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

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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 e4 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.

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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.

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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
(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 Aβ into SPs, with lower levels remaining in the CSF.

Several previous studies have found increased CSF-tau and reduced CSF-AB42 levels in AD. A large multicenter study 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, Andreason et al 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.

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 group (P = .001), MCI (P = .04), LBD (P < .001), and nondemented (P < .001) groups. An increase in CSF-tau levels was also found in the possible AD group compared with the LBD (P = .002), nondemented (P < .001), and VAD (P = .04) groups. No significant differences were found among the other diagnostic groups (Table 2).
There was a marked decrease in CSF-Aβ42 levels in the probable AD group compared with the VAD (P = .006), psychiatric disorders (P = .003), and nondemented (P < .001) groups. A decrease in the CSF-Aβ42 level was also found in the possible AD group compared with the psychiatric disorders (P = .02) and nondemented (P < .001) groups, in the MCI group compared with the nondemented group (P = .006), and in the LBD group compared with the nondemented group (P = .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 = −.10; P = .32) or CSF-Aβ42 (r = .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\textsuperscript{10} 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 nondemented 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...

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We evaluated the utility of the combination of CSF-tau and CSF-Aβ42 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-Aβ42 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 immunoassays. 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-Aβ42 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-Aβ42 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-Aβ42 levels in VAD were found in patients with the ApoE e4 allele, raising the question of whether these patients harbor...
bor concomitant AD pathologic findings. It is clear that studies with neuropathologically confirmed cases are needed to determine with certainty the sensitivity and specificity of CSF-tau and CSF-AB42 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 2. Cerebrospinal Fluid (CSF) Levels of tau and Aβ42 in the Diagnostic Groups*

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Patients, No.</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>46 (29-67)</td>
</tr>
<tr>
<td>MCI</td>
<td>20</td>
<td>517 ± 190</td>
<td>646 ± 260</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 β-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.

Figure 2. Individual values for cerebrospinal fluid tau and β-amyloid protein ending at amino acid 42 (Aβ42) in the different diagnostic groups. The cutoff line (Aβ42 = 240 + 1.18 × tau) is from a large multicenter study. Black circles and squares indicate patients possessing the ApoE ε4 allele.
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-Aβ42 level, also in agreement with results of a previous study, supporting the fact that a low CSF-Aβ42 level is not specific for AD and questioning the mechanism for the reduction of CSF-Aβ42 levels in AD, which has been suggested to be a consequence of deposition of the Aβ into SPs.

In the present study, we found high sensitivity for the combination of CSF-tau and CSF-Aβ42 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. 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, eg, parieto-temporal 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-Aβ42 values together with normal blood-brain barrier function and absence of pleocytosis or intrathecal immunoglobulin production) and other biochemical tools, eg, ApoE genotyping. As an analogy, the clinical diagnosis of myocardial infarction is based on the combination of clinical symptoms, electrocardiographic findings, and biochemical markers (eg, creatine kinase).

Furthermore, the effect of the lower specificity on the clinical usefulness of CSF-tau and CSF-Aβ42 might be overestimated because not all disorders in which abnormal levels of these biomarkers can be found are important (ie, difficult) differential diagnoses of AD, eg, acute stroke or human immunodeficiency virus dementia. Instead, CSF-tau and CSF-Aβ42 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. 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. In a recent study, we showed that the combination of CSF-tau and CSF-Aβ42 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-Aβ42 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.

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