High Cerebrospinal Fluid Tau and Low Amyloid β42 Levels in the Clinical Diagnosis of Alzheimer Disease and Relation to Apolipoprotein E Genotype

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Objective: To evaluate cerebrospinal fluid (CSF) levels of amyloid β protein ending at amino acid 42 (Aβ42) and tau as markers for Alzheimer disease (AD) and to determine whether clinical variables influence these levels.

Design: Cohort study.

Setting: Six academic research centers with expertise in dementia.

Subjects: Eighty-two patients with probable AD, including 24 with very mild dementia (Mini-Mental State Examination score 23-30) (AD group); 60 cognitively normal elderly control subjects (NC group); and 74 subjects with neurological disorders, including dementia (ND group).

Main Outcome Measures: Levels of Aβ42 and tau were compared among AD, NC, and ND groups. Relationships of age, sex, Mini-Mental State Examination score, and apolipoprotein E (Apo E) genotype with these levels were examined using multiple linear regression. Classification tree models were developed to optimize distinguishing AD from NC groups.

Results: Levels of Aβ42 were significantly lower, and levels of tau were significantly higher, in the AD group than in the NC or ND group. In the AD group, Aβ42 level was inversely associated with Apo E e4 allele dose and weakly related to Mini-Mental State Examination score; tau level was associated with male sex and 1 Apo E e4 allele. Classification tree analysis, comparing the AD and NC groups, was 90% sensitive and 80% specific. With specificity set at greater than 90%, the tree was 77% sensitive for AD. This tree classified 26 of 74 members of the ND group as having AD. They had diagnoses difficult to distinguish from AD clinically and a high Apo E e4 allele frequency. Markers in CSF were used to correctly classify 12 of 13 patients who later underwent autopsy, including 1 with AD not diagnosed clinically.

Conclusions: Levels of CSF Aβ42 decrease and levels of CSF tau increase in AD. Apolipoprotein E e4 had a dose-dependent relationship with CSF levels of Aβ42, but not tau. Other covariates influenced CSF markers minimally. Combined analysis of CSF Aβ42 and tau levels discriminated patients with AD, including patients with mild dementia, from the NC group, supporting use of these proteins to identify AD and to distinguish early AD from aging. In subjects in the ND group with an AD CSF profile, autopsy follow-up will be required to decide whether CSF results are false positive, or whether AD is a primary or concomitant cause of dementia.

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SUBJECTS AND METHODS

SUBJECTS

Subjects were enrolled through AD research clinics and neurology services at 6 academic medical centers. Informed consent was obtained from all participants or their guardians as appropriate. All procedures were performed under institutional guidelines for studies involving human subjects. The evaluation included history from the subject (and an informant if cognitive problems or dementia were apparent), neurological examination, and cognitive screening using the Mini-Mental State Examination (MMSE). The Hachinski Ischemic Index was used to screen all patients with dementia. In subjects suspected of having AD or other dementia, a neuroimaging study and dementia screening blood tests were required. A standardized case report form that documented this information and the diagnosis was recorded for all subjects. In addition, clinical vignettes were provided for all patients thought to have dementia due to reasons other than AD or with atypical dementia syndromes. Diagnoses were made by the neurologist investigator(s) at each site (D.G., L.C., B.M., C.M.C., J.K., D.K., and R.G.), and vignettes were reviewed by a coordinating neurologist (D.G.) to verify subject eligibility and to standardize diagnostic classifications.

AD Group

National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD were required. Patients thought to have very early dementia were included, provided that this diagnosis was supported by results of additional psychometric testing and that follow-up subsequent to the CSF collection showed progression to probable AD. Recruitment was aimed toward mild to moderate degrees of dementia. Only 7 (9%) of 82 patients with AD had MMSE scores below 10 (of a possible 30), whereas 24 (29%) had scores above 23.

NC Group

Subjects were 50 years of age or older, without significant cognitive or neurological symptoms, and had normal results of a neurological examination. A score of at least 28 on the MMSE was required for eligibility. Sixty subjects were included in this group.

ND Group

In addition to patients with diverse neurological conditions, patients with dementia disorders that typically enter into the differential diagnosis with AD were recruited. The neurological diagnoses were based on best clinical judgment. Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Wherever possible, research criteria were applied, eg, in cases of suspected frontotemporal dementia, dementia with Lewy bodies, and vascular dementia. Subjects with depression accompanied by symptoms or signs of impaired cognition (n = 7) were included in this group of 74 patients, as the examining physicians thought that AD was unlikely to be the primary diagnosis. Depression was rated using the Hamilton Depression Scale, and a score of at least 10 was required.

CSF COLLECTION

Cerebrospinal fluid samples were collected using lumbar puncture and tested for protein and glucose levels and cell count. Samples with greater than $5 \times 10^3$ red blood cells per liter or $5 \times 10^3$ white blood cells per liter were excluded. Samples were stored at 4°C for up to 24 hours or frozen if longer storage times were needed, before being shipped to Athena Diagnostics, Inc, Worcester, Mass, for evaluation. Our study included 81 subjects from a previous study by Motter et al. The original CSF samples from these subjects were stored at −80°C until reassyay in our study. The concentrations of Ab42 and tau in CSF do not change appreciably after storage for up to 2 years under these conditions (data not shown).

Biochemical markers for AD have been sought for many years. Recent progress has focused on analytes in cerebrospinal fluid (CSF) that are based on the pathologically altered proteins found in the brains of patients with AD. Specifically, studies have measured CSF levels of the microtubule-associated protein tau, the primary constituent of neurofibrillary tangles, and of a form of amyloid β protein Ab ending at amino acid 42 (Ab42), the major component of the parenchymal amyloid deposits. Several groups have now confirmed that tau levels are increased and Ab42 levels are decreased in the CSF of patients with AD, compared with nondemented elderly control subjects. Clinical or demographic factors have not been shown to have a strong effect on variation in levels of these CSF markers, although contradictory effects of dementia severity on CSF tau levels have been reported.

Apolipoprotein E (Apo E) genotype has a major effect on the risk for development of AD and the age of onset, with the Apo E e4 allele increasing the risk and the
Aβ42 ENZYME-LINKED IMMUNOSORBENT ASSAY

Levels of Aβ42 were quantified as described previously. Briefly, the capture antibody 266, which recognizes Aβ residues 13 through 28, and the Aβ42-specific reporter antibody 277-2 were used as the sandwich enzyme-linked immunosorbent assay (ELISA) pair. Insignificant cross-reactivity with Aβ40 occurs using this assay. The Aβ42 peptide (Bachem, Torrance, Calif) used as the standard was dissolved in dimethyl sulfoxide, sonicated, filtered, and immediately diluted in specimen diluent to final working concentrations before freezing. Standards were stable for more than 1 year when prepared in this manner. Despite the fact that amino acid analysis was used in this study and the study by Motter et al to establish the peptide stock concentrations, we observed a difference of approximately 2-fold in standard quantitation. Our absolute results were thus not directly comparable to those of Motter et al. Although the Aβ42 values quantitated relatively higher than the original determinations, the paired values of the original and repeated assays were strongly correlated (Pearson $r^2 = 0.68; n = 77$).

Total levels of Aβ in CSF, which consist primarily of Aβ peptides ending at position 40, were not routinely analyzed in this study, as the study by Motter et al showed that this measure, used alone or in a ratio with other measures, did not increase ability to discriminate the AD from the NC groups.

TAU ELISA

Tau levels in CSF were measured as previously described. The tau standard, prepared from human brain as previously described, is a different lot than used in the previous studies, yielding slightly different quantitation of samples, with higher levels than previously reported. Reassayed samples again showed a strong correlation with the original measures (Pearson $r^2 = 0.91$).

Apo E GENOTYPING

Apolipoprotein E genotypes were determined using standard polymerase chain reaction methods with DNA derived from blood samples obtained from subjects. Apo E ε2 allele protecting against it, relative to the Apo E ε3 allele. Protein interactions between Apo E and tau or Aβ have been proposed as mechanisms that could explain this genetic effect. Previous reports have not found an effect of Apo E genotype on CSF tau and Aβ42 levels, but the number of subjects in each genotype category was fairly small. We herein extend observations on the use of CSF tau and Aβ42 levels to distinguish patients with AD (AD group) from normal elderly controls (NC group) and patients with other neurologic and dementing disorders (ND group). In addition, we explore the relationships between CSF tau and Aβ42 levels and clinical variables such as age, sex, dementia severity, and Apo E genotype.

The analysis included data from a total of 82 subjects in the AD group, 60 in the NC group, and 74 in the ND group. Of these, 31 subjects in the AD group, 19 in the NC group, and 31 in the ND group had been included in the previous study by Motter et al and had sufficient stored CSF for reassy; updated clinical information was taken into account to verify clinical diagnoses for these subjects. Table 1 shows that the AD and NC groups did not differ significantly regarding age and sex. All 3 groups covered a wide age range (42-85 years; median age, 73 years) for the AD group; 52-82 years (median age, 70 years) for the NC group; and 48-89 years (median age, 65 years) for the ND group. The ND group was slightly younger than the NC and AD groups. The AD group had a mean ± SD MMSE score of 19.3 ± 6.8 and included 24 subjects with very mild dementia, defined as an MMSE score of at least 24. Follow-up information and results of detailed psychometric testing on these mildly demented subjects indicated progressive cognitive and functional decline consistent with AD.

Apo E ε4 allele frequencies of 41% in the AD group and 17% in the NC group were similar to those of published clinical series and showed the expected in-
crease in Apo E ε4 allele frequency associated with AD. However, the Apo E allele distribution in the ND group differed significantly from that of the NC group (χ², P = .04) and included 7 patients homozygous for the Apo E ε4 allele. This raised the possibility that unrecognized cases of AD existed among the ND group. The ND group included patients with the following clinical diagnoses: frontotemporal dementia (n = 19), Parkinson disease (PD) (with or without dementia) (n = 10, of whom 5 were clinically demented), vascular dementia (n = 7), depression (n = 7), progressive aphasia (n = 6), Lewy body dementia (n = 3), amyotrophic lateral sclerosis (n = 3), progressive supranuclear palsy (n = 4), cortical-basal ganglia degeneration (n = 2), cerebellar ataxia (n = 3), mild cognitive impairment (n = 3), nonprogressive amnesia after head trauma (n = 1), normal-pressure hydrocephalus (n = 1), dementia with motor neuron disease (n = 1), multiple sclerosis with dementia (n = 1), cognitive symptoms after treatment of Lyme disease (n = 1), ganglioglioma with partial complex seizures (n = 1), and myotonic dystrophy (n = 1).

**Aβ42 LEVELS**

Cerebrospinal fluid levels of Aβ42 were significantly lower in the AD group compared with the other groups (Table 1). Mean levels of Aβ42 were lowest in the AD group, intermediate in the ND group, and highest in the NC group. We analyzed the effects of age, sex, severity of dementia, and Apo E ε4 allele on Aβ42 levels using multiple linear regression. In the AD group, age and sex were not significant covariates, while MMSE scores showed a slight positive association (higher MMSE scores correlated with higher Aβ42 levels; r² = 0.12; P = .007). The strongest covariate was Apo E ε4, which showed a highly significant negative correlation with Aβ42 level dependent on the number of Apo E ε4 alleles. All of these covariates accounted for only a small amount of the variance of Aβ42 level, since overall, r² = 0.33 (P < .001). The extent of the correlation due to Apo E ε4 copy number alone was 0.26. As shown in Figure 1, CSF Aβ42 levels in the AD group were highest in subjects with no Apo E ε4 alleles (1.067 ± 10⁻⁷ ± 4.49 ± 10⁻⁷ g/L [1067 ± 449 pg/mL]), intermediate in patients with a single Apo E ε4 copy (7.72 ± 10⁻⁷ ± 2.65 ± 10⁻⁷ g/L [772 ± 265 pg/mL]), and lowest in patients homozygous for the Apo E ε4 allele (5.66 ± 10⁻⁷ g/L ± 2.01 ± 10⁻⁷ g/L [566 ± 201 pg/mL]). Levels of CSF Aβ42 in the subgroup of the AD group with no Apo E ε4 alleles were significantly lower than in the NC group (P < .001). For Aβ42 levels among the NC group, multiple linear regression showed a minimal decline with age (r² = 0.11; P = .04), whereas sex and Apo E ε4 allele count (0 or 1) had no significant effects; the model accounted for a very small amount of variance (overall, r² = 0.06; P = .04). Among the ND group, MMSE score was positively associated (P = .02) and Apo E ε4 allele count was negatively associated (P = .02) with Aβ42 levels, whereas age and sex were not significant for the overall model (r² = 0.24; P < .001).
Scores and age were not significant predictors of tau levels in patients homozygous for the Apo E4 allele. However, with increased tau levels in patients heterozygous for the Apo E4 allele, and decreased tau levels in patients homozygous for the Apo E4 allele compared with those without the Apo E4 allele, and decreased tau levels in patients homozygous for the Apo E4 allele compared with those without the Apo E4 allele. The MMSE scores and age were not significant predictors of tau levels in patients heterozygous for the Apo E4 allele. Similar models examining CSF tau levels among the NC group showed no significant effects of age, sex, or Apo E (overall, r² = 0.12). Among the ND group, the overall correlation coefficient was only 0.09, and no predictors attained statistical significance.

**DIFFERENTIATING AD FROM NC GROUPS**

We examined CSF Aβ42 and tau levels individually for their ability to discriminate between the AD and NC groups. For Aβ42 levels, the optimal cutoff for differential classification was 1.0315 × 10⁻⁶ g/L (1031.5 pg/mL), which was used to classify correctly 115 (81.0%) of 142 subjects in the AD and NC groups, overall, with sensitivity of 78% and specificity of 83% for the diagnosis of AD. For tau levels alone, the best cutoff was 5.025 × 10⁻⁷ g/L (502.5 pg/mL), which was used to classify correctly 97 (68.3%) of 142 subjects in the AD and NC groups, overall, with sensitivity of 75% and specificity of 83% for the diagnosis of AD.

Better resolution of the groups was realized by applying the binary tree–structured classification system, in which tau and Aβ42 levels were considered simultaneously. This produced a tree (Figure 2) that correctly classified 121 (85.2%) of 142 subjects, with sensitivity of 90% and specificity of 80% for the diagnosis of AD. Because Apo E4 influenced Aβ42 levels, a separate classification tree analysis used Apo E4 allele count and CSF Aβ42 and tau levels as possible predictors. The Apo E4 allele count did not enter into the optimal tree, which remained identical to that in Figure 2.

For a biomarker test to be a useful adjunct in the clinical workup of AD, it should have high sensitivity. In addition, given the consequences of a positive diagnosis, very high specificity is desirable. To achieve a useful balance of sensitivity and very high specificity, we selected terminal nodes of the classification tree analysis as being diagnostically useful only if they contained rela-
The ND group was also classified by applying the high-sensitivity 3-zone scheme used to differentiate the AD from the NC groups (Figure 3). Twenty-six subjects were in the AD group, including 15 classified in the AD zone, 3 in the non-AD zone, and 6 in the undefined zone, resulting in 15 classified in the AD zone, 3 in the non-AD zone, and 6 in the undefined zone.

One interesting footnote to this group concerned a subject whose test results were positive for AD using CSF test results (3 of 18), compared with patients with conditions associated with dementia or memory problems (23 of 56). The breakdown into specific disorders (Table 3) shows that within each diagnostic group, fewer of the ND group were classified as having AD using CSF levels of Aβ42 and tau. Among these disorders were dementias that are clinically difficult to distinguish from AD, ie, frontotemporal dementia, vascular dementia, progressive aphasia, and PD with dementia. Two of 3 patients with mild cognitive impairment, a possible prodrome of AD, had an AD profile. Further evidence that subjects in the ND group with an AD profile actually may have AD was provided by the Apo E ε4 allele frequencies. Overall, the ε4 allele frequency was 45%, similar to the 41% of the AD group. Among these disorders were dementias, such as vascular dementia, which are clinically difficult to distinguish from AD, and multiple sclerosis with dementia, normal pressure hydrocephalus, and temporal lobe ganglioglioma and seizures; classified as undefined, atypical dementia with amyotrophy and progressive supranuclear palsy (n = 2); and classified as non-AD, cortical basal ganglia degeneration (n = 2), cerebellar ataxia after meningitis, and posttraumatic amnesia.

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cient quantities to meet a neuropathological diagnosis of AD. The second subject had seizures and cognitive decline. A right temporal lobe ganglioglioma was found on biopsy, and examination of the temporal lobe tissue removed during surgery to resect the tumor did not indicate the presence of AD. Another 4 patients in the ND group who were not classified in the AD zone using CSF markers have since undergone autopsy, and all were confirmed not to have AD. Seven autopsy-confirmed AD cases were AD positive based on results of CSF testing.

The 9 patients in the ND group with Ab42 levels below $7.61 \times 10^{-7}$ g/L (761 pg/mL), a classification tree zone occupied almost exclusively by patients with AD in the AD vs NC group comparison, consisted of 4 patients with frontotemporal dementia and 1 patient each for diagnoses of primary progressive aphasia (Apo E e4/e4), depression with cognitive changes (MMSE score, 21; Apo E e4/e4), vascular dementia, PD with depression and memory complaints (Apo E e4/e4), and Lyme disease followed by cognitive complaints (MMSE score, 20; Apo E e3/e4). All of these patients presented with dementia or cognitive impairment, while none of the cognitively normal subjects in the ND group had an Ab42 level of less than $7.61 \times 10^{-7}$ g/L (761 pg/mL). Alzheimer disease likely contributed to the clinical picture in some of these cognitively impaired patients.

**COMMENT**

Our study is consistent with and extends the results of a previous report showing that Ab42 levels are decreased and tau levels are increased in CSF in AD.11 The larger number of subjects in our report, recruitment of very mildly demented individuals, and the larger number of subjects with Apo E genotype provided adequate statistical power to examine the effects of a number of covariates. Across an age range of 52 to 82 years, cognitively normal individuals showed only a small trend toward increased CSF tau levels and a minimal effect on Ab42 levels. Dementia severity did not influence tau levels, as we and others11,12 have previously reported, and in fact tau levels have been shown to be elevated in very mild AD.38,39 Interestingly, the extent of cognitive impairment slightly affected Ab42 levels. The decrease in this marker with increasing dementia is consistent with a reduction in viable neurons producing Ab42 or a larger fraction of Ab42 being sequestered in plaque or otherwise unable to enter the CSF. The fact that total Ab levels do not decrease in the CSF of patients with AD favors the latter argument.

Apolipoprotein E genotype was the major significant covariate related to Ab42 levels in the AD group in an Apo E e4 allele dose-dependent fashion. Patients homozygous for the Apo E e4 allele had the lowest mean level of Ab42, while those lacking an Apo E e4 allele had the highest level. Regardless of whether subjects had 0, 1, or 2 Apo E e4 alleles, the AD group showed lower Ab42 mean levels than the NC group. One possible explanation for the genotype effect is that the frequency of misdiagnosis may be higher in subjects lacking an Apo E e4 allele.37 artifactually raising the group mean. However, tau levels did not show a similar Apo E e4 dose dependence, and we would have expected both measures to be similarly distorted by misdiagnoses. Failure to find this genotypic effect on Ab42 levels in an earlier study11 was likely due to the insufficient number of patients with AD lacking an Apo E e4 allele, as that study had an unusually high Apo E e4 frequency (58%).

It was suggested originally that the decrease in CSF Ab42 levels was related to the specific deposition of this protein, as opposed to the bulk Ab levels, in amyloid plaque.11 Our data strengthen this idea by linking Ab42 levels inversely to Apo E e4 gene dosage. The plaque burden in AD has been well documented to increase with Apo E e4 gene dosage,40,41 consistent with the lowering of CSF Ab42 levels being most pronounced in patients homozygous for the Apo E e4 allele. A link between CSF Ab42 levels and plaque burden would also explain the diagnostic specificity for AD associated with the Apo E genotype and CSF Ab42 levels. Ongoing studies will use neuropathological correlates to further test this idea.

The undefined zone in Figure 3 included patients who showed high CSF tau and Ab42 levels. Numerous studies have shown elevation of CSF tau levels can occur not only in AD but also in other neurological and neurodegenerative disorders. The tau released into CSF has been shown, in patients with AD or other disorders, to be a fragment lacking much of the portion of tau thought to be critical in paired helical filament formation.42 Only rarely have elevated CSF tau levels been observed in normal controls, suggesting that the finding of high CSF tau levels indicates an underlying neuropathological process.

The ND group included the most diagnostically challenging patients, and CSF Ab42 and tau levels could not be fully interpreted in the absence of autopsy examination. Thus the patients with non-AD dementias enrolled in our study may not be typical of those seen in community practice settings. Although AD is by far the most common cause of dementia, its distinction from other conditions associated with dementia can be clinically difficult. One factor that may lead to misdiagnoses is the lack of robust clinical criteria for identifying patients with specific non-AD dementing conditions. Another confounding factor is that AD may coexist with other causes of dementia, making the clinical diagnosis of non-AD dementias more uncertain than that of probable AD. For example, studies of dementia conditions clinically diagnosed as frontotemporal dementia,44,45 progressive aphasia,44,45 progressive supranuclear palsy,46 and cortical-basal ganglia degeneration47 have all revealed a few patients who have AD lesions at autopsy, alone or in conjunction with another degenerative condition. In vascular dementia and dementia associated with PD, coexistence of a significant burden of AD lesions is a common finding.47,48

In view of these reservations, interpretation of the CSF data in the ND group can only be tentative. Nonetheless, we identified several interesting observations and trends. First, there was a high Apo E e4 allele frequency among the ND group, especially those with an AD-like profile of CSF Ab42 and tau levels (Table 3). In clinical series, association between the Apo E e4 allele and disorders such as PD49 and Pick disease50,51 have not been

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found, and in autopsy series, the presence of the Apo E ε4 allele in non-AD dementias can be related to coexisting AD abnormalities. This is consistent with the possibility that patients with non-AD dementia and the Apo E ε4 allele are more likely to harbor AD abnormalities, which fits with the striking increase in Apo E ε4 allele frequency (45%) in such patients with an AD-CSF profile.

Second, no particular subgroup of the ND group was classified consistently as having AD. Third, only 9 patients in the ND group were classified as having AD because of high CSF tau values (Aβ42, 7.61 × 10⁻⁷-1.031 × 10⁻⁷ g/L [761-1031 pg/mL]; tau, >5.03 × 10⁻⁷ g/L [>503 pg/mL]).

Therefore, low CSF Aβ42 levels were more important than tau levels in determining the classification of the ND group. As there is no evidence that Aβ deposition occurs nonspecifically in other neurological conditions besides AD, the CSF results hinted at undiagnosed AD rather than false positive results in the ND group, assuming the lowering of CSF Aβ42 levels is related to plaque formation.

Our study has confirmed and extended earlier findings that low Aβ42 and high tau levels characterize the CSF of most patients with AD and supports several potential clinical applications of these measures. In patients suspected of having AD, but in whom the clinical diagnosis is uncertain, CSF Aβ42 and tau levels can be used to strengthen the diagnosis. When more than 1 potential cause of dementia is suspected, these CSF markers may help to establish that AD is a contributory factor. With the advent of symptomatic treatment for cognitive symptoms of AD, and as drugs are developed to slow the progression of AD, early diagnosis is important to define the earliest window of opportunity to apply such treatments. At this early stage of AD, it is more difficult to document a history of progressive cognitive and functional decline or to demonstrate deficits on cognitive testing. This often raises the clinical question of whether symptoms represent age-associated changes or AD, a decision that the biomarker tests may help to resolve. A major future focus of further CSF studies and studies of other biological markers will be subjects with mild cognitive impairment or with risk factors for dementia combined with minimal cognitive symptoms. In this regard, it is encouraging that most patients with AD and very mild dementia (MMSE score ≥24) were classified as having an AD CSF profile, indicating that measuring CSF Aβ42 and tau levels may be helpful in diagnosing very early or mild AD.

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