Evaluation of CSF-tau and CSF-Aβ42 as Diagnostic Markers for Alzheimer Disease in Clinical Practice

Niels Andreasen, MD, PhD; Lennart Minthon, MD, PhD; Pia Davidsson, PhD; Eugeen Vanmechelen, PhD; Hugo Vanderstichele, PhD; Bengt Winblad, MD, PhD; Kaj Blennow, MD, PhD

Objective: To evaluate the diagnostic potential of cerebrospinal fluid (CSF) levels of tau and β-amyloid protein ending at amino acid 42 (Aβ42) as biomarkers for Alzheimer disease (AD) in clinical practice.


Setting: Community population–based sample of all consecutive patients admitted for investigation of cognitive symptoms to the Piteå River Valley Hospital, Piteå, Sweden.

Patients: A total of 241 patients with probable AD (n=105), possible AD (n=58), vascular dementia (n=23), mild cognitive impairment (n=20), Lewy body dementia (n=9), other neurological disorders (n=3), and psychiatric disorders (n=5) and nondemented individuals (n=18).

Main Outcome Measures: Cerebrospinal fluid tau and CSF-Aβ42 were assayed each week as routine clinical neurochemical analyses. Sensitivity and specificity were defined using the regression line from 100 control subjects from a multicenter study. Positive and negative predictive values were calculated for different prevalence rates of AD.

Results: We found increased CSF-tau and decreased CSF-Aβ42 levels in probable and possible AD. Sensitivity was 94% for probable AD, 88% for possible AD, and 75% for mild cognitive impairment, whereas specificity was 100% for psychiatric disorders and 89% for nondemented. Specificity was lower in Lewy body dementia (67%) mainly because of low CSF-Aβ42 levels and in vascular dementia (48%) mainly because of high CSF-tau levels. Sensitivity for CSF-tau and CSF-Aβ42 increased in patients with AD possessing the ApoE ε4 allele, approaching 100%. At a prevalence of AD of 45%, the positive predictive value was 90% and the negative predictive value was 95%.

Conclusions: Cerebrospinal fluid tau and CSF-Aβ42 have so far been studied in research settings, under conditions providing data on the optimal performance. We examined a prospective patient sample, with assays run in clinical routine, giving figures closer to the true performance of CSF-tau and CSF-Aβ42. The predictive value for AD was greater than 90%. Therefore, these biomarkers may have a role in the clinical workup of patients with cognitive impairment, especially to differentiate early AD from normal aging and psychiatric disorders.

Arch Neurol. 2001;58:373-379

The clinical diagnosis of sporadic Alzheimer disease (AD) is based on the identification of dementia with a clinical profile suggestive of AD from the medical history and clinical examination together with the exclusion of other causes of dementia using brain imaging and laboratory tests. There are no established (ie, used in clinical routine) biochemical markers to identify AD. Such biochemical markers might increase diagnostic accuracy, especially early in the course of the disease, when clinical symptoms might be mild and vague and overlap with cognitive changes accompanying aging and other brain disorders. Especially in view of future disease-modifying compounds, which are likely to have their maximal benefit before neurodegeneration is widespread, there is a great need for reliable biochemical diagnostic markers of AD.

For editorial comment see page 349

A diagnostic marker for AD should reflect a central pathogenic process of the disease, ie, the degeneration of the neurons and their synapses and the defining lesion’s senile plaques (SPs) and neurofibrillary tangles. Two such biomarkers are tau and β-amyloid protein ending at amino acid 42 (Aβ42). The cerebrospinal fluid
PATIENTS AND METHODS

STUDY POPULATION

This investigation was part of the longitudinal geriatric population study in Piteå, Sweden,12 with a population of approximately 60,000 individuals. All individuals with cognitive impairment must be referred for medical examination at the hospital. Patients were admitted from the local general practitioner or the community health service. The study included all consecutive patients (N = 263) admitted during 1 year (September 1, 1998, to August 31, 1999). A lumbar puncture (LP) was performed on all patients who accepted (n = 241; acceptance rate, 91%).

Clinical evaluation was performed in a standardized way, and all data were recorded in research protocols.14 Diagnostic evaluation in all patients included a clinical examination (detailed medical history and somatic, neuropsychiatric, and neurological status), a neuropsychologic test battery, assessment of activities of daily living, routine blood tests to exclude secondary dementias (eg, vitamin B12, folate, albumin, calcium, and thyroid-stimulating hormone), routine CSF tests to identify blood-brain barrier damage and infectious and inflammatory disorders, an electroencephalogram (to evaluate α-frequency and focal abnormalities), and a computed tomographic scan (to evaluate cortical atrophy, white matter lesions, and infarcts and lacunas). Clinical diagnoses were based on summarized information from the diagnostic evaluation and were made by one of us (N.A., a geriatrician).

The presence or absence of dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), criteria.15 Probable and possible AD were diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria,1 and vascular dementia (VAD) according to the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neurosciences criteria.14 Patients with probable AD had an insidious onset and even progression of dementia, which could not be explained by systemic or brain disorders other than AD. No patient had prominent frontal lobe symptoms or history, clinical, or brain imaging signs of cerebrovascular disease, except for mild white matter lesions. Vascular dementia was diagnosed in patients with a history of transitory ischemic attacks or stroke episodes with a temporal relation to development of dementia together with computed tomographic and magnetic resonance tomographic findings of lacunas, infarcts, and often moderate or marked white matter lesions. The possible AD group preferentially consisted of patients with mixed AD/VAD, ie, those with even progression of dementia but with a history of transitory ischemic attacks or stroke episodes without temporal relation to development of dementia or with accidental findings of lacunas, minor infarcts, or moderate white matter lesions on computed tomography. Patients with clinical findings suggestive of AD but also with signs of other degenerative disorders (eg, frontal lobe symptoms) were also diagnosed as having possible AD.

Mild cognitive impairment (MCI) was diagnosed in patients with memory impairment but no other symptoms of dementia according to established criteria.15 Of patients with MCI, 3 (13%) of 20 progressed to AD with dementia during follow-up. Lewy body dementia (LBD) was diagnosed according to consensus criteria.16 The nonmented group included individuals with subjective minor memory complaints but without objective signs of memory (CSF) level of tau has been suggested to reflect neuronal and axonal degeneration or possibly formation of neurofibrillary tangles, whereas the CSF-Ab42 level might reflect the deposition of Ab into SPs, with lower levels remaining in the CSF.3

Several previous studies have found increased CSF-tau6,7 and reduced CSF-Ab428,9 levels in AD. A large multicenter study10 found that the combination of CSF-tau and CSF-Ab42 gave approximately 85% sensitivity and specificity for AD. However, all previous studies are based on patient series from research centers with analyses run at a single occasion in research laboratories.

To further evaluate the clinical usefulness of CSF markers, sensitivity and specificity data must be calculated on consecutive patients and biochemical analyses must be run in routine clinical neurochemistry. In a recent study, Andreassen et al11 showed that CSF-tau has high sensitivity for AD, also, in clinical practice. In this study, we present data for the combination of CSF-tau and CSF-Ab42 as diagnostic markers for AD based on all patients admitted for dementia examination to Piteå River Valley Hospital, Piteå, Sweden, during a 1-year period, where CSF analyses were run each week in routine clinical neurochemistry.

RESULTS

The coefficient of variance for the internal control samples, run on 76 different ELISA plates during 1 year, was 18.9% for CSF-tau and 10.7% for CSF-Ab42 for the normal control and 10.1% for CSF-tau and 11.0% for CSF-Ab42 for the AD control.

We also studied the analytical variation for the CSF-Ab42 assay and the stability of CSF-Ab42 by reanalyzing 41 stored (>6 months) CSF samples on 1 ELISA plate. The correlation between Ab42 run in clinical routine at different times during 1 year and the same samples rerun at one occasion was high (r = 0.96; P < .001) (Figure 1).

Of 241 patients included in the study, 10 (4.1%) had post-LP headaches (mild in 4 patients, moderate in 4, and severe in 2).

There was a significant increase in the level of CSF-tau in the probable AD group compared with the VAD (P = .001), MCI (P = .04), LBD (P < .001), and nonmented (P < .001) groups. An increase in CSF-tau levels was also found in the possible AD group compared with the LBD (P = .002), nonmented (P < .001), and VAD (P = .04) groups. No significant differences were found among the other diagnostic groups (Table 2).
impairment or dementia symptoms at the clinical examination or neuropsychological assessment. In the non-demented group, an outcome observation and criteria was that no progression was found during follow-up. All other clinical diagnoses were made according to established criteria (DSM-IV) and International Classification of Diseases, 10th Revision (ICD-10).

All clinical diagnoses and evaluations were made without knowledge of the results of the biochemical analyses and vice versa. The clinical characteristics of the patients are given in Table 1. Severity of dementia was evaluated using the Mini-Mental State Examination. The ethics committees in Umeå and Göteborg, Sweden, approved the study.

The regression line from a large multicenter study in which the same enzyme-linked immunosorbent assays (ELISAs) for tau and Aβ42 determinations were used defined the cutoff levels for CSF-tau and CSF-Aβ42 (Aβ42 = 240 + 1.18 X tau). This study included CSF samples from 100 healthy volunteers or patients without brain disorders.

CSF ANALYSES

Samples of CSF were taken in polypropylene tubes to avoid absorption of Aβ into the test tubes and were sent by ordinary mail to the Clinical Neurochemistry Laboratory at Sahlgren’s University Hospital in Mölndal, Sweden. After arrival (the day after LP), samples were aliquoted and frozen pending biochemical analyses, which were performed within 1 week.

The incidence of post-LP headache was recorded prospectively. Post-LP headache was graded on a scale from 0 to 3 (0, absent; 1, mild headache with duration <2 days; 2, moderate headache with duration <2 days requiring administration of oral analgesics; and 3, severe headache with duration >2 days requiring treatment with an epidural blood patch).

The level of CSF-tau was determined using an ELISA (Innotest hTAU-Ag; Innogenetics NV, Gent, Belgium) constructed to measure both normal tau and phosphorylated tau. The level of CSF-Aβ42 was determined using an ELISA (INNOTEST β-amyloid(1-42); Innogenetics) specific for Aβ42.

Assays of CSF-tau and CSF-Aβ42 were run as routine clinical neurochemical analyses. Analyses were run every week, and all samples were run in duplicate. Two CSF pools were made for use as internal controls: a normal pool (CSF samples from patients with psychiatric or minor neurological disorders) with a mean tau value of 288 pg/mL and a mean Aβ42 value of 700 pg/mL, and an AD pool with a mean tau value of 904 pg/mL and a mean Aβ42 level of 383 pg/mL. Control pools were stored at −80°C and were run on every ELISA plate analyzed (n=76).

ApoE GENOTYPING

Apolipoprotein E genotyping was performed by polymerase chain reaction followed by minisequencing as described previously.

STATISTICAL ANALYSIS

Comparisons between groups were performed using factor analysis of variance with post hoc analyses (Tukey honestly significant difference test for unequal N). The Pearson correlation coefficient was used for correlations. Sensitivity (ie, the proportion of patients with AD and high tau and low Aβ42 levels) and specificity (ie, the proportion of other patients with normal tau and Aβ42 levels) were calculated using the cutoff line from a multicenter study.

There was a marked decrease in CSF-Aβ42 levels in the probable AD group compared with the VAD (P = 0.006), psychiatric disorders (P = 0.003), and non-demented (P<.001) groups. A decrease in the CSF-Aβ42 level was also found in the possible AD group compared with the psychiatric disorders (P = 0.02) and non-demented (P<.001) groups, in the MCI group compared with the non-demented group (P = 0.006), and in the LBD group compared with the non-demented group (P = 0.004). No significant differences were found among the other diagnostic groups (Table 2).

Within the AD group, there were no significant correlations between age and either CSF-tau (r = −0.10; P = .32) or CSF-Aβ42 (r = 0.003; P = .98). However, because there were significant differences in age among the diagnostic groups, we performed multiple analyses of variance with CSF-tau or CSF-Aβ42 as dependent variables and age as a covariate, which showed an effect by diagnosis (P<.001) but not by age for CSF-tau (P = .83) or CSF-Aβ42 (P = .54).

Sensitivity and specificity data for the combination of CSF-tau and CSF-Aβ42 using the cutoff line from the multicenter study are presented in Table 2, and the individual values are given in Figure 2. Sensitivity was 94% for probable AD, 88% for possible AD, and 75% for MCI (Table 2). Specificity was 100% for psychiatric disorders and 89% for the non-demented group (Table 2). Specificity was lower in the LBD group (67%) mainly because of low CSF-Aβ42 levels. The lowest separation was found in the VAD group, with a specificity of 48% mainly because of high CSF-tau levels.

Sensitivity for the combination of CSF-tau and CSF-Aβ42 in patients possessing the ApoE ε4 allele increased from 94% to 99% (73/74) for probable AD, from 88% to 100% (27/27) for possible AD, and from 75% to 88% (7/8) for MCI (Figure 2). In VAD, all 3 ApoE ε4–positive patients had pathologic values for CSF-tau and CSF-Aβ42 (Figure 2).

Positive and negative predictive values for the combination of tau and Aβ42 at different disease prevalences are given in Figure 3. The prevalence of probable AD was 105 (44%) of 241, resulting in a positive predictive value of 90% and a negative predictive value of 95%. Positive and negative predictive values were 82% and 97%, respectively, at a prevalence of 30% and 73% and 98%, respectively, at a prevalence of 20% (Figure 3).

There were no significant differences in CSF-tau levels between patients without vs with the ApoE ε4 allele in the probable AD (892 ± 590 vs 730 ± 319 pg/mL; P = .23), possible AD (716 ± 310 vs 680 ± 234 pg/mL; P = .23), VAD
were included. Assays of CSF samples were run each week.

We evaluated the utility of the combination of CSF-tau and CSF-β42 as diagnostic markers for AD in clinical practice. All patients admitted for evaluation of suspected dementia to a community hospital during 1 year were included. Assays of CSF samples were run each week as routine analyses in a clinical neurochemical laboratory. This setting gives the opportunity to further evaluate the diagnostic potential of diagnostic markers for AD.

Samples of CSF were sent at room temperature over a substantial distance (approximately 1600 km). Reanalysis of CSF-β42 on a single occasion gave values similar to those obtained at several runs during 1 year. The stability of the ELISAs, as determined by running both high and low control samples on each plate, was also acceptable and in the range expected for immunoasays. These findings suggest that the present procedure for handling and analyzing CSF samples for routine analyses is accurate and that the ELISAs are robust.

We found an increase in CSF-tau and a decrease in CSF-β42 levels in AD, in agreement with results of several previous studies. Using the cutoff line from a multicenter study, the sensitivity to identify AD was high, greater than 90%, and the positive and negative predictive values for AD were both high. Furthermore, sensitivity increased if the ApoE genotype also was taken into consideration. Academic centers report accuracy rates for the clinical diagnosis of AD of 65% to 90%, although some studies have reported lower figures. Thus, higher sensitivity figures than those obtained in the present study might not be expected for diagnostic markers when evaluated in clinically diagnosed patients.

Specificity was high to differentiate AD from psychiatric disorders and nondemented. However, specificity was lower in the LBD group mainly because several patients had low CSF-β42 levels. This might be a consequence of patients with LBD harboring SPs in the brain. The lowest specificity was found in the VAD group. One possible explanation is that patients with VAD, in addition to cerebrovascular abnormalities, might have concomitant AD pathologic findings, which is impossible to exclude clinically. Neuropathologic studies have found that a high proportion of patients with clinically diagnosed VAD (40%-80%) has notable concomitant AD pathologic findings. Indeed, the lowest CSF-β42 levels in VAD were found in patients with the ApoE ε4 allele, raising the question of whether these patients har-

### Table 1. Basic Clinical Characteristics of the Diagnostic Groups

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Patients, No. (n = 241)</th>
<th>Sex, M/F, No.</th>
<th>Age, Mean ± SD, y†</th>
<th>Duration, Mean ± SD, y</th>
<th>MMSE Score, Mean ± SD‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD</td>
<td>105</td>
<td>39/66</td>
<td>75.9 ± 6.8</td>
<td>3.3 ± 2.9</td>
<td>22.8 ± 4.9</td>
</tr>
<tr>
<td>Possible AD</td>
<td>58</td>
<td>34/24</td>
<td>77.4 ± 6.4</td>
<td>3.4 ± 2.4</td>
<td>21.6 ± 5.1</td>
</tr>
<tr>
<td>VAD</td>
<td>23</td>
<td>14/9</td>
<td>76.5 ± 7.4</td>
<td>3.2 ± 2.9</td>
<td>22.3 ± 5.0</td>
</tr>
<tr>
<td>MCI</td>
<td>20</td>
<td>8/12</td>
<td>70.9 ± 6.4</td>
<td>2.6 ± 2.7</td>
<td>27.8 ± 2.0</td>
</tr>
<tr>
<td>LBD</td>
<td>9</td>
<td>5/4</td>
<td>74.6 ± 7.0</td>
<td>2.1 ± 1.0</td>
<td>20.9 ± 4.9</td>
</tr>
<tr>
<td>Other neurological disorders§</td>
<td>3</td>
<td>2/1</td>
<td>64.7 ± 10.1</td>
<td>3.5 ± 2.8</td>
<td>243 ± 2.5</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>5</td>
<td>3/2</td>
<td>67.5 ± 4.7</td>
<td>3.3 ± 4.6</td>
<td>25.4 ± 4.4</td>
</tr>
<tr>
<td>Nondemented</td>
<td>18</td>
<td>5/13</td>
<td>60.8 ± 12.1</td>
<td>2.8 ± 1.6</td>
<td>28.4 ± 2.2</td>
</tr>
<tr>
<td>Possible AD</td>
<td>58</td>
<td>34/24</td>
<td>77.4 ± 6.4</td>
<td>3.4 ± 2.4</td>
<td>21.6 ± 5.1</td>
</tr>
<tr>
<td>Possible AD</td>
<td>105</td>
<td>39/66</td>
<td>75.9 ± 6.8</td>
<td>3.3 ± 2.9</td>
<td>22.8 ± 4.9</td>
</tr>
<tr>
<td>Probable AD</td>
<td>105</td>
<td>39/66</td>
<td>75.9 ± 6.8</td>
<td>3.3 ± 2.9</td>
<td>22.8 ± 4.9</td>
</tr>
</tbody>
</table>

*MMSE indicates Mini-Mental State Examination; AD, Alzheimer disease; VAD, vascular dementia; MCI, mild cognitive impairment; and LBD, Lewy body dementia.
†Significances for age: nondemented vs probable AD, P < .001; possible AD, P < .001; and LBD, P = .002. Possible AD vs MCI, P = .01.
‡Significances for MMSE: nondemented vs probable AD, P < .001; possible AD, P < .001; and LBD, P = .002. Possible AD vs MCI, P < .001; possible AD, P < .001; VAD, P = .002; and LBD, P = .003.
§Includes frontotemporal dementia (n = 1), cerebrovascular disorder (n = 1), and Creutzfeldt-Jakob disease (n = 1).
¶Includes depression (n = 3) and alcoholism (n = 2).
It is clear that studies with neuropathologically confirmed cases are needed to determine with certainty the sensitivity and specificity of CSF-tau and CSF-Aβ42 as diagnostic markers for AD. Also, the 3 patients with other neurological disorders had abnormal CSF markers. The highest CSF-tau level in the present study was found in a patient with Creutzfeldt-Jakob disease (CJD), in agreement with results of previous studies. The level of CSF-tau has been suggested to reflect neuronal and axonal degeneration, which is very intense in CJD. The patient with CJD had an even higher CSF-tau value (14600 pg/mL) at follow-up 1 month later. Thus, very high CSF-tau

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Patients, No. (n = 241)</th>
<th>CSF-tau, Mean ± SD, pg/mL†</th>
<th>CSF-Aβ42, Mean ± SD, pg/mL‡</th>
<th>Sensitivity for a Diagnosis of AD, % (95% CI)</th>
<th>Specificity for a Diagnosis of Non-AD, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD</td>
<td>105</td>
<td>759 ± 417</td>
<td>523 ± 180</td>
<td>94 (88-97)</td>
<td>NA</td>
</tr>
<tr>
<td>Possible AD</td>
<td>58</td>
<td>699 ± 275</td>
<td>572 ± 225</td>
<td>88 (77-94)</td>
<td>NA</td>
</tr>
<tr>
<td>VAD</td>
<td>23</td>
<td>461 ± 280</td>
<td>704 ± 321</td>
<td>NA</td>
<td>48 (29-67)</td>
</tr>
<tr>
<td>MCI</td>
<td>20</td>
<td>517 ± 190</td>
<td>640 ± 280</td>
<td>75 (53-89)</td>
<td>NA</td>
</tr>
<tr>
<td>LBD</td>
<td>9</td>
<td>239 ± 97</td>
<td>568 ± 183</td>
<td>NA</td>
<td>67 (35-88)</td>
</tr>
<tr>
<td>Other neurological disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>1</td>
<td>961</td>
<td>1060</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>1</td>
<td>3280</td>
<td>464</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cerebrovascular disorder</td>
<td>1</td>
<td>392</td>
<td>467</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>5</td>
<td>400 ± 115</td>
<td>901 ± 109</td>
<td>NA</td>
<td>100 (57-100)</td>
</tr>
<tr>
<td>Nondemented</td>
<td>18</td>
<td>264 ± 102</td>
<td>897 ± 242</td>
<td>NA</td>
<td>89 (67-97)</td>
</tr>
</tbody>
</table>

* Aβ42 indicates -amyloid protein ending at amino acid 42; AD, Alzheimer disease; CI, confidence interval; VAD, vascular dementia; MCI, mild cognitive impairment; LBD, Lewy body dementia; and NA, not applicable.
†Significances for CSF-tau: probable AD vs VAD, P = .001; MCI, P = .04; LBD, P < .001; and nondemented, P < .001. Possible AD vs LBD, P = .002; nondemented, P < .001; and VAD, P = .04.
‡Significances for CSF-Aβ42: probable AD vs VAD, P = .006; psychiatric disorders, P = .003; nondemented, P < .001. Possible AD vs psychiatric disorders, P = .02; and nondemented, P < .001. MCI vs nondemented, P = .006. LBD vs nondemented, P = .004.
levels may raise suspicion of CJD, although the sensitivity of CSF-tau to identify CJD has to be further evaluated. The patient with CJD also had low a CSF-Ab42 level, also in agreement with results of a previous study,30 supporting the fact that a low CSF-Ab42 level is not specific for AD and questioning the mechanism for the reduction of CSF-Ab42 levels in AD, which has been suggested to be a consequence of deposition of the Ab into SPs.5,8

In the present study, we found high sensitivity for the combination of CSF-tau and CSF-Ab42 for AD, whereas specificity was lower, especially for some other dementias and neurological disorders. Although this reduces the clinical diagnostic utility, we think that this drawback can, at least partly, be overcome by using CSF markers together with the summarized information gained from the clinical examination.31 We suggest that AD can be diagnosed on the basis of a combination of (1) characteristic symptoms of, in the initial stage, memory disturbances and, later on, parietal symptoms; (2) characteristic brain imaging findings, e.g., parietotemporal blood flow defect on single-photon emission computed tomography and hippocampal and cortical atrophy together with absence of cerebrovascular changes on computed tomographic or magnetic resonance tomographic scans; and (3) a characteristic pattern of CSF biomarkers (high CSF-tau and low CSF-Ab42 values together with normal blood-brain barrier function and absence of pleocytosis or intrathecal immunoglobulin production) and other biochemical tools, e.g., ApoE genotyping.31 As an analogy, the clinical diagnosis of myocardial infarction is based on the combination of clinical symptoms, electrocardiographic findings, and biochemical markers (e.g., creatine kinase).

Furthermore, the effect of the lower specificity on the clinical usefulness of CSF-tau and CSF-Ab42 might be overestimated because not all disorders in which abnormal levels of these biomarkers can be found are important (i.e., difficult) differential diagnoses of AD, e.g., acute stroke32 or human immunodeficiency virus dementia.33 Instead, CSF-tau and CSF-Ab42 might have their major use as an adjunct to help to differentiate AD from the most problematic differential diagnoses, especially age-associated memory impairment, depressive pseudodementia, Parkinson disease, progressive supranuclear palsy, and alcoholic dementia.

Lumbar puncture is easy to perform, with a low risk for complications.34 In the present study, the incidence of post-LP headache was low, also in clinical routine evaluation of patients admitted for cognitive impairment. Therefore, LP can be regarded as a feasible, moderately invasive test with a low risk for complications that can be included in the clinical diagnostic workup. In our view, CSF biomarkers might be especially important to be able to start treatment early in the course of the disease, when age-associated memory impairment and depressive pseudodementia are some of the most problematic differential diagnoses.35 In a recent study,36 we showed that the combination of CSF-tau and CSF-Ab42 also might help identify patients with MCI who will develop AD.

In summary, CSF biomarkers for AD so far have been studied in research settings under conditions providing data on their optimal performance. We evaluated the combination of CSF-tau and CSF-Ab42 prospectively in a community-based sample of patients, and ELISAs were run each week in clinical neurochemical routine. Also, under these conditions, these biomarkers have positive and negative predictive values for AD greater than 90% and therefore might have a role in the clinical workup of patients with cognitive impairment, especially to differentiate early AD from normal aging and psychiatric disorders such as depressive pseudodementia.

Accepted for publication July 5, 2000.

From the Department of Rehabilitation, Piteå River Valley Hospital, Piteå, Sweden (Dr Andreason); the Department of Psychiatry, Neuropsychiatric Clinic, Malmö University Hospital, Malmö, Sweden (Dr Minthon); the Department of Clinical Neuroscience, Unit of Neurochemistry, University of Göteborg, Sahlgren's University Hospital, Mölndal, Sweden (Drs Davidsson and Blennow); Innogenetics NV, Gent, Belgium (Drs Vanmechelen and Vanderstichele); the Section of Geriatric Medicine, Department of Clinical Neuroscience and Family Medicine, Karolinska Institute, Huddinge University Hospital, Stockholm, Sweden (Dr Winblad); and The Medical Research Council, Stockholm, Sweden (Dr Blennow). Dr Winblad is now with the Department of Clinical Neuroscience, Occupational Therapy and Elderly Care Research, Division of Geriatric Medicine, Karolinska Institute, Huddinge University Hospital, Stockholm.

This work was supported by grants 11560 and 12103 from the Swedish Medical Research Council, Stockholm; by Alzheimerfonden, Lund, Sweden; by Stiftelsen for Gamla Tjänarinnor, Stockholm, Sweden; by the Tore Nilssons Fond for Medicinsk Forskning, Stockholm; by the Norrbottens Läns Landstings FoU Fond, Luleå Sweden; by Svenska Läkare-sällskapet, Stockholm; and by Åke Wibergs Stiftelse, Stockholm.

We are grateful to everyone at the CSF Protein Section at the Neurochemistry Laboratory, University of...
REFERENCES


