Measuring Cerebral Atrophy and White Matter Hyperintensity Burden to Predict the Rate of Cognitive Decline in Alzheimer Disease

Adam M. Brickman, PhD; Lawrence S. Honig, MD, PhD; Nikolaos Scarmeas, MD; Oksana Tatarina, BA; Linda Sanders, BA; Marilyn S. Albert, PhD; Jason Brandt, PhD; Deborah Blacker, MD, ScD; Yaakov Stern, PhD

Objective: To determine if baseline measurements of cerebral atrophy and severity of white matter hyperintensity (WMH) predict the rate of future cognitive decline in patients with Alzheimer disease (AD).

Design: Data were drawn from the Predictors Study, a longitudinal study that enrolls patients with mild AD and reassesses them every 6 months with use of the Columbia modified Mini-Mental State (mMMS) examination (score range, 0-57). Magnetic resonance images were analyzed to determine the severity of WMH, using the Scheltens scale, and the degree of atrophy, using the bicaudate ratio. Generalized estimating equations were used to determine whether severity of baseline magnetic resonance image measurements and their interaction predicted the rate of mMMS score decline at subsequent visits.

Setting: Three university-based AD centers in the United States.

Participants: At baseline, 84 patients with AD from the Predictors Study received structural magnetic resonance imaging and were selected for analysis. They had a mean of 6 follow-up evaluations.

Main Outcome Measure: The mMMS score.

Results: Generalized estimating equation models demonstrated that the degree of baseline atrophy ($\beta = -0.316; P = .04$), the severity of WMH ($\beta = -0.173; P = .03$), and their interaction ($\beta = -0.061; P = .02$) predicted the rate of decline in mMMS scores.

Conclusions: Both degree of cerebral atrophy and severity of WMH are associated with the rapidity of cognitive decline in AD. Atrophy and WMH may have a synergistic effect on future decline in AD, such that patients with a high degree of both have a particularly precipitous cognitive course. These findings lend further support to the hypothesis that cerebrovascular pathological abnormalities contribute to the clinical syndrome of AD.

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tricular volume and severity of WMH predicted the rate of future decline among healthy older adults, but only ventricular volume predicted the rate of decline among those with mild cognitive impairment and AD. However, only 39 patients with AD were included in the study, and the investigators did not examine the interaction between ventricular volume and WMH severity. Examining the 2 imaging markers together may help determine the relative importance of cerebrovascular disease in the course of AD and whether it synergistically interacts with disease state.

In the current study, we used data from the Predictors Study cohort to examine the prognostic utility of baseline measurements of atrophy and cerebrovascular disease on rates of cognitive decline during the early stages of AD. An overarching goal of the Predictors Study is to elucidate the determinants of the cognitive and functional course of AD. A subset of participants received standard MRI studies as part of their diagnostic workup. We used these data and rated the severity of cerebral atrophy and WMH to predict future decline in cognitive abilities. We hypothesized that baseline atrophy and WMH ratings would predict future decline in cognition and that the 2 measures would interact.

METHODS

SAMPLE CHARACTERISTICS

The sample was drawn from the Predictors Study cohort and included individuals with AD. Complete inclusion criteria and other details of the study are described elsewhere. Briefly, participants met diagnostic criteria for dementia of the Alzheimer type and probable AD. Exclusion criteria included participants met diagnostic criteria for dementia of the Alzheimer type and probable AD. Exclusion criteria included participants with paroxysmal atrial fibrillation, stroke, alcoholism, schizophrenia, schizoaffective disorder, and history of electroconvulsive treatments. Participants were recruited from Columbia University, Johns Hopkins School of Medicine, and Massachusetts General Hospital between April 1989 and September 2005. The study was approved by local ethics committees. Neuroimaging was acquired for clinical diagnostic purposes, and images were available for 84 individuals in the study cohort. These subjects constitute the current study sample. Mean (SD) age at the time of the neuroimaging study was 73.2 (8.0) years; 40 subjects (48%) were male, and 76 (90%) were white. Mean (SD) number of years of education was 14.8 (3.7). Participants were relatively mildly impaired at the time of their neuroimaging studies, as indicated by a mean (SD) Columbia modified Mini-Mental State (mMMS) examination score of 41.3 (7.1), which is comparable to a Mini-Mental State Examination (MMSE) score of approximately 22. The mean (SD) number of follow-up visits, at approximate 6-month intervals, was 3.8 (3.0).

Of 62 subjects for whom data were available, 31 (50%) had the apolipoprotein E ε4 (APOE ε4) allele. At baseline, 8 of 84 (10%) had a self-reported history of diabetes mellitus, 14 (17%) had dyslipidemia, 14 (17%) had coronary artery disease, and 30 (36%) had hypertension. Compared with the participants without available neuroimages (n=456) in the Predictors Study, the current study participants were similar in age, sex, number of evaluations, and proportion with the APOE ε4 allele, diabetes mellitus, dyslipidemia, coronary artery disease, and hypertension. Those without available neuroimages had fewer years of education than those with available neuroimages (mean [SD], 13.4 [3.5] vs 14.8 [3.7]; P=0.001).

NEUROIMAGING

Estimates of total brain atrophy were computed primarily from T1-weighted images, which were available for 53 (63%) of 84 participants with neuroimaging data; atrophy measurements were computed for the remaining participants on FLAIR–, proton–, or T2-weighted images. Findings did not change when we included image sequence as a dummy-coded covariate. Bicaudate ratios were derived from axially acquired images as an estimate of total brain atrophy following established protocols. To derive the bicaudate ratio, the axial slice on which the caudate nuclei produced the greatest amount of indentation on the lateral ventricles was identified, and the distance between the 2 caudate apices was measured in millimeters. This value was divided by the maximum width of the skull at the same level as the caudate measurement (Figure 1). Using this approach, enlarged ventricles increase the distance between the 2 caudate nuclei, resulting in a higher bicaudate ratio. Therefore, a larger value indicates a greater degree of atrophy. Bicaudate ratio measurements were made by 2 experienced raters (A.M.B. and L.S.H.). Inter-rater reliability, computed for 12 images, was good for bicaudate distance (intraclass correlation coefficient, 0.861), skull width (0.991), and bicaudate ratio (0.740). Furthermore, in an independent sample of digital T1-weighted MRIs from 17 patients with dementia, we calculated bicaudate ratios and compared them with manually derived full relative brain volumes and found a strong relationship between the 2 measures (Spearman ρ=−0.814; P<0.001). These findings suggest that the bicaudate ratio is a reliable and valid index of cerebral atrophy.

The WMH severity ratings were attained from FLAIR– and T2-weighted images using the Scheltens scale. The Scheltens scale is a visual rating scale that includes anchored 7-point severity ratings in periventricular (ie, frontal horn, occipital horn, and lateral bands), cortical (ie, frontal, temporal, parietal, and
Model 2b

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The regression model testing the association of WMH severity with baseline cognition was not significant with ($F_{2,57} = 1.981; P = .07$) or without ($F_{1,76} = 2.302; P = .07$) risk factor variables included. Similarly, when the 2 MRI measurements and their interaction terms were included, the model was not significant whether risk factor variables were ($F_{11,33} = 1.898; P = .07$) or were not ($F_{6,76} = 1.960; P = .08$) included.

In a separate bivariate correlational analysis, controlling for age, severity of WMH was not significantly associated with atrophy ratings ($r_{24} = .103; P = .38$).

LONGITUDINAL ANALYSIS

The mMMS scores declined a mean of 3.5 points per year (estimated $\beta = -3.455; P < .001$). The Table displays the primary results of the 3 GEE analyses. For every 1% increase in baseline bicaudate ratio, there was an additional 0.316-point decrease in mMMS score per year (significant time $\times$ bicaudate interaction). Increased age ($\beta = 0.452; P = .04$), being male ($\beta = 5.263; P = .04$), and lower educational level ($\beta = 1.239; P < .001$) were associated with poorer mMMS scores. The effect of bicaudate ratio on mMMS score decline was similar when the vascular risk factors were excluded. Figure 2 displays the estimated rate of decline in mMMS scores in participants with low and high bicaudate ratio values, which were defined on the basis of a median split (median, 0.1567). Note that a higher bicaudate ratio indicates greater amount of atrophy.

Figure 2. Predicted rates of cognitive change based on baseline characterization of bicaudate ratio. Baseline bicaudate ratio is presented as a dichotomous variable based on the median split of the entire sample (median, 0.1567). Note that a higher bicaudate ratio indicates greater amount of atrophy. The results from the generalized estimating equation analysis suggest that the greater the amount of atrophy at baseline, the greater the rate of cognitive decline. mMMS indicates modified Mini-Mental State.

The current study sought to determine whether measures of cerebral atrophy and WMH severity were associated with cognitive function and the rate of future cognitive decline in AD. Several important findings emerged. First, when examined cross-sectionally, increased atrophy was modestly associated with poorer cognitive performance, but the relationship between severity of WMH and cognition was unremarkable. When examined longitudinally, severity of baseline atrophy and severity of baseline WMH were associated with a faster rate of future cognitive decline. When both severity measures were considered in the same statistical model, they interacted and had an effect on future decline. Taken together, the findings suggest a synergistic interaction of AD pathology and small vessel vascular disease on the course of cognitive symptoms in AD.

The results add to a growing corpus of work examining the associations among measures of AD pathology, vascular disease, and their clinical expression. In most studies, atrophy is more prominent among patients with AD than controls and is associated with more severe cognitive symptoms. Others have reported that increased...
atrophy is associated with future risk of developing AD and that the rate of regional atrophy predicts decline among patients with mild cognitive impairment and AD. The current study extends these findings. Although cross-sectional associations with cognitive abilities were weak, global atrophy was robustly associated with a more precipitous cognitive decline. The findings suggest that, among individuals with mild AD, the severity of pathology-associated atrophy at one point in time has prognostic utility. Whole brain atrophy is not specific to the diagnosis of AD; however, within a sample of well-defined patients with AD, it is a good marker of disease severity. Thus, the current study supports previous cognitive studies showing an accelerated rate of future decline among more severely affected patients with AD.

White matter hyperintensity burden has been reported to be more severe among patients with AD than non-demented elderly persons, although not all studies have shown this association. Furthermore, some studies have shown that increased burden is associated with poorer cognitive abilities in AD, whereas others have not, but the relationship between severity of WMH and cognitive abilities among older adults without dementia has been more consistently demonstrated. It is possible that small vessel vascular disease, reflected in the severity of WMH, significantly affects cognitive abilities among individuals with no or very little AD pathology. Among those with more severe manifestations of disease, AD pathology may play a more salient role in cognitive abilities, effectively concealing the effect of small vessel vascular disease. Our results partially support this idea: on a cross-sectional basis, the severity of WMH was not associated with severity of cognitive impairment.

Our findings are consistent with the idea that cerebrovascular pathology interacts with AD pathology. Whereas severity of baseline atrophy and severity of baseline WMH were associated with the rate of cognitive decline, when the 2 measures were included in the same model, the interaction effect was significant and the individual main effects were not. The observation is reminiscent of autopsy studies that have shown that individuals with vascular disease and AD pathology were more likely to have clinical dementia compared with those without vascular disease or findings that less AD pathology is required to produce the same degree of cognitive impairment when vascular disease is present. Our findings are most consistent with a report that demonstrated a significant interaction of WMH and medial temporal lobe atrophy in the classification of older adults as AD or being normal; the risk associated with having a high degree of atrophy and a high degree of WMH was greater than the risk incurred by the product of the 2 factors. Although we did not observe an interaction between degree of atrophy and WMH cross-sectionally, the significant effect on future decline suggests a synergistic interaction of the 2 pathologies on the course of AD.

From a mechanistic perspective, the interaction of cerebrovascular and AD pathology may be a reflection of β-amyloid (Aβ) peptide deposition, which comprises the senile plaques characteristic of AD pathology, in the Aβ42 species, and cerebrovascular amyloid, in its Aβ40 form. Indeed, plasma concentrations of Aβ40 peptide were associated with increased WMH volume among patients with AD and cerebral amyloid angiopathy in a clinic-based sample and among participants in the population-based Rotterdam study. In the current study, WMH severity predicted rate of cognitive decline among patients with AD only after statistical adjustment for common vascular risk factors (Table), suggesting that the variance in WMH related to cognitive course in AD is not owing to these risk factors. Rather, it is possible that WMH-associated cerebrovascular Aβ deposition specifically accounts for this association. Future work should examine the association among concentrations of plasma Aβ, WMH, and longitudinal changes in cognition.

Although inconsistencies exist in the literature regarding the exact relationship among AD pathological characteristics, vascular abnormalities, and cognition, findings do converge in demonstrating that increased cerebrovascular disease burden is not beneficial and is most likely harmful. At present, there are no available disease-modifying treatments for AD. However, there are a number of potentially modifiable risk factors and behaviors for cerebrovascular disease. The reduction of these conditions could have therapeutic effects for the treatment of AD.
The study also has a number of particular strengths. To our knowledge, this is among the largest studies that have examined prognostic utility of baseline neuroimaging characteristics on future cognitive decline in AD. Patients were carefully diagnosed at academic medical centers with specific expertise in aging and dementia, and diagnoses were based on uniform application of widely accepted criteria via consensus diagnosis procedures. Diagnoses from the Predictors Study are accurate. For example, 93% of patients that came to autopsy had pathologically confirmed AD at postmortem evaluation. Patients were evaluated prospectively and relatively frequently (ie, biannually). Because participants were generally mildly demented at their baseline evaluation, we were able to capture a large range of progression over time.

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Author Affiliations: Taub Institute for Research on Alzheimer’s Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University (Drs Brickman, Honig, Scarmeas, and Stern and Ms Tatarina and Sanders); and Department of Neurology, Columbia University Medical Center (Drs Brickman, Honig, Scarmeas, and Stern), New York, New York; Departments of Neurology (Drs Albert and Brandt) and Psychiatry and Behavioral Sciences (Dr Brandt), The Johns Hopkins University, Baltimore, Maryland; and Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston (Dr Blacker).

Correspondence: Adam M. Brickman, PhD, Taub Institute for Research on Alzheimer’s Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, 630 W 168th St, Campus Box 16, New York, NY 10032 (amb2139@columbia.edu).


