Predicting Aggressive Decline in Mild Cognitive Impairment
The Importance of White Matter Hyperintensities

Giuseppe Tosto, MD; Molly E. Zimmerman, PhD; Owen T. Carmichael, PhD; Adam M. Brickman, PhD; for the Alzheimer’s Disease Neuroimaging Initiative

IMPORTANCE Although white matter hyperintensities (WMHs) are associated with the risk for Alzheimer disease, it is unknown whether they represent an independent source of impairment or interact with known markers of disease.

OBJECTIVE To examine the degree to which WMHs predict aggressive cognitive decline among individuals with mild cognitive impairment, either independently or by modifying the effects of entorhinal cortex volume (ECV), a marker of Alzheimer disease–related neurodegeneration.

DESIGN, SETTING, AND PARTICIPANTS The Alzheimer’s Disease Neuroimaging Initiative is a longitudinal study with 6-month follow-up visits. Three hundred thirty-two participants (mean [SD] age, 74.6 [7.4] years; 118 women) of a total of 374 participants diagnosed as having mild cognitive impairment were included. Participants were excluded if they did not have longitudinal data, apolipoprotein E genotype data, or had evidence of supratentorial infarct.

MAIN OUTCOMES AND MEASURES A decline in Mini-Mental State Examination score of 3 points over 6 months or 6 points over 1 year between consecutive visits was defined as aggressive decline. White matter hyperintensity volume and ECV were entered as predictors in Cox proportional hazards models and Wilcoxon-Breslow tests to examine their impact on this outcome, adjusting for sex, age, education, and apolipoprotein E status.

RESULTS Greater WMH volume at baseline, apolipoprotein E ε4 status, and smaller ECV at baseline were associated with an increased risk for aggressive decline (hazard ratio [HR], 1.23; 95% CI, 1.05-1.43; P = .01 for WMH volume; HR, 1.49; 95% CI, 1.09-2.05; P = .04 for apolipoprotein E ε4 status; HR, 0.66; 95% CI, 0.55-0.79; P < .001 for ECV). White matter hyperintensity volume modified the effect of ECV on aggressive decline risk: individuals with high ECV and low WMH were at particularly low likelihood of decline (χ² = 15, P = .001). Participants with Mini-Mental State Examination scores that declined by 3 or more points over 6 months or 6 or more points over 12 months were more likely to have converted to Alzheimer disease by the end of the follow-up period (χ² = 82, P < .001).

CONCLUSIONS AND RELEVANCE White matter hyperintensity burden and ECV predict rapid cognitive decline among individuals with mild cognitive impairment both additively and multiplicatively.
Despite contemporary models of Alzheimer disease (AD) pathogenesis, which emphasize the precipitating role of β-amyloid and subsequent neurodegenerative changes due to tau pathology, small-vessel cerebrovascular disease has emerged as an important driver of risk and clinical expression of the disease. We previously showed that individuals with prevalent AD and those at risk for AD have an increased burden of small-vessel cerebrovascular changes, visualized as increased white matter hyperintensities (WMHs) on T2-weighted magnetic resonance imaging (MRI). Increased WMH burden also predicts incident AD and individuals with evidence of amyloidosis are more likely to exhibit symptoms of dementia if they have substantial WMH burden. The degree to which WMH burden contributes to clinically meaningful decline in individuals at risk for AD remains an important question.

The diagnostic category of mild cognitive impairment (MCI) refers to the intermediate stage of a 3-part journey that begins with normal cognitive aging and ends with dementia due to AD. Individuals with MCI have objective evidence of cognitive impairment but without the functional impairment that interferes with their daily activities. When clinically defined, there is much heterogeneity in the rate of cognitive decline among individuals with MCI, with some progressing quite precipitously while others remain cognitively stable and functionally unimpaired. Work that has examined clinical outcomes in MCI tends to focus on conversion to AD, where the threshold between the two is defined by a switch from a functionally unimpaired state to a cognitive syndrome defined by functional impairment.

The Mini-Mental State Examination (MMSE) is one of the most common tools used by clinicians to follow up patients’ progression over time. Many efforts to classify progression rates in MCI, as well as AD stages, relied on the MMSE and showed great heterogeneity, possibly owing to real individual difference in progression rates, biased sampling in terms of baseline characteristics, and/or floor and ceiling effects of the scales administered. Operational definitions of MMSE decline thresholds to assess the rapidity or aggressiveness of progression have been long debated: declines of 3 points over 1 year, 4 or 7 points over 1 year, and 3 points over 6 months have been proposed as classification criteria. However, confusion exists not only in terms of cutoffs, but also regarding baseline level of impairment and observational periods; previous studies applied these thresholds to a wide range of baseline MMSE scores, including mild to moderate AD across a large range of follow-up periods (MMSE decline in 6 to 24 months, escalating cognitive impairment in 3 years, or survival time of less than 4 years). A recent study, based on extensive review of previous studies, suggested that a decline of 6 points per year on the MMSE should be used as the optimal threshold to define rapidly progressive AD.

Regardless of the threshold chosen, the value of this approach is that it clusters patients within discrete classes of progression by defining a rapid event as an MMSE point decline that deviates from what is the average point decline in AD (2.5 per year) and obviously in MCI (1 per year). This approach may be ideal for clinical practice because it provides an operational definition that can be applied to an individual patient.

The purpose of this study was to examine whether WMHs predict the rapidity of cognitive decline in MCI as measured by clinically defined categorical changes in MMSE scores over time. We hypothesized that WMH burden would predict clinical outcomes independent of a measure of entorhinal cortex atrophy, a putative biological marker of neurodegeneration due to AD, and apolipoprotein E (APOE) ε4, a well-known genetic risk factor for AD. We also explored whether WMH volume and entorhinal cortex atrophy interact to predict clinical outcome.

Methods
Alzheimer’s Disease Neuroimaging Initiative
Data used in the preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations as a $60 million, 5-year public–private partnership. The primary goal of the ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as decrease the time and cost of clinical trials.

This research was approved by the institutional review boards of all participating institutions. Written informed consent was obtained from all participants or their surrogates.

The principal investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California–San Francisco. The ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and participants have been recruited from more than 50 sites across the United States and Canada. The initial goal of the ADNI was to recruit 800 participants but the ADNI has been followed by ADNI GO (Grand Opportunity) and ADNI 2. To date, these 3 protocols have recruited more than 1500 adults, ages 55 to 90 years, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD to participate in the research. The follow-up duration of each group is specified in the protocols for ADNI 1, ADNI 2, and ADNI GO. Participants originally recruited for ADNI 1 and ADNI GO had the option to be followed up in ADNI 2. Up-to-date information is available at www.adni-info.org.

Participants
Data from patients diagnosed as having MCI (n = 374) were downloaded from the ADNI database (www.loni.usc.edu/ADNI) and included demographic, genetic, and structural MRI scan data. All participants included had amnestic MCI. The ADNI study was designed to parallel procedures used in a clini-
cal trial and thus only included participants who were in good medical health. Importantly, individuals were excluded from participation if they had a significant vascular disease risk history, defined as a modified Hachinski score greater than 4. Diagnosis of MCI was based on standard research criteria and included age between 55 and 90 years; a memory symptom (study participant or informant); objective evidence of abnormal memory; Clinical Dementia Rating score of 0.5, with a diagnosis of AD could not be made; stable medication; and not depression. A proton density/T2-weighted fast spin echo sequence was acquired in the axial orientation. Sites included in the ADNI protocol were required to pass rigorous scanner validation tests and scan acquisitions for each participant included a fluid-filled phantom. Details of the validation procedures are provided elsewhere (www.loni.usc.edu/ADNI).

WMH Quantification
White matter hyperintensity volumetric quantification has been described in detail elsewhere. Briefly, the T1-, T2-, and proton density–weighted MRI scans were coregistered and skull-stripped. After bias field correction, WMHs were detected in minimum deformation template space at each voxel based on corresponding proton density, T1, and T2 intensities; the prior probability of WMH; and the conditional probability of WMH based on the presence of WMH at neighboring voxels. Labeled voxels were summed and multiplied by voxel dimensions to yield total WMH volumes. White matter hyperintensity volumes estimated with this method agreed strongly with WMH volumes estimated from fluid attenuated inverse recovery MRI in a large, diverse elderly sample.

Entorhinal Cortex Volume
Structural MRI parcellation and segmentation data were downloaded from the ADNI website. The ADNI structural MRI data were analyzed with FreeSurfer version 4.3 (https://surfer.nmr.mgh.harvard.edu) at the University of California–San Francisco after the T1-weighted MRI scans were converted to NIfTI format and preprocessed at Mayo Clinic. For the purposes of the current analyses, we focused on entorhinal cortex volumes (ECVs).

Covariates and APOE Genotyping
Sex, education, and age at baseline were included as covariates in all the models presented. Apolipoprotein E genotyping was based on allelic combinations of single-nucleotide polymorphisms rs7412 and rs429358.

Statistical Analysis
Cox proportional hazards models and the Wilcoxon-Breslow test were constructed to examine the impact of baseline WMH volume on clinical outcome. Visits that occurred outside the tolerance range of ±2 months per expected visit agenda were excluded. A 48-month follow-up period was defined for our analysis. As secondary analyses, both ECV and WMH were dichotomized to define low and high WMH load and ECV subgroups.

Entry selection method was carried out to identify independent factors prognostic for survival: total WMH together with age, sex, and education as covariates were included in the primary analysis. Secondary analyses were carried out including well-established risk factors for conversion and rapid progression: APOE ε4 status and ECV.

To weigh more the early occurrence of the defined event, survival curves constructed through Wilcoxon-Breslow test were computed contrasting 4 subpopulations (high vs low entorhinal cortex groups stratified by high and low WMH groups, both defined by median split).
The importance of a prognostic variable was assessed via Wald-type test statistics, the hazard ratio (HR), and its 95% CI for survival. Alpha levels were set a priori at .05. Additional sensitivity analysis was performed through 1000 bootstrap-generated simulation data sets to confirm the results obtained in the Cox regression model.

**Results**

Descriptive data for participants’ characteristics are presented in Table 1. Participants labeled as rapid progressors did not differ from the rest of the sample in terms of sex distribution, age at baseline, and number of years of education.

Results of the Cox regression analyses are presented in Table 2. Higher WMH volume at baseline was associated with an increased risk for rapid decline over the follow-up period (HR, 1.23; 95% CI, 1.05-1.43; \( P = .01 \)). None of the other covariates included reliably predicted rapid decline.

The Wilcoxon-Breslow survival analysis was significant (\( P = .001 \)) for the 4 subgroups identified by dichotomized ECV, stratified by WMH severity; individuals with high ECV and low WMH appeared to be at particularly low likelihood of decline. The clinicalevent was defined as a decline of 3 points over 6 months or 6 points over 1 year on the Mini-Mental State Examination. Both WMH and ECV were related to clinical outcome; the 2 predictors interacted such that individuals with high ECV and low WMH were at particularly low likelihood of decline.

*Figure 1* displays the cumulative survival of individuals with high and low amounts of WMH. When APOE ε4 status and ECV were included in the model, total WMH remained a predictor with similar magnitude (HR, 1.2; 95% CI, 1.02-1.4; \( P = .03 \)). In the full model, both APOE ε4 and ECV predicted outcomes (HR, 1.4; \( P = .03 \); and HR, 0.66, \( P < .001 \), respectively).

The Wilcoxon-Breslow survival analysis was significant (\( P = .001 \)) for the 4 subgroups identified by dichotomized ECV, stratified by WMH severity; individuals with high ECV and low WMH appeared to be at particularly low likelihood of declining rapidly (*Figure 2*).

Participants experiencing MMSE point declines of 3 or greater over 6 months or 6 or more over 12 months were more likely to have converted to AD by the end of the follow-up period (\( \chi^2 = 82, P < .001 \)).

**Table 2. Cox Regression Model Results**

<table>
<thead>
<tr>
<th>Variable</th>
<th>ADNI Patients With MCI (N = 332)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.2 (0.9-1.64)</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.97-1.01)</td>
</tr>
<tr>
<td>Education</td>
<td>0.98 (0.92-1.02)</td>
</tr>
<tr>
<td>APOE ε4</td>
<td>1.49 (1.09-2.05)</td>
</tr>
<tr>
<td>ECV</td>
<td>1.23 (1.05-1.43)</td>
</tr>
</tbody>
</table>

Abbreviations: ADNI, Alzheimer’s Disease Neuroimaging Initiative; APOE, apolipoprotein E; ECV, entorhinal cortex volume; HR, hazard ratio; MCI, mild cognitive impairment; NS, not significant; WMHs, white matter hyperintensities.
Discussion

By focusing on clinically meaningful definitions that use the MMSE, one of the most widely used clinical instruments, we demonstrated that the severity of WMH predicts the likelihood that individuals with MCI have an aggressive clinical course. We also confirmed that diminished ECV, a marker of neurodegeneration associated with AD, predicts an aggressive course with similar magnitude. Importantly, the 2 biological markers interact such that individuals with large ECV and a small amount of WMH burden appear to have synergistically diminished risk for decline. This latter finding suggests a mechanistic interaction between the 2 pathologic markers on clinical course.

A diagnosis of MCI increases individuals’ risk for future development of AD, but it is not synonymous with a diagnosis of early AD. Indeed, several individuals with MCI do not ultimately convert to AD or have a precipitous clinical decline.27 However, the design of the ADNI study included individuals with late MCI thought to be at high risk to develop clinical AD. The question of what factors have prognostic use in determining which individuals diagnosed as having MCI have a precipitous clinical event through their follow-up is critical to both clinicians making the MCI diagnosis and to the individuals receiving the diagnosis. Here, we showed that the burden of WMH is a reliable predictor of which patients, diagnosed as having MCI at baseline, will decline with an aggressive clinical course. We purposefully focused on a psychometrically defined criterion for aggressive course rather than, for example, conversion to AD, to parallel explicitly outcomes that are common in clinical settings where research diagnostic procedures (eg, amyloid imaging and cerebrospinal fluid studies) are less available. Nonetheless, we recognize that aggressive course in MCI overlaps to a certain extent with conversion to AD and demonstrated that those who had a more precipitous decline were indeed more likely to carry an AD diagnosis on follow-up examination.

To capture important prognostic information, we applied an operational cutoff that defines an aggressive decline in cognitive performance during a narrow observational window in participants at risk for or in the very early stages of the disease. Previous research has applied a similar approach to a wide range of AD severity. For example, Doody and colleagues28 showed that estimated progression rates prior to enrollment in the study (computed with the formula [30 – baseline MMSE score] / year since symptom onset) predicted future changes in cognition, activities of daily living, and mortality. The baseline measure identified slow-, intermediate-, and fast-progressing groups and reliable differences among the 3 groups persisted or increased even on a long-term follow-up observation. The MMSE has a well-known floor effect among patients with prevalent AD29; thus, its use in detecting dementia progression is somewhat limited among more impaired patients. By examining patients with MCI in the current study, we avoided the problem of floor effects.

Our observations add to a growing body of literature that implicates WMH in the clinical course and, possibly, pathogenesis of AD. In community-based studies, we previously showed that WMH volume is elevated in individuals with MCI and AD,30 predicts future incident AD among nondemented older adults,3 progresses over time in individuals with incident AD, and predicts the rate of cognitive decline among individuals with prevalent AD.31 Our previous efforts in the ADNI showed that among individuals with evidence of amyloidosis, those with elevated WMH were more likely to meet clinical criteria for AD than those with lower amounts of WMH.4 We also showed that WMH volume is correlated with the degree of atrophy in the entorhinal cortex among individuals with MCI.32 Here, we extend those findings and suggest that medial temporal lobe atrophy, reflecting neurodegeneration, and WMHs may interact mechanistically or result from a common upstream driver. Whether the relationship between WMH and neurodegenerative changes is fundamental or epiphenomenological may still be up for debate; however, what is clear is that WMHs at least contribute additively to clinical course in the context of other AD biological markers.

Conclusions

Our findings demonstrate that both WMH and ECV predict rapid progression in the early stages of the disease and interact synergistically. The findings may be useful for prognosis of outcomes, especially in clinical settings, but also contribute to a growing body of work that implicates small-vessel cerebrovascular disease in AD pathogenesis and clinical expression. Furthermore, because many of the risk factors for WMH have been established and are modifiable through lifestyle or pharmacological intervention, our findings suggest avenues for prevention or treatment of rapid-progressing course among patients with MCI.

ARTICLE INFORMATION

Accepted for Publication: March 10, 2014.
Published Online: May 12, 2014.

Author Contributions: Dr Brickman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Tosto, Brickman.
Acquisition, analysis, or interpretation of data: Zimmerman, Carmichael, Brickman.
Drafting of the manuscript: Tosto, Brickman.
Critical review of the manuscript for important intellectual content: Zimmerman, Carmichael, Brickman.
Statistical analysis: Tosto, Zimmerman, Brickman.
Conflict of Interest Disclosures: None reported.
Funding/Support: Data collection and sharing for this project was funded by the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (National Institutes of Health grant U01 AG024904) and Department of Defense ADNI (award number W81XWH-12-0012). The ADNI is funded by the National Institute on Aging and the National Institute of Biomedical Imaging and Bioengineering, as well as through generous contributions from the following: Alzheimer’s Association; Alzheimer’s Drug Discovery Foundation; BioClinica Inc; Biogen Idec Inc; Bristol-Myers Squibb Co; Eisai Inc; Elan Pharmaceuticals Inc; Eli Lilly and Co; F. Hoffmann-La Roche Ltd and its affiliated company Genentech Inc; GE Healthcare; Innogenetics NV; IXICO Ltd; Janssen Alzheimer Immunotherapy Research & Development LLC; Johnson & Johnson Pharmaceutical Research & Development LLC; Medpace Inc; Merck & Co Inc; Meso Scale Diagnostics LLC; NeuroRx Research; Novartis; Pfizer Inc; Piramal Imaging; Servier; and Synarc Inc.

Copyright 2014 American Medical Association. All rights reserved.
WMHs and Decline in MCI

Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. 

Regional white matter hyperintensity volume, not hippocampal atrophy, predicts incident Alzheimer's disease. 

Hippocampal atrophy, predicts incident Alzheimer's disease in the community. 

The progression of cognitive impairment in dementia with Lewy bodies, vascular dementia and Alzheimer's disease. 

Cognitive and behavioural predictors of progression rates in Alzheimer's disease. 

Copyright 2014 American Medical Association. All rights reserved.