 2-fold: to describe the MR imaging characteristics of a large population with MCI and to investigate how these characteristics relate to cognitive measures.

METHODS

STUDY DESIGN AND SUBJECTS

Baseline data were obtained from the Galantamine International-11 trial (Trial Registration: clinicaltrials.gov Identifier: NCT00236574), a 24-month, randomized, double-blind, placebo-controlled clinical trial that studied the effect of galantamine on cognitive decline in MCI (Johnson & Johnson Pharmaceutical Research & Development, LLC, Raritan, New Jersey). In total, 995 subjects were randomized. Enrollment criteria stated that subjects were aged 50 years or older and had a history of cognitive decline with insufficient impairment of activities of daily living for a diagnosis of dementia. Subjects were to have a global Clinical Dementia Rating scale17 score of 0.5 with a memory score of at least 0.5 and a delayed recall score on the New York University Paragraph Recall Test18 of 10 or less. Exclusion criteria were as follows: contraindication for MR imaging, clinically significant neurodegenerative disorders or other conditions possibly resulting in cognitive impairment, substantial intracranial pathologic features on MR images, severe comorbidity, current treatment for dementia, and a history of drug or alcohol abuse. All subjects gave written informed consent. The study was approved by the local medicothetical committees. For the current study, data were available for 896 subjects from 83 centers.

BASELINE CLINICAL ASSESSMENT

History taking, physical and neuropsychological examinations, and clinical laboratory tests were performed. The following variables were included in the analyses: sex, age at study enrollment, site of origin, vascular risk factors including hypertension (systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg [mean of 2 measurements obtained on 2 different occasions using the right arm with the subject sitting] or a history of hypertension or use of antihypertensive medication), diabetes mellitus (a history of diabetes mellitus type 2 or use of antidiabetic medication), hyperlipidemia (a history of hyperlipidemia or use of lipid-lowering medication), and current smoking status (yes or no).

NEUROPSYCHOLOGICAL ASSESSMENT

Cognition was assessed using 3 neuropsychological tests. Global cognition was assessed using the Alzheimer Disease Assessment Scale, cognitive subscale, MCI version (ADAS-cog/MCI).21 The ADAS-cog was modified to include a concentration and distractibility item, a delayed word recall test, the maze test, and ADAS-cog was scored on the Digit Symbol Substitution Test (DSST), correctly restated after 5 minutes. The number of correct items correctly drawn within a 120-second time limit. Higher ADAS-cog/MCI scores correspond with poorer performance, and higher delayed recall and DSST scores indicate better performance.

ACQUISITION OF MR IMAGES

Within 4 weeks before the baseline examination, all subjects underwent MR imaging using a standard protocol. Magnetic resonance imaging was performed on 1.5-T imagers (GE Medical Systems, Milwaukee, Wisconsin; Philips Medical Systems, Eindhoven, the Netherlands; or Siemens Medical Systems, Erlangen, Germany) and included a 3-dimensional, T1-weighted, gradient-echo sequence (coronal views, 1.5-mm section thickness, and 1-mm in-plane resolution) and a fast fluid-attenuated inversion recovery sequence (axial views, 5-mm contiguous sections, and 1-mm in-plane resolution). Visual ratings were performed at the Image Analysis Centre of the VU Medical Centre, Amsterdam, the Netherlands.

VISUAL RATING

Medial temporal lobe atrophy was rated on coronal T1-weighted images using a 5-point visual rating scale based on the height of the hippocampal formation and the surrounding cerebrospinal fluid space. An MTA grade of 0 or 1 is considered normal; a grade of 2 or higher corresponds with atrophy. Severity of WMH was rated on images obtained with fast fluid-attenuated inversion recovery using the 4-point Age-Related White Matter Changes Scale.23 We used the total degree of WMHs (range, 0-30).

Lacunes were defined as hypodense foci 3 mm or larger on fast fluid-attenuated inversion recovery and T1-weighted images, surrounded by white matter or subcortical gray matter, not located in areas with a high prevalence of widened perivascular spaces (eg, the anterior commissure). All visual ratings were carried out by 1 of us (E.S.C.K.), who was blinded to clinical information. Previous studies showed good intrarater agreement for the MTA scale (κ value, 0.70-0.76).6 The intraclass correlation coefficient for the total Age-Related White Matter Changes Scale score, determined on 19 randomly selected images scored twice, was 0.99.

STATISTICAL ANALYSIS

Associations between the MR imaging measures were assessed using Spearman rank correlations and partial correlations, controlling for age and sex. Associations between MTA (score, 0-4), WMHs (recoded into quintiles), lacunes (dichotomized; score, 0 or ≥1), and cognitive measures were assessed using general linear models with ADAS-cog/MCI, New York University Paragraph Recall Test, and DSSTs as dependent variables. Basic associations between MR images and cognitive measures were assessed in unadjusted analyses (model 1). Age and sex were entered as covariates (model 2). To assess the independent contributions of each MR imaging predictor, MTA, WMHs, and lacunes were entered simultaneously in multivariable models, adjusting for age and sex (model 3). Interactions between pairs of MR imaging measures were tested. Significant interactions were included in the model. In addition, corrections were made for vascular risk factors. Because different sites were involved, all models were repeated adding site of origin as a categorical covariate.

RESULTS

Subject characteristics are given in Table 1. Medial temporal lobe atrophy (score ≥2) was present in 50% of subjects. Most subjects (89%) had some small-vessel dis-
ease (Age-Related White Matter Changes Scale score >0). Fourteen percent of subjects had an Age-Related White Matter Changes Scale score of 10 or higher. One or more lacunes were present in 33% of subjects.

Medial temporal lobe atrophy was weakly correlated with WMHs ($r=0.32; P < .001$) and poorly correlated with the number of lacunes ($r=0.09; P < .1$). White matter intensity and the number of lacunes were also marginally correlated ($r=0.14; P < .001$). Adjusting for age and sex, the correlations between MTA and WMHs (partial $r=0.11; P < .001$) and between WMHs and the number of lacunes (partial $r=0.10; P < .01$) became less strong, whereas the association between MTA and the number of lacunes became almost zero and statistically nonsignificant ($r=0.01; P = .83$).

Table 2 gives the association between MR imaging and cognitive measures. General linear models were performed for MTA, WMH, and lacunes separately, with the 3 cognitive tests as dependent variables (model 1). In these basic models, MTA and WMHs each were associated with poorer performance on the ADAS-cog/MCI, New York University Paragraph Recall Test, and DSST. Lacunes were associated with ADAS-cog/MCI and DSST scores, whereas there was no association between lacunes and delayed recall. Adjusting for age and sex (model 2), MTA remained associated with poorer performance on all cognitive measures, whereas the severity of WMHs and lacunes no longer predicted any of the cognitive tests’ outcomes. To assess the independent effects of MTA, WMHs, and lacunes on cognition, all MR imaging measures were entered simultaneously into general linear models, adjusting for age and sex (model 3). Performance on the ADAS-cog/MCI and New York University Paragraph Recall Test was predicted by the severity of MTA, whereas WMHs and lacunes were not independently associated with these measures. Performance on the DSST was associated with the severity of MTA and the presence of lacunes but not with WMHs. An interaction ($P = .03$) between MTA and lacunes indicated that the strength of the association of lacunes with poorer performance on the DSST increased with decreasing MTA. Correction for vascular risk factors or site of origin did not essentially change the results (data not shown).

Table 1. Baseline Characteristics in 896 Subjectsa

<table>
<thead>
<tr>
<th>Demographic Data</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70 (9)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>416 (46)</td>
</tr>
<tr>
<td>Neurropsychology</td>
<td></td>
</tr>
<tr>
<td>ADAS-cog/MCI</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Paragraph Recall Test</td>
<td>4 (3)</td>
</tr>
<tr>
<td>DSST</td>
<td>47 (20)</td>
</tr>
<tr>
<td>Vascular risk factors, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>525 (59)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>78 (9)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>266 (30)</td>
</tr>
<tr>
<td>Smoking</td>
<td>62 (7)</td>
</tr>
<tr>
<td>MR imaging</td>
<td></td>
</tr>
<tr>
<td>MTA, 0-4, median (range)</td>
<td>2 (0-4)</td>
</tr>
<tr>
<td>WMHs, 0-30b</td>
<td>6.0 (4.7)</td>
</tr>
<tr>
<td>Lacunes, &gt;1, No. (%)</td>
<td>299 (33)</td>
</tr>
</tbody>
</table>

Abbreviations: ADAS-cog/MCI, Alzheimer’s Disease Assessment Scale, cognitive subscale, mild cognitive impairment version; DSST, Digit Symbol Substitution Test; MTA, medial temporal lobe atrophy; WMHs, white matter hyperintensities (score, 0-30).

aScores are given as mean (SD) unless otherwise stated.

bScored using the Age-Related White Matter Changes Scale.

Table 2. Associations Between MR Imaging Measures and Measures of Cognition in 896 Subjectsa

<table>
<thead>
<tr>
<th>Test</th>
<th>MTA</th>
<th>WMHs</th>
<th>Lacunes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model</td>
<td>Score</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>ADAS-cog/MCI</td>
<td>1</td>
<td>3.7 (0.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.8 (0.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2.8 (0.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>New York University</td>
<td>1</td>
<td>-0.6 (0.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Paragraph Recall Test</td>
<td>2</td>
<td>-0.5 (0.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>-0.5 (0.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DSST</td>
<td>1</td>
<td>-5.5 (0.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-2.0 (0.7)</td>
<td>&lt;.1</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>-3.0 (0.9)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations: ADAS-cog/MCI, Alzheimer’s Disease Assessment Scale, cognitive subscale, mild cognitive impairment version; DSST, Digit Symbol Substitution Test; MTA, medial temporal lobe atrophy (score, 0-4); WMHs, white matter hyperintensities in quintiles.

aValues are given as $b$ (SE). General linear models were constructed. In model 1, MTA, WMHs, and lacunes were entered in separate models as predictors, with ADAS-cog/MCI, New York University Paragraph Recall Test, and DSST scores as dependent variables. In model 2, age and sex were added as covariates. In model 3, MTA, WMHs, and lacunes were entered simultaneously as predictors, and ADAS-cog/MCI and Paragraph Recall Test as dependent variables, controlling for age and sex. In model 3, with DSST as the dependent variable, the significant interaction term MTA*Lacunes ($P = .03$) was added.

To our knowledge, this study is one of the first to describe the MR imaging characteristics and their associations with cognitive performance in a large population with MCI in the setting of a clinical trial. Medial temporal lobe atrophy was observed in half of the subjects, and evidence of small-vessel disease was present in most subjects. Severity of MTA was associated with general cognition, episodic memory performance, and DSST score, independent of age, sex, and the other MR imaging measures. Lacunes were associated with performance on the DSST, especially in subjects with milder MTA. Despite a
high prevalence, the severity of WMHs was not independently associated with any cognitive measure used in this study, after adjustment for age.

Our results are in keeping with those of a previous study that reported MTA in 51% of subjects with MCI. An association between MTA and delayed recall is to be expected in patients with AD and control subjects. In this population with MCI, with a limited degree of cognitive impairment as a result of inclusion criteria, an association between MTA and delayed recall was still significant. An association between MTA and ADAS-cog/MCI score was also found, possibly reflecting that it is largely memory functions that are being determined by the ADAS-cog/MCI in subjects with mild disease stage. That MTA was associated with DSST score as well may reflect the well-recognized involvement even in MCI of multiple cognitive domains.

Small-vessel disease was prevalent: only 11% of subjects were free of any WMHs, and 33% had lacunes. Similar numbers have been described in earlier studies reporting the presence of WMHs in 92% of elderly subjects, the presence of lacunes in 23% of a large population-based cohort, and in 44% of subjects in an MCI cohort.

Figure. Box plots of scores (median, quartile, and extreme values) on the Alzheimer’s Disease Assessment Scale, cognitive subscale, for mild cognitive impairment (ADAS-cog/MCI). A, Medial temporal lobe atrophy (MTA) severity. B, White matter hyperintensities (WMHs), in quintiles. C, Number of lacunes (none vs ≥1).
In common with previous studies, MTA seemed to be a more important determinant of cognitive performance, at least as measured by the tests used in this study, than did small-vessel disease. Using unadjusted analyses, WMH severity was associated with the cognitive measures. This association was no longer apparent once corrected for age. In parallel, the correlation between MTA and WMHs was also influenced by age. In unadjusted analyses, the presence of lacunes was associated with ADAS-cog/MCI and DSST scores but not with delayed recall. Again, these associations disappeared after adjusting for age. However, there was an interaction between MTA and lacunes, indicating that the strength of the association between lacunes and poorer performance on the DSST was strongest in subjects with less severe MTA. This may indicate that, within the known heterogeneity of MCI, there will be subjects with relatively less severe AD-type pathology (and less severe MTA) and relatively more severe cerebrovascular disease (lacunes). In those subjects with mild AD-type pathologic features, the effect of the lacunar infarcts will be easier to discern (without the confounds of AD-related deficits). In contrast, it has been suggested that the contribution of small-vessel disease to cognition only becomes clinically apparent in the presence of a certain degree of AD-type pathology. It is conceivable that the neuropathologic burden of AD in our population with MCI was not severe enough to disclose such effects. Furthermore, it is possible that the location of the lacunes might modify the association with cognition. This may be an interesting topic for further research.

Previous studies reported WMHs to be associated with poorer cognitive performance, although these efforts were usually modest or related to severe WMHs only. In our study, the association of WMHs with cognition disappeared after adjustment for age. White matter hyperintensities were prevalent and strongly correlated with age. The wide age range (50-94 years) of our subjects may have influenced the association between WMHs and cognition. In addition, inclusion of subjects mainly focused on memory impairment. This may have caused underestimation of the role of small-vessel disease, which is expected to particularly influence the nonmemory domains. Moreover, neuropsychological tests used in this randomized clinical trial were not specifically selected to assess WMH-related functions.

Further longitudinal analysis may reveal which of the MR imaging characteristics predicts progression of cognitive decline. The cross-sectional design of this study limits interpretation about causal mechanisms underlying the associations of MR imaging and cognitive measures. Furthermore, these associations may have been underestimated because of limited variation in cognition as a result of inclusion of only subjects with MCI and possible ceiling effects on the neuropsychological tests. Among the strengths of this study is the large sample size with available MR images. All images were analyzed centrally, which reduced the variability of MR imaging measures to a large extent.

This study may have important clinical implications. Our findings show heterogeneity for MR imaging findings in MCI and, to our knowledge, is the largest study to date to assess MR imaging measures in MCI. Identification of subjects with preclinical AD remains an important challenge. Our study emphasizes the important role of MTA, in contrast to the modest contribution of small-vessel disease to cognitive deficits in subjects considered to have MCI.

Accepted for Publication: October 18, 2006.

Correspondence: Laura A. van de Pol, MD, Department of Neurology, Alzheimer Centre, VU Medical Centre, Vrije Universiteit Amsterdam, De Boelelaan, 1117, PO Box 7057, 1007 MB Amsterdam, the Netherlands (L.vandepol@vumc.nl).

Author Contributions: Study concept and design: van de Pol, van der Flier, Brashear, Barkhof, and Scheltens. Acquisition of data: van de Pol, Korf, Brashear, Fox, Barkhof, and Scheltens. Analysis and interpretation of data: van de Pol, Korf, van der Flier, Brashear, Fox, Barkhof, and Scheltens. Drafting of the manuscript: van de Pol, Korf, van der Flier, Barkhof, and Scheltens. Critical revision of the manuscript for important intellectual content: van de Pol, Korf, van der Flier, Brashear, Fox, Barkhof, and Scheltens. Statistical analysis: van der Flier. Obtained funding: van de Pol and Brashear. Administrative, technical, and material support: van de Pol, Korf, Brashear, Barkhof, and Scheltens. Study supervision: van der Flier, Fox, Barkhof, and Scheltens.

Financial Disclosure: None reported.

Funding/Support: This study was supported by the Image Analysis Centre at the VU Medical Centre (L.A.V.) and by the Stichting Alzheimer and Neuropsychiatric Foundation. The Alzheimer Center is supported by the VUmc Fonds. The Image Analysis Center and the Dementia Research Centre received fees for analyzing images and for consulting services from the Janssen Research Foundation. Dr Brashear is employed by Johnson & Johnson Pharmaceutical Research and Development.

Role of the Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Additional Contributions: Luc Truyen, MD, Johnson & Johnson Pharmaceutical Research and Development, provided contributions in design and planning of the Galant-11 trial.

REFERENCES