Cerebrospinal Fluid Biomarkers and Rate of Cognitive Decline in Very Mild Dementia of the Alzheimer Type

Barbara J. Snider, MD, PhD; Anne M. Fagan, PhD; Catherine Roe, PhD; Aarti R. Shah, MS; Elizabeth A. Grant, PhD; Chengjie Xiong, PhD; John C. Morris, MD; David M. Holtzman, MD

Background: Cerebrospinal fluid (CSF) levels of Aβ peptide 1-42 (Aβ42), tau, and phosphorylated tau (ptau) are potential biomarkers of Alzheimer disease.

Objective: To determine whether Aβ42, tau, and ptau predict the rate of cognitive change in individuals with very mild dementia of the Alzheimer type (DAT).

Design: Retrospective analysis of CSF biomarkers and clinical data.

Setting: An academic Alzheimer disease research center.

Participants: Research volunteers in a longitudinal study of aging and cognition. Participants (n=49) had a clinical diagnosis of very mild DAT with a Clinical Dementia Rating (CDR) of 0.5 at the time of lumbar puncture. All the participants had at least 1 follow-up assessment (mean [SD] follow-up, 3.5 [1.8] years).

Main Outcome Measures: Baseline CSF levels of Aβ42, Aβ40, tau, and ptau at threonine 181 (ptau181) and the rate of dementia progression as measured using the CDR sum of boxes (CDR-SB) score and psychometric performance.

Results: The rate of dementia progression was significantly more rapid in individuals with lower baseline CSF Aβ42 levels, higher tau or ptau181 levels, or high tau: Aβ42 ratios. For example, the annual change in the CDR-SB score was 1.1 for the lowest 2 tertiles of Aβ42 values and 0.3 for the highest tertile of Aβ42 values.

Conclusions: In individuals with very mild DAT, lower CSF Aβ42 levels, high tau or ptau181 levels, or high tau: Aβ42 ratios quantitatively predict more rapid progression of cognitive deficits and dementia. Biomarkers of CSF may be useful prognostically and to identify individuals who are more likely to progress for participation in therapeutic clinical trials.

Arch Neurol. 2009;66(5):638-645

THE EFFICACY OF TREATMENTS FOR ALZHEIMER DISEASE (AD) WILL LIKELY DEPEND ON ACCURATELY IDENTIFYING INDIVIDUALS WITH UNDERLYING AD PATHOLOGY (EG, PLAQUES AND TANGLES) EARLY IN THE COURSE OF DISEASE. ALTHOUGH THE CLINICAL DIAGNOSIS OF DEMENTIA OF THE ALZHEIMER TYPE (DAT) IS ACCURATE IN SPECIALIZED CENTERS, THE SENSITIVITY OF DIAGNOSIS, PARTICULARLY AT Milder STAGES OF DISEASE OR WITH A SINGLE CLINICAL EVALUATION, MAY BE MUCH LOWER.1-3 BECAUSE THERE IS A GROWING EMPHASIS ON ENROLLING INDIVIDUALS WITH LESS COGNITIVE IMPAIRMENT INTO CLINICAL TRIALS OF PUTATIVE ANTI-AD AGENTS, METHODS ARE NEEDED THAT WILL IDENTIFY INDIVIDUALS WITH VERY MILD DAT WHO ARE MORE LIKELY TO EXHIBIT MEASURABLE COGNITIVE DECLINE DURING THE STUDY.

Disease-specific biomarkers, such as levels of Aβ peptide 1-42 (Aβ42), tau, and phosphorylated tau (ptau) in cerebrospinal fluid (CSF), have reasonable levels of sensitivity and specificity for the diagnosis of DAT.4-6 Recent studies7,8 combining amyloid imaging using Pittsburgh Compound B with analysis of CSF biomarkers have shown that levels of CSF Aβ42 can accurately separate individuals who have appreciable deposits of neocortical amyloid from those who do not. In a recent study, individuals diagnosed as having “mild cognitive impairment” (MCI9,10) who had “pathologic” concentrations of CSF tau or Aβ42 had a 17.7-fold increased risk of progressing to diagnosed DAT during a 5-year period.11 The CSF Aβ42: tau and Aβ42: ptau ratios also identify cognitively healthy individuals who have a 4- to 5-fold increased risk of dementia progression.11

Author Affiliations:
Department of Neurology (Drs Snider, Fagan, Roe, Morris, and Holtzman and Ms Shah) and Division of Biostatistics (Drs Grant and Xiong), Alzheimer’s Disease Research Center, Washington University School of Medicine, St Louis, Missouri.
risk of progressing to very mild DAT (Clinical Dementia Rating [CDR] of 0.5) within 3 to 4 years. If CSF biomarkers reflect underlying pathophysiological mechanisms that govern Aβ deposition and injury to neurons, levels of these biomarkers might correlate with the actual rate of cognitive decline in individuals with MCI or very mild dementia. We hypothesized that individuals with very mild DAT who had low CSF Aβ42 levels or high tau: Aβ42 ratios might undergo more rapid cognitive decline than mildly impaired individuals with higher CSF Aβ42 levels or lower tau: Aβ42 ratios. The ability of these CSF markers to predict rate of disease progression has implications for diagnosis and treatment of very mild DAT and for clinical trial design.

METHODS

PARTICIPANTS AND CLINICAL ASSESSMENTS

Participants were a subset of individuals enrolled in longitudinal studies of healthy aging and dementia at the Washington University Alzheimer’s Disease Research Center (WU-ADRC). All participants enrolled in the longitudinal studies were at least 60 years old at enrollment and were in good general health. All agreed to undergo lumbar puncture (LP); historically, 72% of participants enrolled complete LP and 78% return for annual follow-up. Individuals were selected for analysis herein if they had a diagnosis of DAT with a CDR of 0.5 (very mild impairment) at the time of LP and had at least 1 follow-up clinical assessment after LP. Participants underwent annual assessments that included assignment of CDR and a 1.5-hour psychometric test battery. The CDR, an assessment of the presence or absence of dementia and of dementia severity, is based on semistructured interviews with the individual and a collateral source. The CDR and diagnosis were determined independently of psychometric test results. The CDR sum of boxes (CDR-SB) score is a more quantitative representation of cognitive functioning is indicated by lower scores on the CDR-SB and by higher scores on the psychometric composite.

All clinical diagnoses, including DAT and depression, were made in accordance with standard criteria. At the WU-ADRC, a CDR of 0.5 originally denoted individuals whose mental state was “neither clearly demented nor healthy;” the criteria for MCI also include a CDR of 0.5 to indicate the absence of clear dementia. With experience, the WU-ADRC has successfully identified the subset of individuals for whom the MCI is caused by underlying AD as subsequently determined by progression to greater stages of dementia severity and by histopathologic confirmation of AD. The CDR 0.5 designation in the WU-ADRC now denotes very mild dementia; in all the individuals with a CDR of 0.5 included herein, the clinical diagnosis was DAT. Some of these individuals would be considered to have MCI at other medical centers, but many were insufficiently impaired to meet the criteria for MCI and might be designated as “pre-MCI.” For comparison, we applied revised criteria for MCI to identify individuals with a CDR of 0.5 and DAT who scored 1.5 SDs or more below the mean of a comparison group of nondemented individuals on a measure of episodic memory (the Associate Memory subscale of the WMS). Studies were approved by the institutional review board at Washington University, and informed consent was obtained from all the participants.

CSF COLLECTION AND ANALYSIS

All individuals underwent LP for the collection of CSF using a standard procedure. The CSF samples were analyzed for total tau, ptau at threonine 181 (ptau181), and Aβ42 by means of a commercial enzyme-linked immunosorbent assay (Innotest; Innogenetics NV, Ghent, Belgium) as previously described. The Aβ40 was analyzed using an enzyme-linked immunosorbent assay as previously reported.

STATISTICAL ANALYSES

Associations between each of the CSF biomarkers at the time of LP and years of education and age were tested using Pearson product moment correlations; t tests for independent samples were used to determine whether mean biomarker values differed by sex or by the presence of at least 1 APOE4 allele. General linear models (PROC GLM; SAS Institute Inc, Cary, North Carolina) were used to test whether there was a significant association between each of the CSF biomarkers and having a depression diagnosis while adjusting for the effects of age, sex, and education. We used mixed linear models (PROC MIXED; SAS Institute Inc) to determine whether there was a relationship between the slope of the CDR-SB score and time after the LP as a function of biomarker values after controlling for age, sex, and education. Similar analyses were conducted to examine biomarker-related differences in the slope of the psychometric composite scores after the LP.

DEMOGRAPHIC AND BIOMARKER VALUES AT BASELINE ASSESSMENT IN INDIVIDUALS WITH VERY MILD DAT

Forty-nine participants with a CDR of 0.5 and DAT underwent LP and had at least 1 follow-up clinical assessment. Follow-up varied because enrollment was ongoing. Demographic variables at the baseline assessment (before LP) are given in Table 1, and CSF biomarker values are given in Table 2. More than half of these participants performed better than the cutoff score for MCI on episodic memory performance and can be considered to be pre-MCI. Twenty-nine of these participants were included in the data set of Fagan et al. There were no significant correlations between the biomarkers and age, years of education, the CDR-SB score, or the psychometric composite score at the time of LP (see the eTable; http://www.archneurol.com). Individuals with 1 or more APOE4 alleles had lower mean CSF.

©2009 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Non-Human Traffic (NHT) User on 06/04/2021
ptau181, phosphorylated tau at threonine 181.

We first compared the unadjusted change in the CDR-SB score across time in the 10 individuals with the lowest CSF Aβ42 levels (182-263 pg/mL) with those of the 10 individuals with the highest Aβ42 levels (588-1179 pg/mL). Individuals with the lowest CSF Aβ42 levels had a consistent and more rapid increase in the CDR-SB score (indicative of more impairment) (Figure 1A) than those with the highest levels of Aβ42 (Figure 1B).

We next analyzed whether CSF biomarker levels at the baseline assessment were associated with the subsequent rate of change of cognitive variables across time for the entire group. Mean follow-up after LP was 3.5 years (range, 0.9-7 years). The slope of the CDR-SB score correlated significantly with baseline levels of CSF Aβ42 (P=.02), tau (P=.007), and ptau (P=.004) and with ratios of tau:Aβ42 and ptau:Aβ42 (P=.003 and .001, respectively) but not with levels of Aβ40 (P=.49). For illustrative purposes, we divided the participants into tertiles based on levels of each of the biomarkers and plotted the change in the CDR-SB score across time for each tertile; mean slopes and intercepts for each tertile for each biomarker and the absolute levels of biomarkers for each tertile are shown in Figure 2. We found that there were differences in the slopes of the CDR-SB score between tertiles as a function of CSF Aβ42 (P=.03), tau (P=.01), and ptau181 (P=.009) but not as a function of CSF Aβ40 (P=.47). The ratio measures (tau:Aβ42 and ptau181:Aβ42) were closely correlated (r=0.97, P<.001) and also indicated a difference in the slope of the CDR-SB score with time (P=.005).

Slope values (change in the CDR-SB score per year) were 1.1 for the lowest and middle tertiles for CSF Aβ42 and 0.3 for the highest tertile. Findings were similar for individuals with the highest tertile values of CSF tau, ptau181, and the tau:Aβ42 ratio. Those with values in the highest tertile for tau:Aβ42 had an increase in the CDR-SB score of 1.5 boxes per year, the most rapid increase for any of the markers studied herein.

CORRELATION OF BIOMARKER VALUES WITH SUBSEQUENT CHANGE IN PSYCHOMETRIC COMPOSITE SCORES

We performed a similar analysis to compare the rate of change in the psychometric composite scores with the CSF biomarker values, again dividing the cohort into tertiles based on the distribution of the biomarker values for illustrative purposes. Individuals with lower Aβ42 values exhibited a more rapid rate of decline in the psychometric composite score after LP than did individuals with higher levels (P=.03). The slope of change was −0.6 points per year for the lowest tertile (CSF Aβ42, <319 pg/mL), −0.5 points per year for the middle tertile (CSF Aβ42, 319-411.2 pg/mL), and −0.06 points per year for the highest tertile (CSF Aβ42, ≥411.2 pg/mL). There was a faster rate of decline in the psychometric composite score for those with higher values of tau (P=.05), ptau181 (P=.04), and the ratio measures (P=.03) (Figure 3). Like the CDR-SB score, the slope of the psychometric composite score was not significantly associated with CSF Aβ40 values (P=.16).

USE OF A “CUTOFF” VALUE TO IDENTIFY INDIVIDUALS WITH VERY MILD DAT LIKELY TO HAVE MORE RAPID COGNITIVE DECLINE

The utility of CSF biomarkers in clinical practice will require practical guidelines for interpretation of individual results. For example, we tested the ability of a CSF Aβ42 value of 411 pg/mL or less to predict more rapid disease progression. These values encompass the lower 2 tertiles of CSF Aβ42 values, and previous studies suggest that such individuals will uniformly demonstrate increased cortical binding of Pittsburgh Compound B consistent with deposition of amyloid in the brain. A CSF Aβ42 level of 411 pg/mL or less predicted a significant increase in the CDR-SB score.
cantly more rapid rate of cognitive decline, as measured by the CDR-SB score \((P = .008)\) and the psychometric composite score \((P = .008)\). Quantitatively, individuals with CSF A\(\beta\)42 values of 411 pg/mL or less had a mean yearly increase in the CDR-SB score of 1.10 (95% confidence interval [CI], 0.74-1.47), whereas those with a CSF A\(\beta\)42 level greater than 411 pg/mL had a mean yearly increase in the CDR-SB score of 0.32 (95% CI, -0.11 to 0.74). Alternatively, using the highest tertile of values for the tau: A\(\beta\)42 ratio (ratio >0.81), the mean yearly increase in the CDR-SB score was 1.49 (95% CI, 0.99-1.98), whereas those with a tau: A\(\beta\)42 ratio of 0.81 or less had a mean yearly increase in the CDR-SB score of 0.43 (95% CI, 0.08-0.76).

**COMMENT**

The main finding of this study is that baseline levels of the AD-related CSF biomarkers A\(\beta\)42, tau, and ptau181 and the tau: A\(\beta\)42 ratio quantitatively predict the rate of cognitive decline across time in individuals with very mild dementia. This study differs importantly from earlier studies in that we show that levels of biomarkers are strongly predictive of the actual rate of decline rather than with a dichotomous assessment of conversion/no conversion from mild impairment to diagnosed DAT. These findings are consistent with those from previous studies showing that CSF levels of A\(\beta\)42, tau, and ptau can be used to predict the likelihood that individuals without dementia will develop MCI\(^1\) or very mild dementia\(^2\) and with studies\(^{11,24-27}\) showing that biomarkers predict progression from MCI to DAT. The only published studies correlating AD-related CSF biomarkers with rate of cognitive decline showed that increased levels of 3 different ptau epitopes (ptau181, ptau231, and ptau199) correlated with a decline in the Mini-Mental State Examination score in individuals with MCI observed for 1 year.\(^{28,29}\)

The present study differs from those linking CSF biomarkers to “conversion” from MCI to DAT because although some of these individuals would be diagnosed as having MCI at other centers, most diagnosed as having very mild DAT at the WU-ADRC did not have sufficient impairment on objective memory testing to meet the MCI criteria. Their mean Mini-Mental State Examination scores were similar to those of individuals with MCI in other studies. The mild impairment, slow disease progression, and higher levels of CSF A\(\beta\)42 in some individuals raise the possibility that some of these individuals do not have underlying AD pathology. Clinical diagnosis is subsequently confirmed on neuropathologic examination approximately 90% of the time at the WU-ADRC,\(^{10}\) even at such mild levels of impairment. In one series, in individuals diagnosed as having mild DAT (CDR of 0.5) who did not meet the MCI criteria, at autopsy, 43 of 47 had AD, 1 had corticobasal degeneration, and 3 had healthy brains.\(^{19}\) In the present study, 5 of 16 individuals in the highest tertile for CSF A\(\beta\)42 had A\(\beta\)42 levels greater than 715 pg/mL, the highest level reported to date in autopsy-confirmed AD,\(^{30}\) which makes it unlikely that these individuals have underlying AD pathology. The CSF biomarker levels may accurately identify the 10% of individuals clinically diagnosed as having mild DAT who do not have underlying AD pathology, but pathologic studies are required to test this hypothesis. Most individuals in the highest tertile (11 of 16) had CSF A\(\beta\)42 levels less than 715 pg/mL, a finding consistent with possible AD pathology. Although the rate of progression in these individuals (0.3 boxes per year) is slow, such slow progression has been observed in individuals with autopsy-confirmed AD. For example, at the WU-ADRC a recent individual with autopsy-confirmed AD had no increase in the CDR-SB score for the first 2 years after LP; the CSF A\(\beta\)42 level was 457 pg/mL. Progression may not be linear throughout the course of disease and may be slower at milder stages of dementia.\(^{31}\)

The relationship between CSF A\(\beta\)42 and the A\(\beta\)42 pools in the brain, both soluble and in plaques, is likely complex and may change during the course of dis-
ease, but there is substantial evidence that once CSF levels of A\(\beta\)42 are low, they remain stable for several years in unimpaired and impaired individuals.\(^3^\)\(^3^\)\(^7\)\(^7\)\(^8\)\(^8\)\(^9\)\(^9\)\(^1\)\(^1\)\(^2\)\(^2\)\(^3\)\(^3\)\(^4\)\(^4\)\(^5\)\(^5\)\(^6\)\(^6\) The idea that changes in A\(\beta\) homeostasis, including the decrease in CSF A\(\beta\)42 levels, precede clinically detectable cognitive decline in late-onset AD by at least several years and perhaps by 10 to 15 years is supported by the correlation between CSF A\(\beta\)42 levels and the presence of cortical amyloid deposition even in cognitively healthy individuals and by the finding that an increased ratio of tau:A\(\beta\)42 is predictive of short-term decline from normal to very mild dementia.\(^7\)\(^7\)\(^8\)\(^8\)\(^9\)\(^9\)\(^1\)\(^1\)\(^2\)\(^2\)\(^3\)\(^3\)\(^4\)\(^4\)\(^5\)\(^5\)\(^6\)\(^6\)\(^7\)\(^7\) The recent study by Sluimer et al,\(^3\)\(^3\) which shows that change in levels of CSF biomarkers with time in mildly impaired individuals did not correlate with cognitive change as quantified by Mini-Mental State Examination scores,

Figure 2. Slope of the Clinical Dementia Rating sum of boxes (CDR-SB) score across time in biomarker tertiles. For each individual biomarker, the sample was divided into tertiles (ie, low, middle, and high biomarker groups) based on a frequency distribution of the baseline biomarker values. The change in CDR-SB score across time was calculated for each tertile. The slope and intercept for each tertile are plotted for each biomarker: A, cerebrospinal fluid (CSF) A\(\beta\) peptide 1-42 (A\(\beta\)42); B, CSF A\(\beta\)40; C, CSF tau; D, CSF phosphorylated tau (ptau); and E, tau:A\(\beta\)42 ratio. LP indicates lumbar puncture.

©2009 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Non-Human Traffic (NHT) User on 06/04/2021
supports the idea that biomarker levels remain stable across time even after the onset of impairment. These findings support a model in which, in individuals destined to develop AD, CSF Aβ42 levels decrease from normal to a new steady state before any symptoms of cognitive impairment develop. This decrease might be triggered by deposition of Aβ plaques in some brain regions. The present findings suggest that this new "set point" for Aβ42 will correlate with the rate of disease progression once impairment is present.

Although the number of participants in this study was relatively small, the results suggest that CSF biomarkers might be useful as entry criteria for clinical trials of disease-modifying therapies for MCI and very mild DAT. Limiting enrollment to individuals with CSF Aβ42 values below a certain cutoff point might ameliorate the difficulties...
caused by lack of disease progression in some individuals during the trial. For example, in this study, individuals with CSF β-amyloid42 values of 411 pg/mL or less progressed at a rate of 1.11 boxes per year, with a variance of 0.49, whereas the unselected group of all individuals with a CDR of 0.5 progressed more slowly, at a rate of 0.78 boxes per year, with a variance of 0.70. Using these group characteristics, we calculated how many participants would be needed to power a hypothetical clinical trial, assuming a 2-armed study (1:1 treatment vs placebo). If all individuals with a diagnosis of very mild dementia and a CDR of 0.5 were enrolled, 354 participants would be needed to detect a 50% treatment effect on the CDR-SB score after 1.5 years using a standard normal test at a significance level of 5%, whereas less than half as many participants (n = 154) would be needed if CSF β-amyloid42 levels less than 411 pg/mL were included as an inclusion/exclusion criterion to select participants. These findings are likely to have important implications for reducing the number of participants needed to show an effect in clinical trials for very mild DAT and MCI and, ultimately, to assist in making treatment decisions as more invasive and potentially harmful disease-modifying treatments for AD become available.

Accepted for Publication: November 26, 2008.

Correspondence: Barbara Joy Snider, MD, PhD, Department of Neurology, Washington University School of Medicine, Campus Box 8111, 660 S Euclid, St Louis, MO 63110 (snider@neuro.wustl.edu).

Author Contributions: Dr Snider had full access to 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: Snider, Fagan, Grant, Morris, and Holtzman. Acquisition of data: Fagan, Shah, Morris, and Holtzman. Analysis and interpretation of data: Snider, Fagan, Grant, Morris, and Holtzman. Drafting of the manuscript: Snider, Shah, and Holtzman. Critical revision of the manuscript for important intellectual content: Snider, Fagan, Grant, Morris, and Holtzman. Statistical analysis: Roe and Xiong. Obtained funding: Morris and Holtzman. Administrative, technical, and material support: Grant, Morris, and Holtzman. Study supervision: Snider, Fagan, Morris, and Holtzman.

Financial Disclosure: None reported.

Funding/Support: This study was supported by grants P01AG033991 and P50AG05681 from the National Institutes of Health and by the Charles and Joanne Knight Alzheimer Research Initiative of the WU-ADRC.

Additional Information: The eTable is available at http://www.archneur.com.

Additional Contributions: The WU-ADRC Clinical Core assessed the participants and Martha Storandt, PhD, assisted with the psychometric data. We thank all the participants and Eli Lilly for its gift of antibodies to Aβ40.

REFERENCES


---

**Call for Papers**

The Archives launched a new *Archives Express* section in the September 2000 issue. This section will enable the editors to publish highly selected papers within approximately 2 months of acceptance. We will consider only the most significant research, the top 1% of accepted papers, on new important insights into the pathogenesis of disease, brain function, and therapy. We encourage authors to send their most exceptional clinical or basic research, designating in the cover letter a request for expedited *Archives Express* review. We look forward to publishing your important new research in this accelerated manner.

Roger N. Rosenberg, MD