

Cerebrospinal Fluid Tau and β -Amyloid

How Well Do These Biomarkers Reflect Autopsy-Confirmed Dementia Diagnoses?

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Background: Tau and β -amyloid ($A\beta$) are proposed diagnostic biomarkers for Alzheimer disease (AD). Previous studies report their relationship to clinical diagnoses of AD and other dementias. To understand their value as predictors of disease-specific pathology, levels determined during life must be correlated with definitive diagnoses in mixed dementia groups and cognitively normal subjects.

Objectives: To correlate antemortem cerebrospinal fluid (CSF) tau and $A\beta$ levels with definitive dementia diagnosis in a diverse group of patients; to calculate statistics for CSF tau and $A\beta$.

Design: Prospective study.

Setting: Ten clinics experienced in the diagnosis of neurodegenerative dementias.

Patients: One hundred six patients with dementia and 4 cognitively normal subjects with a definitive diagnosis, and 69 clinically diagnosed cognitively normal subjects.

Main Outcome Measures: Correlation of CSF tau and $A\beta$ with final diagnosis.

Results: Mean tau level was 612 pg/mL for the 74 patients with AD, 272 pg/mL for 10 patients with frontal dementia, 282 pg/mL for 3 patients with dementia with Lewy bodies, and 140 pg/mL for 73 cognitively normal control subjects. Tau was less than 334 pg/mL for 20 patients with AD. $A\beta_{42}$ was reduced in patients with AD (61 fmol/mL) compared with patients with frontal dementia (133 fmol/mL) and control subjects (109 fmol/mL), but not compared with patients with dementia with Lewy bodies (14 fmol/mL) or prion disease (60 fmol/mL).

Conclusions: Elevated CSF tau levels are associated with AD pathology and can help discriminate AD from other dementing disorders. However, some patients with AD have a level less than the mean \pm 2 SDs of the cognitively normal cohort.

Arch Neurol. 2003;60:1696-1702

ALZHEIMER DISEASE (AD) is a neurodegenerative disorder that produces progressive impairments in memory, language, judgment, insight, behavior, and personality. Pathological features include neurofibrillary tangles composed of hyperphosphorylated tau, neuritic plaques composed of β -amyloid ($A\beta$) fibrils, and neuronal death with associated cerebral atrophy and gliosis. These pathological changes are most prominent in the hippocampus, entorhinal cortex, and association areas of the neocortex and are believed to be responsible for the clinical features.¹

The clinical diagnosis of probable AD requires the presence of dementia symptoms characterized by a history of progressive memory loss and decline in one or more other areas of cognition that is sufficient to interfere with everyday func-

tioning, documentation of the cognitive impairment with psychometric testing, and the exclusion of alternative explanations for the dementia syndrome.² On the basis of prospective longitudinal clinical-pathological studies performed primarily in academic centers specializing in memory disorders, the clinical diagnosis of AD has a positive predictive value of 84%, a negative predictive value of 66%, a sensitivity of 90%, a specificity of 56%, and a positive likelihood ratio of 2.9.³ Data from community-based studies often report a lower sensitivity and specificity.^{4,5} This is because clinical diagnostic accuracy often is confounded when the core symptoms of AD are shared by other pathologically distinct neurodegenerative dementias. In addition, cognitive impairment may be difficult to assess reliably in individuals with low education and in those who cannot be tested in their preferred language. Fi-

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nally, because most dementing illnesses impair insight, clinicians usually must obtain additional information from someone who knows the individual well. The combination of these factors may delay a patient's evaluation and present difficulties establishing a correct diagnosis during the earliest symptomatic stage of the illness. The development of new therapies for AD, particularly those that target the core pathologic features, increases the need to improve diagnostic accuracy and efficiency, particularly during the earliest phase when attempts to halt or slow the progression are most appropriate.⁶⁻¹⁰

Tau and A β are components of the core neuropathological changes of AD that can be measured in the cerebrospinal fluid (CSF) and have been the most frequently studied of the candidate diagnostic biomarkers.^{11,12} They have been measured in patients with a variety of clinically diagnosed conditions,^{13,14} yet there is limited information relating premortem levels to a pathologically established diagnosis.

The purpose of this study was to determine the CSF levels of tau and A β in individuals undergoing an evaluation for dementia in university specialty clinics and to compare these levels with their confirmed diagnosis based on the presence of a disease-causing mutation, a protein marker (eg, 14-3-3) in a typical clinical presentation, or the neuropathological findings at autopsy. In addition, CSF tau and A β from a group of cognitively normal elderly subjects observed longitudinally who have not come to autopsy provided a second reference cohort.

METHODS

Clinicians experienced in the diagnosis of neurodegenerative dementias participated in this study. Eight of the 10 clinics were Clinical Cores of Alzheimer's Disease Centers funded by the National Institute on Aging of the National Institutes of Health, Bethesda, Md. The subjects included 107 patients undergoing a clinical evaluation for dementia, 4 pathologically confirmed normal elderly control subjects, and 69 cognitively normal elderly subjects with 2 to 8 years of longitudinal follow-up since their lumbar puncture (LP).

Appropriate consent was obtained from all subjects or their caregivers in accordance with protocols approved by the institutional review board at each participating site.

CLINICAL EVALUATION

All participants received a standard neurologic evaluation, including cognitive testing. Additional clinical and laboratory tests were done at the discretion of the evaluating physician. Controls were comprehensively assessed to ensure the absence of dementia. Although specific methods varied among the sites, all controls were assessed using clinical and cognitive measures that are standard in the field (eg, Mini-Mental State Examination [MMSE]; psychometric batteries and functional assessments) at entry and follow-up examinations.

Cerebrospinal fluid was obtained by standard clinical procedures. All samples were free of blood contamination. For some subjects, the LP was done as part of a separate research study. For others, CSF was obtained as part of their routine clinical evaluation. Residual CSF aliquots were stored in polypropylene tubes at -80°C at the participating site and then transferred on dry ice to the Center for Neurodegenerative Disease Research at the University of Pennsylvania, Philadelphia, where they were maintained at -80°C until assayed for tau and A β peptides.

ASSIGNMENT OF THE DEFINITIVE DIAGNOSIS

The definitive diagnosis was based on the findings at autopsy or the identification in a symptomatic patient of a genetic mutation known to cause AD, Gerstmann-Straussler-Scheinker syndrome, or Huntington disease. All 5 patients with a diagnosis of Creutzfeldt-Jakob disease had a typical clinical picture and either a positive CSF 14-3-3 marker¹⁵ (2 patients) or neuropathological findings of Creutzfeldt-Jakob disease at autopsy (3 patients). The final diagnosis for the 104 subjects who came to autopsy was assigned by the study neuropathologist (J.Q.T.) after a review of the pathological findings and without knowledge of the CSF results.

GENETIC MUTATIONS

Participating sites used established methods to identify disease-causing mutations in the amyloid precursor protein, presenilin 2, prion, or Huntington genes (for a review, see Rosenberg et al¹⁶).

CSF TAU ANALYSIS

Cerebrospinal fluid tau levels were determined by a sandwich enzyme-linked immunosorbent assay (Innotest hTAU-Ag; Innogenetics Nv, Ghent, Belgium) that uses the phosphorylation-independent anti-tau capture antibody AT120 and phosphorylation-independent monoclonal antibodies HT7 and BT2 as reporting antibodies.¹⁷ The assay was done as described previously¹⁸ and without knowledge of the clinical or pathological diagnosis.

CSF A β ANALYSIS

Cerebrospinal fluid A β levels were determined by the sandwich enzyme-linked immunosorbent assay developed by Suzuki et al¹⁹ as described previously.¹⁸ This assay provides a separate quantitative measure for all A β peptides ending at amino acid residue 40 (A β ₄₀) and those ending at amino acid 42 (eg, 1-42 and 17-42). Briefly, a monoclonal antibody raised to A β ₁₋₁₆ (BAN50) served as the capture antibody, and monoclonal antibodies raised to A β ₄₀ (BA27) or to A β ₃₅₋₄₃ (BC05) as the reporting antibodies to detect A β ₄₀ and A β ₄₂, respectively. The assay for CSF A β ₄₀ and A β ₄₂ levels was done without knowledge of the subject's diagnosis.

STATISTICAL ANALYSIS

Differences between mean tau and A β levels across groups were evaluated with the 2-sample *t* test. Associations between patient characteristics and tau or A β levels within the whole AD group were examined by multiple linear regressions. A stepwise model selection procedure was used to select the final models. The covariates of interest included sex, age at symptom onset, age at LP, duration of symptoms at the time of LP, MMSE score when the CSF was obtained, and apolipoprotein E genotype. The effect of clinical center was also considered. The assumptions of *t* test and multiple linear regressions were checked. Because the distribution of tau values was skewed, a logarithmic transformation was applied when 2-sample *t* test and regression analyses were performed so that the normality assumption of these analyses could be met.

The reliability of the CSF tau and A β data was estimated by repeating the analysis of selected samples and comparing the means and the correlation between the 2 assays. Standard decision statistics such as specificity, sensitivity, and positive predictive value were generated by means of a logistic regression model.²⁰ We used CSF tau as a predictor in the logistic

Table 1. Cohort Demographics

Diagnostic Category	No. of Subjects	Age at Dementia Onset, Mean (SD), y	Age at LP, Mean (Range), y	Years of Symptoms at Time of LP, Mean (SD)	Duration of Symptoms Before Death, Mean (SD), y
AD	74	63 (11.2)	69 (37-90)	5.9 (4.9)	10 (5.4)
Control subjects*	73	NA	71 (52-87)	NA	NA
DLB	3	71 (8.5)	74 (70-79)	2.9 (3.8)	9 (2.0)
FD	10	61.2 (11.6)	66 (44-81)	5.4 (3.6)	8 (5.4)
Prion disease†	8	60 (7.1)	63 (56-73)	3.2 (4.0)	5 (5.2)
Other	11	63.6 (9.2)	67 (44-82)	3.9 (3.4)	6 (5.0)

Abbreviations: AD, Alzheimer disease; DLB, dementia with Lewy bodies; FD, frontal dementia; LP, lumbar puncture; NA, not applicable.

*Includes 4 subjects with autopsy confirmation.

†Includes Creutzfeldt-Jakob disease (n = 5) and Gerstmann-Straussler-Scheinker syndrome (n = 3).

Table 2. Tau Values by Diagnostic Category

Diagnosis	No. of Subjects	Tau, pg/mL		Log Tau, Mean (SD)
		Mean (SD)	Range	
AD	60	627 (446)	89-2206	6.21 (0.70)
LBVAD	10	449 (258)	108-1006	5.97 (0.55)
Genetic AD*	4	784 (487)	361-1422	6.52 (0.63)
AD all†	74	612 (430)	89-2206	6.20 (0.68)
Controls‡	73	140 (97)	59-500	4.73 (0.64)
DLB	3	282 (22)	257-300	5.64 (0.08)
FD	10	272 (120)	93-427	5.50 (0.51)
Prion§	8	2302 (2300)	118-6908	7.06 (1.47)
Other	11	403 (372)	119-1239	5.71 (0.74)

Abbreviations: AD, Alzheimer disease; DLB, dementia with Lewy bodies; FD, frontal dementia; LBVAD, Lewy body variant of Alzheimer disease.

*Amyloid precursor protein mutations (n = 3) and presenilin 2 mutation (n = 1).

†Includes LBVAD and genetic AD.

‡Includes 4 subjects with autopsy confirmation.

§Includes Creutzfeldt-Jakob disease (n = 5) and Gerstmann-Straussler-Scheinker syndrome (n = 3).

regression model when generating decision statistics for tau. We used A β as a predictor in the logistic regression model when generating decision statistics for A β . When comparing the 2 areas under the receiver operating characteristic (ROC) curve, we used the algorithm suggested by DeLong et al.²¹

All statistical analyses were performed with the SAS²² and STATA²³ software systems. Unless otherwise stated, all statistical tests are 2-sided and have a .05 significance level.

RESULTS

STUDY COHORT

Demographic and clinical information is presented in **Table 1** and **Table 2**. The cohort had a mean of 14 years of education (range, 6-20 years) and was primarily white (95%). The diagnostic categories, average age at symptom onset, duration of dementia symptoms at the time of LP, and duration of symptoms before death are presented in Table 1.

The AD group included 10 patients with Lewy body variant of AD (LBVAD), 3 patients with an amyloid precursor protein mutation, and 1 with a presenilin 2 mutation. Five of the 8 patients with prion disease had Creutzfeldt-Jakob disease and 3 had Gerstmann-Straussler-Scheinker syndrome. All 11 patients in the "Other" category had clinical signs and symptoms of dementia. They included 3 with progressive supranuclear

palsy and 1 each with Huntington disease (verified by an expanded CAG repeat in the Huntington gene), motor neuron disease, bipolar depression, nondominant anterior temporal lobe ganglioglioma, ischemic vascular dementia, multiple sclerosis, progressive multifocal leukoencephalopathy, and Parkinson disease.

CSF TAU VALUES

Since we performed 5 mean comparisons for CSF tau level, we adjusted the significance level from .05 to .01 by means of Bonferroni correction.

The mean (\pm SD) CSF tau level for the 60 patients with pathologically proven nongenetic AD without Lewy bodies was 627 \pm 446 pg/mL. While this level was above the mean level of 449 \pm 258 pg/mL for the 10 patients with LBVAD, there was no statistically significant difference at the .01 level between the 2 values ($P = .30$).

With the use of a cutoff value of 234 pg/mL, CSF tau had a sensitivity of 85%, specificity of 84%, positive predictive value of 87%, and positive likelihood ratio of 5.3 to correctly distinguish patients with AD from cognitively normal control subjects (**Figure 1**).

Compared with values in the cognitively normal cohort, the mean CSF tau level was slightly elevated in 2 diagnostic groups that can be difficult to separate from AD on clinical grounds: frontal dementia (FD) (272 \pm 120

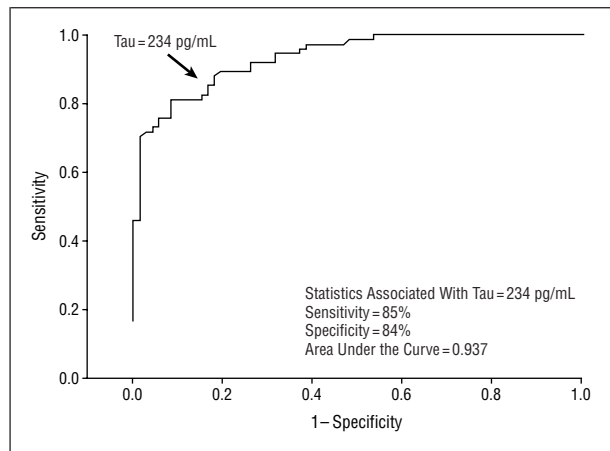


Figure 1. Receiver operating characteristic curve: sensitivity and specificity of cerebrospinal fluid tau to correctly categorize patients with Alzheimer disease (n=73) and cognitively normal subjects (n=74).

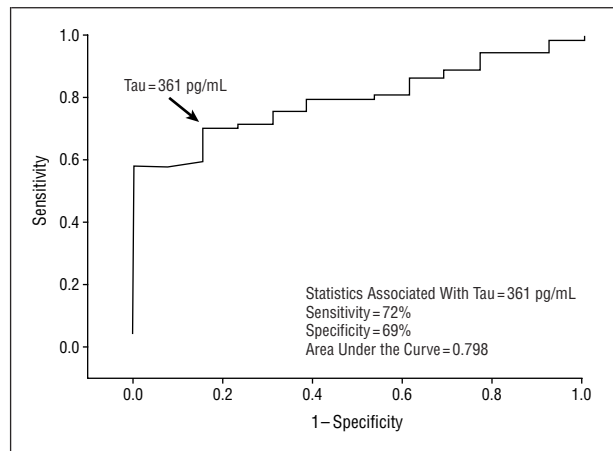


Figure 2. Receiver operating characteristic curve: sensitivity and specificity of cerebrospinal fluid tau to correctly categorize patients with Alzheimer disease (n=74) and those with frontal dementia or Lewy body dementia (n=13).

pg/mL) and dementia with Lewy bodies (DLB) (282 ± 22 pg/mL). For each of these 2 groups, the mean tau value was significantly different at .01 level from the mean value for the AD group as a whole (FD vs AD [all], $P = .002$; DLB vs AD [all], $P < .001$), but not significantly different at .01 level for the cohort with LBVAD (FD vs LBVAD, $P = .06$; DLB vs LBVAD, $P = .10$) (Table 2). With the use of a more diagnostically challenging mixture of patients with AD, FD, and DLB, a cutoff value for CSF tau of 361 pg/mL had a sensitivity of 72%, specificity of 69%, positive predictive value of 80%, and positive likelihood ratio of 3.1 to correctly distinguish those with AD from the patients with FD and DLB (**Figure 2**).

Three of the 7 patients with cognitive impairment and elevated tau levels in the "Other" pathological category had neurologic diseases that are readily distinguished from AD by standard clinical criteria. These included 1 patient each with motor neuron disease (1116 pg/mL), temporal lobe ganglioglioma (1239 pg/mL), and progressive multifocal leukoencephalopathy (381 pg/mL). The individual values for each patient in the "Other" neurologic disease category are presented in **Table 3**.

Within the AD cohort, there was no relationship between the patient's CSF tau level, apolipoprotein E genotype, degree of cognitive impairment as indicated by their MMSE score, or the proportion of the patient's total duration of illness at the time of LP (onset to LP/onset to death) that had passed by the time the CSF was obtained (linear regression analyses, data not reported). In the entire AD cohort (n=74), there was an inverse correlation between the duration of dementia symptoms at the time of LP and the level of tau in the CSF ($P < .03$). On average, there was a 4% decline in tau level for each additional year of symptoms.

Despite the difference in the average CSF tau values between the AD group and the other pathologically defined diagnostic groups, there was considerable overlap with respect to individual subject values. Twelve (16%) of the 74 patients with a confirmed diagnosis of AD had CSF tau values of 234 pg/mL or less, including 3 of the 10 patients with LBVAD.

Table 3. Individual Values for Subjects With Miscellaneous Neurologic Conditions

Diagnosis	Tau, pg/mL	A β_{42} , %*	A β_{42} , fmol/mL
ALS dementia	1116	5.3	68
Depression	372	6.0	60
Ganglioglioma	1239	2.7	7
HD	259	10.1	225
IVD	296	6.2	164
MS	232	4.2	78
PML	381	6.2	63
PD	119	16.8	44
PSP	160	21.7	59
PSP	122	14.8	30
PSP	313	NA	NA

Abbreviations: A β_{42} , β -amyloid 42-amino acid peptide; ALS, amyotrophic lateral sclerosis; HD, Huntington disease; IVD, ischemic vascular dementia; MS, multiple sclerosis; NA, not available; PML, progressive multifocal leukoencephalopathy; PD, Parkinson disease; PSP, progressive supranuclear palsy.

*A $\beta_{42}/(A\beta_{42} + A\beta_{40})$ expressed as a percentage.

CSF A β VALUES

The β -amyloid values are presented in **Table 4**. While we found the expected reduced A β_{42} in the AD cohort compared with cognitively normal subjects, the addition of this information did not add to the diagnostic value of tau level when compared by a nonparametric approach.²¹ Specifically, there was no meaningful increase in the area under the curve when the ROC curve for the combination of tau and β -amyloid levels was compared with the ROC curve for tau level alone. For patients with AD vs cognitively normal controls, the AUC was 0.937 for tau level alone and 0.942 for tau plus β -amyloid levels ($P = .71$). For patients with AD vs the combined FD and DLB cohort, the AUC was 0.798 for tau level alone and 0.809 for tau plus β -amyloid levels ($P = .60$). Similar results were seen regardless of whether the absolute A β_{42} or percentage A β_{42} values were used. Likewise, restricting the AD cohort to patients whose tau values were below 470 pg/mL (the median cohort value) or below the

Table 4. A β ₄₂ Values by Diagnostic Category

Diagnosis	No. of Subjects	A β ₄₂ , %*		A β ₄₂ , fmol/mL	
		Mean (SD)	Range	Mean (SD)	Range
AD sporadic	60	7.1 (4.3)	0.2-22.0	67.0 (127.8)	0-872
LBVAD	10	8.2 (3.7)	0.9-12.6	20.2 (11.7)	3-43
Genetic AD†	4	5.2 (3.5)	1.8-9.8	77.8 (60.0)	27-152
AD (all)‡	74	7.1 (4.1)	0.2-22.0	61.3 (116.8)	0-872
Controls§	73	6.0 (2.9)	1.4-16.6	109.4 (61.2)	28-379
DLB	3	8.0 (2.4)	6.1-10.7	13.7 (6.4)	9-21
FD	10	7.5 (3.4)	2.1-13.4	132.6 (117.6)	5-414
Prion	8	8.5 (3.7)	4.0-16.3	59.6 (40.8)	2-131
Other	11	9.5 (6.0)	2.7-21.7	84.7 (64.0)	7-225

Abbreviations: A β ₄₂, β -amyloid 42-amino acid peptide; AD, Alzheimer disease; DLB, dementia with Lewy bodies; FD, frontal dementia; LBVAD, Lewy body variant of Alzheimer disease.

*A β ₄₂/(A β ₄₂ + A β ₄₀) expressed as a percentage.

†Includes mutations on amyloid precursor protein (n = 3) and presenilin 2 (n = 1).

‡Includes sporadic, genetic, and LBVAD.

§Includes 4 subjects with autopsy confirmation.

||Includes Creutzfeldt-Jakob disease (n = 5) and Gerstmann-Straussler-Scheinker syndrome (n = 3).

ROC cutoff value failed to demonstrate added value for the A β ₄₂ measurement (data not shown).

Within the AD cohort, there was no relationship between the absolute A β ₄₂ level or percentage A β ₄₂ and the patient's sex, age at symptom onset, age at LP, duration of symptoms at the time of LP, MMSE score at the time of LP, or apolipoprotein E genotype. However, there was a weak association (borderline significant) between the percentage A β ₄₂ and the degree of cognitive impairment as judged by their MMSE score ($P = .04$). A 1-point increase in MMSE was associated with 0.14% decrease in percentage A β ₄₂.

To evaluate the effect of storage time on A β levels, we examined 33 stored samples obtained over a 3-year period from a separate cohort of patients with a variety of dementing conditions. The initial values of the samples spanned the range of percentage A β levels (mean, 4.6%; range, 2.1%-12.4%) found for most of the subjects in the autopsy cohort and had an average storage time since first assayed of 326 days (range, 50-832 days). The mean percentage A β ₄₂ did not change significantly (from 4.77% to 5.03%; range of changes, 0.1%-3.0%), indicating that the value was not significantly affected by storage at -80°C. The correlation between the values for the first and second assay was 0.88.

COMMENT

Our study addressed the relevance of CSF tau and A β levels in the differential diagnosis of AD by comparing premortem CSF values with the definitive diagnosis in a well-characterized and diverse group of patients with dementia. We confirmed an association between elevated CSF tau levels premortem and the pathological hallmarks of AD, indicating that high CSF tau levels, in the appropriate clinical setting, strongly supports a diagnosis of AD. Nevertheless, some patients who meet clinical and pathological criteria for AD had CSF tau levels below the balanced sensitivity-specificity ROC cutoff value of 234 pg/mL. Determining the A β level by means of the Suzuki et al enzyme-linked immunosorbent assay did not

improve the diagnostic accuracy. Therefore, CSF tau and A β values cannot be used to exclude a diagnosis of AD in a patient who meets consensus criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association for that diagnosis.

We used an assay that recognized total levels of CSF tau. It remains to be seen whether assays using an antibody targeting a phosphorylated tau epitope²⁴⁻²⁸ will improve the specificity of CSF tau for a definitive diagnosis of AD.

The source of CSF tau remains unclear but most likely is related to the degeneration of neurofibrillary tangle-laden neurons. The protein has not been well characterized in the CSF and may exist in fragmented forms.²⁹ There is no information on the steady-state kinetics of CSF tau in normal individuals. Although a recent report indicates that it may require 3 to 5 months for elevated CSF tau levels to return to normal after an acute stroke,³⁰ the clearance rate of tau from the CSF in patients with neurodegenerative dementia remains unknown.

The average tau value for the group with LBVAD in our study was lower than the value for patients with AD free of Lewy body pathological findings. Although the reason for this has yet to be established, the finding is consistent with reports that these patients have fewer neurofibrillary tangles and more amyloid plaques than patients with AD without LB pathological findings.

Several conditions that are clinically distinct from AD are associated with marked elevations in CSF tau level, including acute stroke,³⁰⁻³² multiple sclerosis,³³ AIDS dementia,³⁴ and head trauma.³⁵ In addition, in our study, patients with amyotrophic lateral sclerosis and ganglioglioma had elevated values.

Elevated CSF tau levels have also been reported in patients with clinical diagnoses of corticobasal degeneration³⁶ and one,³⁷ but not all, studies of FD.^{38,39} These 2 neuropathologically distinct dementias can be difficult to distinguish from AD on clinical criteria alone. In addition, several of our patients with prion diseases had high CSF tau and low A β ₄₂ values that overlapped with

those found for patients with AD. The CSF tau level is known to be elevated in many, but not all, patients with Creutzfeldt-Jakob disease.⁴⁰

The CSF A β_{42} levels were less informative than CSF tau levels in this study cohort. Our finding of a reduced ratio of A β_{42} to total A β in the CSF of patients with AD is consistent with previous reports in clinically diagnosed cohorts.^{14,41-45} However, because of the broad range of values found in this study, neither the absolute level of A β_{42} nor the percentage A β_{42} in CSF provided meaningful additional diagnostic information when the tau level was elevated.

An important limitation of our study is the use of patients undergoing an evaluation in a specialty referral clinic. Nevertheless, the descriptive characteristics of our subjects are similar to those reported in other clinical-pathological studies of patients with dementia in diverse settings. The inclusion of 3 patients with AD with an amyloid precursor protein mutation and 1 with a presenilin 2 mutation made the average age at onset for the members of our AD group lower than typically reported, but it broadened the populations in which these CSF data have been gathered.

The emergence of disease-specific therapy and the prospect of treatment to stabilize and perhaps reverse the neuropathological changes associated with AD^{46,47} lend urgency to the effort to identify and characterize pathologically specific biomarkers. In general, an expert clinical diagnosis of probable AD is pathologically verified in 85% to 90% of patients who come to autopsy. The ability of clinicians to reliably predict the absence of AD pathological changes is not as good.³ Our study suggests that elevated CSF tau level may be helpful in distinguishing AD from other forms of dementia, including neurodegenerative disorders such as FD and DLB. These studies are less helpful in identifying patients with AD with concomitant Lewy bodies or in differentiating AD from prion diseases.

Accepted for publication June 18, 2003.

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Author contributions: Study concept and design (Drs Clark, Galasko, Morris, and Farlow); acquisition of data (Drs Peskind, Galasko, Morris, McKeel, Farlow, Quinn, Kaye, Knopman, Arai, Doody, and DeCarli and Mss Weitlauf and Leight); analysis and interpretation of data (Drs Xie, Ewbanks, Galasko, Doody, DeCarli, Lee, and Trojanowski and Mr Chittams); drafting of the manuscript (Drs Clark, Xie, Galasko, Farlow, Arai, and DeCarli); critical revision of the manuscript for important intellectual content (Drs Xie, Ewbanks, Peskind, Galasko, Morris, McKeel, Farlow, Quinn, Kaye, Knopman, Doody, Lee, and Trojanowski, Mr Chittams, and Mss Weitlauf and Leight); statistical expertise (Dr Xie and Ewbanks and Mr Chittams); obtained funding (Drs Morris and Knopman); administrative, technical, and material support (Drs Peskind, McKeel, Arai, DeCarli and Mss Weitlauf and Leight); study supervision (Drs Clark, Farlow, Quinn, Lee, and Trojanowski).

This study was funded in part by grants AG10124 (University of Pennsylvania, Philadelphia); AG05136, AG08419, and the Department of Veterans Affairs (University of Washington, Seattle); AG05131, AG05136, AG08419, and the Department of Veterans Affairs (University of California, San Diego); AG03991 and AG05681 (Washington University, St Louis, Mo); AG08664 (Baylor College of Medicine, Houston, Tex); AG08017 (Oregon Health Sciences University, Portland); and AG10133 (Indiana University, Indianapolis) from the National Institutes of Health, Bethesda, Md.

We are grateful to the following pathologists for the autopsy findings: James B. Leverenz, MD, and David Nochlin, MD, University of Washington; Bernardino Ghetti, MD, Indiana University; and H. Brent Clark, MD, PhD, University of Minnesota, Minneapolis; and to John Csernansky, MD, Washington University, for providing CSF samples.

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