Cerebrospinal Fluid Profiles and Prospective Course and Outcome in Patients With Amnestic Mild Cognitive Impairment

Ozioma C. Okonkwo, PhD; Michelle M. Mielke, PhD; H. Randall Griffith, PhD; Abhay R. Moghekar, MD; Richard J. O’Brien, MD, PhD; Leslie M. Shaw, PhD; John Q. Trojanowski, MD, PhD; Marilyn S. Albert, PhD; for the Alzheimer’s Disease Neuroimaging Initiative

Objectives: To examine the effect of specific cerebrospinal fluid (CSF) profiles on the rate of cognitive decline, disease progression, and risk of conversion to Alzheimer disease (AD) dementia in patients with amnestic mild cognitive impairment (MCI).

Design: Total tau (T-tau), tau phosphorylated at threonine 181, and β-amyloid 1-42 peptide (Aβ42) were immunoassayed in CSF samples obtained from patients with MCI enrolled in the Alzheimer’s Disease Neuroimaging Initiative. Patients were then stratified by CSF profiles: (1) normal T-tau and normal Aβ42 (ie, normal–T-tauAβ42), (2) normal T-tau but abnormal Aβ42 (ie, abnormal–T-tauAβ42), (3) abnormal T-tau but normal Aβ42 (ie, abnormal–T-tau), and (4) abnormal T-tau and abnormal Aβ42 (ie, abnormal–T-tauAβ42).

Setting: Fifty-eight sites in the United States and Canada.

Participants: One hundred ninety-five patients with MCI.

Main Outcome Measures: A composite cognitive measure, the Clinical Dementia Rating Scale–sum of boxes subscale, and conversion to AD dementia.

Results: Patients with MCI with a CSF profile of abnormal-Aβ42 or abnormal–T-tauAβ42 experienced a faster rate of decline on the composite cognitive measure and the Clinical Dementia Rating Scale–sum of boxes subscale compared with those with normal–T-tauAβ42. They also had a greater risk of converting to AD dementia relative to the normal–T-tauAβ42 group. In contrast, those with a CSF profile of abnormal–T-tau did not differ from the normal–T-tauAβ42 group on any outcome. These findings were generally replicated when the sample was reclassified by patterns of tau phosphorylated at threonine 181 and Aβ42 abnormalities.

Conclusions: β-Amyloid abnormalities but not tau alterations are associated with cognitive deterioration, disease progression, and increased risk of conversion to AD dementia in patients with MCI. Patients with abnormal Aβ42 may be prime candidates for drug treatment and clinical trials in MCI.

Arch Neurol. 2011;68(1):113-119

TOTAL TAU (T-TAU), TAU PHOSPHORYLATED AT THREONINE 181 (P-TAU181), AND β-AMYLOID 1-42 PEPTIDE (Aβ42) IN CEREBROSPINAL FLUID (CSF) ARE WELLEDUCATED ALZHEIMER DISEASE (AD) BIOMARKERS.1 The combination of increased T-tau or p-tau181 and decreased Aβ42 is strongly associated with a diagnosis of AD even at its earliest stages.1,2 For this reason, investigators have examined whether CSF analytes have prognostic value with respect to progression to AD dementia among patients with mild cognitive impairment (MCI).3-4 These studies found that patients with MCI who had dual CSF abnormalities (ie, increased T-tau or p-tau181 and decreased Aβ42) are at increased risk of progressing to AD dementia compared with those patients with normal CSF.

A question that has not received much attention is that of the longitudinal course and outcome of patients with MCI who have abnormalities in tau or Aβ42 but not both. To our knowledge, only 2 studies5,6 have examined differences in cognitive performance and clinical attributes among patients with MCI stratified by patterns of CSF alterations. Of note, both studies were performed using cross-sectional data and thus could not provide information regarding the prospective course or long-term outcome of these MCI CSF profiles. In this study, we address this knowledge gap by investigating longitudinal course (decline on measures of global cognition and disease progression) and outcome (risk of conversion to AD dementia) within a well-characterized group of patients with amnestic MCI, subtyped by their pattern of CSF abnormality.
STUDY PARTICIPANTS

The analyses presented here are based on data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI; http://adni.loni.ucla.edu/). The ADNI was launched in 2003 by the National Institute on Aging and other entities (see the “Acknowledgments” section) as a 5-year public-private partnership. Enrollment target was 800 participants—200 healthy control individuals, 400 patients with amnestic MCI, and 200 patients with mild AD—at 58 sites in the United States and Canada. Participants were evaluated at 6-month intervals for 2 (mild AD) or 3 (controls and MCI) years. Further details regarding ADNI, including participant selection procedures and complete study protocol, have been presented elsewhere and can be found online at http://www.alzheimers.org/clinicaltrials/fullrec.asp?PrimaryKey=208.

The present analyses included all 195 patients with amnestic MCI who had valid test results for CSF T-tau, Aβ42, and p-tau181 when data download occurred between September 1 and 30, 2009. Diagnosis of amnestic MCI required subjective memory difficulties, objective memory difficulties (established using education-specific cut scores on the delayed recall of story A measure from the Logical Memory Test), normal activities of daily living, Clinical Dementia Rating Scale (CDR) Global score of 0.5, and Mini-Mental State Examination scores of 24 or higher. Informed consent was obtained from study participants and their families, and the study was approved by the local institutional review board at each participating site.

CSF PROCEDURE AND APOLIPPROTEIN E GENOTYPING

Full details of the collection and analysis of CSF samples in ADNI have been provided elsewhere. Briefly, lumbar puncture was performed in the morning after an overnight fast. Aliquots (0.5 mL) were subsequently prepared from the CSF samples and stored in bar code–labeled polypropylene vials at −80°C. The T-tau, Aβ42, and p-tau181 were assayed from these aliquots using the multiplex xMAP LumineX platform (Luminex Corp, Austin, Texas) with immunoassay kit–based reagents (INNO-BIA AlzBio3; Innogenetics, Ghent, Belgium; for research use only). The distribution of the CSF profiles formed by cross-tabulating abnormalities in T-tau and Aβ42 on the multiplex xMAP platform was determined using education-specific cut scores on the delayed recall of story A measure from the Logical Memory Test, normal activities of daily living, Clinical Dementia Rating Scale (CDR) Global score of 0.5, and Mini-Mental State Examination scores of 24 or higher. Informed consent was obtained from study participants and their families, and the study was approved by the local institutional review board at each participating site.

CLINICAL ASSESSMENT

Participants completed the following neuropsychological measures: story A from the Logical Memory Test, Category Fluency Test (animals and vegetables), the Boston Naming Test, Clock Drawing Test, Digit Span Test, Digit Symbol Substitution Test, Trail Making Test (parts A and B), and the Rey Auditory Verbal Learning Test. Taken together, these tests assess the domains of episodic memory, attention, language, executive function, processing speed, and spatial abilities. For our analyses, participants’ scores on the neuropsychological measures were transformed to z scores using group means and standard deviations at baseline. Next, these z scores were averaged, yielding a composite cognitive measure. Such summary measures reduce floor and ceiling effects and other sources of measurement error. Participants also completed the CDR, the Mini-Mental State Examination, the Neuropsychiatry Inventory Questionnaire, and the Geriatric Depression Scale.

STATISTICAL ANALYSES

Abnormality on CSF biomarkers was defined using cutoffs (T-tau >93 pg/mL, Aβ42 <192 pg/mL, and p-tau181 >23 pg/mL) previously shown to maximally distinguish patients with AD from healthy controls within the ADNI cohort. Next, we created CSF profiles among the patients with MCI by cross-tabulating abnormalities in T-tau and Aβ42 based on these cutoff thresholds to obtain 4 groups of study participants: (1) those who had normal T-tau and normal Aβ42 (normal–T-tau/Aβ42), (2) those who had normal T-tau but abnormal Aβ42 (abnormal–T-tau/Aβ42), (3) those who had abnormal T-tau but normal Aβ42 (abnormal–T-tau), and (4) those who had abnormal T-tau and abnormal Aβ42 (abnormal–T-tau/Aβ42). We also created a second set of CSF profiles by cross-tabulating abnormalities in p-tau181 and Aβ42 to obtain an analogous grouping of study participants.

To investigate potential differences in longitudinal course related to CSF profile, we fitted 2 random coefficient regressions. The first regression modeled rate of change in the composite cognitive measure, whereas the second regression modeled rate of change in the CDR sum of boxes (CDR-SB) subscale. The CDR-SB is a sum of scores for the 6 CDR domains and has proven particularly useful in tracking disease progression and functional impairment over time. Both regression models were adjusted for APOE ε4 because its distribution significantly varied across groups (Table 1 and Table 2). Cox proportional hazards models, adjusted for APOE ε4, were fitted to determine whether risk of converting to AD dementia differed across CSF profiles. Participants were censored at their last visit or the visit at which they were diagnosed as having AD dementia. Analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina), or SPSS statistical software, version 16 (SPSS Inc, Chicago, Illinois).

GROUP CHARACTERISTICS AT BASELINE

The distribution of the CSF profiles formed by cross-tabulating T-tau and Aβ42 findings was as follows: (1) normal–T-tau/Aβ42 (n=47), (2) abnormal–Aβ42 (n=61), (3) abnormal–T-tau (n=3), and (4) abnormal–T-tau/Aβ42 (n=84). For the CSF profiles involving p-tau181 and Aβ42, the distribution was as follows: (1) normal–p-tau181/Aβ42 (n=39), (2) abnormal–Aβ42 (n=19), (3) abnormal–p-tau181 (n=11), and (4) abnormal–p-tau181/Aβ42 (n=126).

Tables 1 and 2 give the results of group comparisons regarding baseline characteristics. The 4 groups formed by cross-tabulating T-tau and Aβ42 were statistically indistinguishable on all measures except for the proportion of persons possessing 1 or more copies of the APOE ε4 allele and scores on the composite cognitive measure. Patients with MCI with abnormal–Aβ42 or abnormal–T-tau/Aβ42 were more likely to possess 1 or more copies of the APOE ε4 allele and to have lower scores on the composite cognitive measure compared with those who had normal–T-tau/Aβ42 or abnormal–T-tau.

The 4 groups formed by cross-tabulating p-tau181 and Aβ42 differed statistically only on these same variables, with a similar pattern of group separation.
The abnormal-\(\text{A}\beta{42} (\beta = -0.06, \text{SE}= 0.02, P = .01)\) and abnormal–\(\text{T-tau}\beta{42} (\beta = -0.11, \text{SE}= 0.02, P = .01)\) groups experienced significantly faster rates of decline in composite cognition relative to the normal–\(\text{T-tau}\beta{42} group. In contrast, the rate of decline within the abnormal–\(\text{T-tau}\) group (\(\beta = -0.02, \text{SE}= 0.07, P = .73\)) did not differ from that of the normal–\(\text{T-tau}\beta{42} group. These findings are shown in Figure 1. As is evident, patients in the abnormal–\(\text{T-tau}\beta{42} group experienced the fastest decline in cognitive function among all groups. Similar results (not shown) were obtained within the groups formed by \(p\text{-tau}_{181}\) and \(\text{A}\beta{42}\).
Examination of rates of change on the CDR-SB revealed that whereas the abnormal–Aβ42 (β=0.31, SE=0.09, P=.001) and abnormal–T-tauAβ42 (β=0.27, SE=0.09, P=.003) groups experienced significantly faster disease progression compared with the normal–T-tauAβ42 group, the abnormal–T-tau group (β=−0.23; SE=0.27; P=.39) did not. These trajectories are displayed in Figure 2. Parallel observations (not shown) were made within the p-tau181Aβ42 groups.

CONVERSION TO AD DEMENTIA DURING THE STUDY PERIOD

Of the 195 patients with MCI included in this study, 76 (39.0%) converted to AD dementia within a median follow-up time of 23 months (range, 6-39 months). For the 4 groups formed by cross-tabulating T-tau and Aβ42, the distribution of conversions to AD dementia was as follows: (1) normal–T-tauAβ42, (7/47 [14.9%]), (2) abnormal–Aβ42, (21/61 [34.4%]), (3) abnormal–T-tau (0/3 [0%]), and (4) abnormal–T-tauAβ42, (5/19 [26.3%]). Within the p-tau181Aβ42 groups, the distribution was as follows: (1) normal–p-tau181Aβ42, (27/84 [32.1%]), (2) abnormal–p-tau181Aβ42, (2/11 [18.2%]), and (4) abnormal–p-tau181Aβ42, (3/126 [48.4%]).

RISK OF CONVERTING TO AD DEMENTIA AS A FUNCTION OF CSF PROFILE

With the normal–T-tauAβ42 group as the reference, the risk of converting to AD dementia was significantly higher in the abnormal–Aβ42 and abnormal–T-tauAβ42 groups (hazard ratio [HR], 2.43; 95% confidence interval [CI], 1.09-5.41; P=.03; and HR, 2.71; 95% CI, 1.25-5.90; P=.01; respectively). The significance test for the abnormal–T-tau group’s risk of conversion (β=−12.29) could not be reliably conducted because none of the 3 individuals in this group converted to AD dementia, which resulted in quasi-complete separation in the data.31 Survival plots for this analysis are shown in Figure 3. Of note, the reported quasi-complete separation did not emerge when the analysis was repeated among the groups formed by the cross-tabulation of p-tau181 and Aβ42.

ANALYSES OF DATA RESTRICTED TO 18 MONTHS OF FOLLOW-UP

Because the typical length of AD clinical trials is 18 months, we repeated the Cox proportional hazards models using only the data acquired within the first 18 months of follow-up to determine whether the foregoing pattern of findings would emerge. There were 55 conversions to AD dementia during this period. Because 76 conversions occurred during the total length of follow-up (maximum of 39 months), most conversions evidently occurred during the initial 18-month period. Within the 4 T-tauAβ42 groups, the distribution of conversions was as follows: (1) normal–T-tauAβ42, (7/47 [14.9%]), (2) abnormal-Aβ42, (21/61 [34.4%]), (3) abnormal–T-tau (0/3 [0%]), and (4) abnormal–T-tauAβ42, (27/84 [32.1%]). Within the 4 p-tau181Aβ42 groups, the distribution was as follows: (1) normal–p-tau181Aβ42, (27/84 [32.1%]), (2) abnormal–p-tau181Aβ42 (5/39 [12.8%]), (3) abnormal–p-tau181Aβ42 (5/19 [26.3%]), and (4) abnormal–p-tau181Aβ42 (3/126 [48.4%]).

The Cox regression analyses showed that the risk for converting to AD dementia was significantly greater for the abnormal–Aβ42 and abnormal–T-tauAβ42 groups (HR, 2.52; 95% CI, 1.03-6.13; P=.04; and HR, 2.46; 95% CI, 1.02-5.96, P=.05; respectively) compared with the normal–T-tauAβ42 group. As with the original analysis, the hazard for the abnormal–T-tau group (β=−12.31) was statistically untestable. These findings were replicated overall within the 4 groups defined by the cross-tabulation of p-tau181 and Aβ42 (data not shown). Thus, the 18-month results are consistent with the findings based on data collected during the entire study period.

ANCILLARY ANALYSES: CSF BIOMARKER CONCENTRATIONS AND LONGITUDINAL COURSE AND OUTCOME

Because prior MCI investigations of the association between CSF biomarkers and prospective course and out-
come have primarily analyzed biomarker concentrations\(^1\),\(^2\),\(^3\),\(^4\),\(^5\) (as opposed to profiles, as we have done here), we repeated our analyses using biomarker concentrations. Briefly, we fit (1) a random-effects regression that simultaneously examined the effects of A\(\beta\)\(^42\), T-tau, p-tau\(_{181}\), the ratio of t-tau to A\(\beta\)\(^42\) (T-tau/A\(\beta\)\(^42\)), and the ratio of p-tau\(_{181}\) to A\(\beta\)\(^42\) (p-tau\(_{181}/A\beta\)\(^42\)) on rate of change on the composite cognitive measure, (2) another random-effects regression that simultaneously examined the effects of these CSF biomarkers on rate of change on the CDR-SB, and finally (3) a Cox proportional hazards model that simultaneously examined the effects of these CSF biomarkers on risk of converting to AD dementia. All analyses adjusted for APOE \(\varepsilon\)4. In summary, only A\(\beta\)\(^42\) (\(P=0.09\)) and p-tau\(_{181}\) (\(P=0.03\)) were associated with rate of cognitive decline, only A\(\beta\)\(^42\) (\(P=0.001\)) was associated with rate of increase in CDR-SB scores, and only A\(\beta\)\(^42\) (\(P=0.001\)) was associated with risk of conversion to AD dementia. These results support our original findings concerning the centrality of A\(\beta\)\(^42\) abnormalities with respect to cognitive decline, disease progression, and conversion to AD dementia in this cohort.

**COMMENT**

In this study, we examined the relationship of 2 sets of CSF profiles to 3 outcome measures: (1) rate of decline on a composite cognitive measure, (2) rate of disease progression (based on change in CDR-SB scores), and (3) risk of converting to AD dementia. Within the 4 groups formed by cross-tabulating T-tau and A\(\beta\)\(^42\), we found that, compared with patients who have normal–T-tauA\(\beta\)\(^42\), (1) those with abnormal-A\(\beta\)\(^42\) or abnormal–T-tauA\(\beta\)\(^42\) had a steeper rate of decline on the composite cognitive measure, whereas those with abnormal–T-tau did not; (2) those with abnormal-A\(\beta\)\(^42\) or abnormal–T-tauA\(\beta\)\(^42\) experienced a significant worsening of disease, whereas those with normal–T-tau did not; and (3) those with abnormal-A\(\beta\)\(^42\) or abnormal–T-tauA\(\beta\)\(^42\) were at increased risk of converting to AD dementia, whereas those with abnormal–T-tau were not any more likely to experience conversion to AD dementia. In summary, these analyses showed that patients with MCI who had abnormal–A\(\beta\)\(^42\), whether the T-tau was normal or not, had worse outcomes, whereas patients with MCI who had normal–A\(\beta\)\(^42\), even when the T-tau was abnormal, had comparatively better outcomes. Similar findings were made when the analyses were repeated within the 4 groups formed by p-tau\(_{181}\) and A\(\beta\)\(^42\).

Our manner of creating the CSF subgroups examined in this study is noteworthy. Recent studies\(^1\),\(^2\),\(^3\) have suggested that biomarker ratios may be more sensitive to incipient AD compared with absolute biomarker levels. However, by virtue of being ratios, such measures obscure an important distinction between individuals who have normal-tau but abnormal-A\(\beta\)\(^42\) and those who have abnormal-tau but normal-A\(\beta\)\(^42\). For instance, exploratory analyses in this study found that the abnormal–T-tau group (mean [SD]=0.31 [0.09]) and the abnormal–A\(\beta\)\(^42\) group (mean [SD]=0.54 [0.23]) did not differ with regard to the T-tau/ A\(\beta\)\(^42\) ratio (\(P=0.79\)). Similarly, the abnormal–p-tau\(_{181}\) group (mean [SD]=0.14 [0.04]) did not differ from the abnormal–A\(\beta\)\(^42\) group (mean [SD]=0.14 [0.07]) on the p-tau\(_{181}/A\beta\)\(^42\) ratio (\(P=.77\)). In contrast to the apparent similarity of these 2 classes of MCI patients (ie, those with only abnormal-tau and those with only abnormal-A\(\beta\)\(^42\)) on the biomarker ratios, our analyses showed that their prospective course and outcome are different.\(^2\)

The overall finding from this study is that, of the 2 types of CSF abnormalities commonly observed in patients with MCI (ie, increased T-tau or p-tau\(_{181}\), and decreased A\(\beta\)\(^42\)), abnormally low A\(\beta\)\(^42\) appears to be most closely associated with cognitive decline, disease progression, and risk of conversion to AD dementia. This finding is consistent with prior investigations\(^6\),\(^7\),\(^9\),\(^10\),\(^11\) that found that CSF A\(\beta\)\(^42\) concentrations are predictive of future conversion to AD dementia among patients with MCI, whereas tau concentrations are not. Because abnormally low CSF A\(\beta\)\(^42\) is presumed to be due to \(\beta\)-amyloid aggregation in the brain,\(^2\) our findings are in accordance with the amyloid cascade hypothesis, which, in brief, argues that deposition of \(\beta\)-amyloid in the brain is an early event in AD pathogenesis.\(^25\) However, we note that the tenets of the amyloid cascade hypothesis remain controversial.\(^26\) Indeed, some evidence exists that elevated CSF T-tau or p-tau\(_{181}\), but not decreased A\(\beta\)\(^42\), predict progression from MCI to AD dementia.\(^27\) The reasons for these seemingly conflicting findings are not fully understood and suggest the need for continued investigation of these important questions.\(^7\),\(^27\) In addition, although our findings suggest that A\(\beta\)\(^42\) abnormalities are prominently associated with risk of progression to dementia, all models tested in this study consistently demonstrated that individuals with combined tau and A\(\beta\)\(^42\) abnormalities had the worst outcomes.\(^3\)

This study contributes to the ongoing attempts to identify subgroups of patients with MCI at increased risk of progressing to AD dementia\(^4\),\(^9\),\(^10\) by demonstrating that patients with MCI who have abnormal A\(\beta\)\(^42\) have an elevated risk of cognitive decline and eventual conversion to AD dementia even when the tau is normal. The ability to detect incipient dementia in patients with MCI has obvious implications for clinical trials. One reason why MCI trials have experienced little success to date is the relatively slow disease progression among some study enrollees, which affects the ability of these trials to test key hypotheses. Enrolling patients with MCI who are more likely to convert to AD dementia could shorten the time to attain the primary milestones, reduce the sample size needed for adequate power, and increase the ability to detect treatment effects.\(^28\) In addition, the finding that abnormal A\(\beta\)\(^42\) is comparatively more strongly associated with progressive decline and eventual conversion to AD suggests that the ability to abrogate the accumulation of A\(\beta\) peptides in the brain and/or restore A\(\beta\)\(^42\) in CSF might be a valid outcome for MCI drug trials, especially those in the phase 2 (proof-of-concept) stage.\(^29\) An important caveat is that, in this ADNI cohort, individuals with abnormal A\(\beta\)\(^42\) were also more likely to possess 1 or more copies of the APOE \(\varepsilon\)4 allele and there is some evidence that APOE \(\varepsilon\)4 carriers might have differential therapeutic response or higher risk of treatment-related adverse effects.\(^30\)
Currently no medications, to our knowledge, have been shown to delay the onset of dementia in patients with MCI.\textsuperscript{31} However, novel and promising AD therapeutics are currently being tested in clinical trials.\textsuperscript{2,32} If these drugs prove to be therapeutic, there would be a viable role for biomarkers of incipient AD dementia in patients with MCI because these drugs are presumably more effective if administered early in the disease process.\textsuperscript{2} Our findings would suggest that patients with MCI who have abnormal CSF Aβ42 might be ideal candidates for such therapies because of their comparatively elevated risk of transitioning to AD dementia. In general, because CSF biomarkers putatively reflect biochemical processes in the brain,\textsuperscript{5,33} it is foreseeable that they could be used for matching patients to treatment approach (eg, CSF Aβ42 findings may be used to assign patients to treatments that target β-amyloid plaques).\textsuperscript{33}

A potential limitation of this study is the small sample size of the group of patients with MCI who have abnormal T-tau, which resulted in an inability to reliably conduct some significance tests in this study. However, we note that the findings in the p-tau\textsubscript{181}/Aβ42 tetrad (in which the distribution of the groups was relatively more proportional) closely mirrored the findings in the T-tau\textsubscript{181}/Aβ42 models, thus lending credibility to the observations made in the T-tauAβ42 groups. It would be of great interest to see whether this study’s key finding—that abnormal Aβ42 is deleterious even when tau is normal—is replicable in other well-characterized and prospectively monitored cohorts of patients with amnestic MCI.

Accepted for Publication: May 18, 2010.

Correspondence: Ozioma C. Okonkwo, PhD, Department of Neurology, The Johns Hopkins University School of Medicine, 1620 McElderry St, Reed Hall East 2, Baltimore, MD 21205 (oziom@jhmi.edu).

Author Contributions: Drs Okonkwo, Griffith, Trojanowski, and Albert had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Okonkwo and Trojanowski. Acquisition of data: O’Brien, Shaw, and Trojanowski. Analysis and interpretation of data: Okonkwo, Mielke, Griffith, Moghekar, Trojanowski, and Albert. Drafting of the manuscript: Okonkwo, Mielke, Griffith, Trojanowski, and Albert. Critical revision of the manuscript for important intellectual content: Okonkwo, Mielke, Griffith, Moghekar, O’Brien, Shaw, and Trojanowski. Statistical analysis: Okonkwo, Mielke, Griffith, Shaw, and Trojanowski. Obtained funding: O’Brien, Shaw, and Trojanowski. Administrative, technical, and material support: Trojanowski. Study supervision: Moghekar, O’Brien, Shaw, Trojanowski, and Albert.

Financial Disclosure: Dr Shaw reports that the primary funding source for his work on the cerebrospinal fluid biomarkers measured as part of the Alzheimer’s Disease Neuroimaging Initiative (ADNI) is from National Institute on Aging grant U01 AG-024904. He also received travel expenses and an honorarium from Pfizer Inc and serves on the technical advisory board for Bristol-Myers Squibb.

Funding/Support: Data collection and sharing for this project was funded by the ADNI (principal investigator: Michael Weiner, MD; National Institutes of Health [NIH] grant U01AG024904). The ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from Pfizer Inc, Wyeth Research, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline plc, Merck & Co Inc, AstraZeneca AB, Novartis Pharmaceuticals Corporation, the Alzheimer’s Association, Eisai Global Clinical Development, Elan Corporation plc, Forest Laboratories, and the Institute for the Study of Aging, with participation from the US Food and Drug Administration. Industry partnerships are coordinated through the Foundation for the National Institutes of Health. The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer’s Disease Cooperative Study at the University of California, San Diego. Data from ADNI are disseminated by the Laboratory of Neuro Imaging at the University of California, Los Angeles. Additional grant support for this project came from the Biomarkers of Cognitive Decline among Normal Individuals study (principal investigator: Dr Albert; National Institutes of Health grant U01AG03655) and from the University of Pennsylvania Alzheimer’s Disease Core Center (principal investigator: Dr Trojanowski; NIH grant P30AG010124).

Additional Contributions: Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI Principal Investigators is available at http://adni.loni.ucla.edu/about/who-we-are/principal-investigators/.

REFERENCES


