The cerebrospinal fluid amyloid β_{42/40} ratio in the differentiation of Alzheimer’s disease from non-Alzheimer’s dementia

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Abstract

Background: Amyloid β40 (Aβ40) is the most abundant Aβ peptide in the brain. The cerebrospinal fluid (CSF) level of Aβ40 might therefore be considered to most closely reflect the total Aβ load in the brain. Both in Alzheimer’s disease (AD) and in normal aging the Aβ load in the brain has a large inter-individual variability. Relating Aβ42 to Aβ40 levels might consequently provide a more valid measure for reflecting the change in Aβ metabolism in dementia patients than the CSF Aβ42 concentrations alone. This measure may also improve differential diagnosis between AD and other dementia syndromes, such as vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD).

Objective: To investigate the diagnostic value of the CSF Aβ42/Aβ40 ratio in differentiating AD from controls, VaD, DLB and FTD.

Methods: We analysed the CSF Aβ42/Aβ40 ratio, phosphorylated tau181 and total tau in 69 patients with AD, 26 patients with VaD, 16 patients with DLB, 27 patients with FTD, and 47 controls.

Results: Mean Aβ40 levels were 2850 pg/ml in VaD and 2830 pg/ml in DLB patients, both significantly lower than in AD patients (3698 pg/ml; p<0.01). Aβ40 levels in AD patients were not significantly different from those in controls (4035 pg/ml; p=0.384). The Aβ42/Aβ40 ratio was significantly lower in AD patients than in all other groups (p <0.001, ANCOVA). Differentiating AD from VaD, DLB and non-AD dementia improved when the Aβ42/Aβ40 ratio was used instead of Aβ42 concentrations alone (p<0.01) The Aβ42/Aβ40 ratio performed equally well as the combination of Aβ42, phosphorylated tau181 and total tau in differentiating AD from FTD and non-AD dementia. The diagnostic performance of the latter combination was not improved when the Aβ42/Aβ40 ratio was used instead of Aβ42 alone.
Conclusion: The CSF Aβ42/Aβ40 ratio improves differentiation of AD patients from VaD, DLB and non-AD dementia patients, when compared to Aβ42 alone, and is a more easily interpretable alternative to the combination of Aβ42, p-tau and t-tau when differentiating AD from either FTD or non-AD dementia.

Key words: Abeta40 protein, Aβ42/Aβ40 ratio, Alzheimer’s disease, vascular dementia, dementia with Lewy bodies.
Introduction

While making an accurate diagnosis is important for management of dementia, differentiating between Alzheimer’s disease (AD) and other types of dementia using clinical criteria is the true clinical challenge: difficult and prone to inaccuracy. The NINCDS-ADRDA criteria for AD[1] have been validated against neuropathological standards and turned out to have a specificity of 23-69% for differentiating AD from other dementias.[2, 3]

Analysis of cerebrospinal fluid (CSF) has been used increasingly to differentiate the various dementia disorders.[4] Although CSF analysis of amyloid β42 (Aβ42), phosphorylated tau181 (p-tau181) and total tau (t-tau) is efficacious in distinguishing between AD dementia and non-demented controls, it is inaccurate in separating AD from other types of dementia.[5-7] CSF biomarker profiles of AD, vascular dementia (VaD), frontotemporal dementia (FTD), and dementia with Lewy bodies (DLB) overlap, which makes discrimination between these various dementias based on CSF analysis alone difficult.

It has been suggested that relating Aβ42 to the concentration of Aβ40 may improve diagnostic accuracy of CSF analysis.[8] Aβ40 is the most abundant Aβ peptide in human CSF, whereas Aβ42 accounts for only 10% of the total Aβ population.[6, 9-11] As such, CSF Aβ40 concentrations could be considered as the closest possible reflection of the total Aβ load in the brain. This total CSF Aβ load shows a large inter-individual variability.[12] Patients with a low total Aβ load and therefore a low CSF Aβ42 concentration[11], might receive an inappropriate diagnosis of AD if only CSF Aβ42 is considered and an absolute cut-off value is used. Similarly, in patients with AD but with a high total Aβ load, CSF Aβ42 concentrations may not decrease below the cut-off value and in those cases rejection of the diagnosis AD might be incorrect. Since the total Aβ concentration was found not to change in various dementia disorders,[8, 10, 13] and Aβ40 concentrations were shown to be similar in groups of AD patients, controls and non-AD dementia patients,[13-17] hypothetically the ratio of Aβ42 to Aβ40 reflects the Aβ changes in the brain more accurately than Aβ42 alone.
It was found in several studies that differentiation between AD and healthy controls, subjects with non-AD dementia, or subjects with other neurological disorders, improved when using the CSF Aβ_{42}/Aβ_{40} ratio compared to Aβ_{42} alone,[15, 17, 18] although these results were not confirmed in other studies.[19, 20] The Aβ_{42}/Aβ_{40} ratio has previously been studied in patients with FTD and AD, and a significantly decreased Aβ_{40} was found in FTD patients, resulting in an increased Aβ_{42}/Aβ_{40} ratio compared to AD patients.[21] In a recent review it was concluded that levels of CSF Aβ_{40} or Aβ_{42} cannot usefully discriminate between AD and DLB,[22] although one study found that the Aβ_{42}/Aβ_{40} ratio improved diagnostic accuracy of AD versus DLB relative to Aβ_{42} alone.[23] To our knowledge, the Aβ_{42}/Aβ_{40} ratio has not been investigated in relation to VaD.

We hypothesized that differentiation between dementia syndromes would improve by using the CSF Aβ_{42}/Aβ_{40} ratio since it may eliminate inter-individual differences in total Aβ load. Therefore, we explored the CSF Aβ_{40} concentration and Aβ_{42}/Aβ_{40} ratio in patients with AD, VaD, DLB, FTD and in controls, and we investigated the diagnostic value of the Aβ_{42}/Aβ_{40} ratio in differentiating AD from each of these groups individually as well as from the total group of non-AD dementia patients.
Materials and methods

Patients
Sixty-nine AD, 26 VaD, 27 FTD, and 16 DLB patients were included in this study that was based on the CSF database of the Alzheimer Centre of the Radboud University Nijmegen Medical Centre. This database contains clinical data as well as biobanked CSF and serum of consecutive patients. All patients or their legal representative had given informed consent for lumbar puncture. We included all patients with a clinically clear-cut dementia diagnosis, whose CSF was available for Aβ40 and Aβ42 analysis. Data on t-tau and p-tau181 were also obtained. A diagnosis was made by a multidisciplinary team, which consisted of a geriatrician, neurologist, neuropsychologist, and – if needed – an old-age psychiatrist. The panel used the accepted clinical diagnostic criteria, i.e. the NINCDS-ADRDA criteria for probable AD, the NINDS-AIREN criteria for probable VaD, the 1998 consensus on clinical diagnostic criteria for FTD and the 1996 consensus guidelines for the clinical and pathologic diagnosis of DLB [1, 24-26] In less than 10% of the cases, the clinicians were aware of the CSF results for Aβ42, p-tau181 and t-tau when establishing the clinical diagnosis, but they were never aware of Aβ20 levels.

The control group consisted of 47 non-demented patients who underwent lumbar puncture for various complaints. Most frequently diagnosed were headache (n=10), polyneuropathy (n=5), radiculopathy (n=4), vertigo (n=3), and delirium (n=2). The remaining controls had a variety of complaints but turned out not to have central neurological problems. CSF cell count, glucose, lactate, haemoglobin, bilirubin, total protein and oligoclonal IgG bands were normal in all controls. Patient characteristics are listed in table 1.

CSF
CSF was collected by lumbar puncture in polypropylene tubes, transported within 30 minutes to the adjacent laboratory at room temperature, centrifuged after routine investigations, and immediately aliquoted and stored at −80 °C until analysis. Levels of Aβ42, t-tau, and p-tau181 in CSF were measured using enzyme linked immunosorbent assays (Innogenetics NV, Gent, Belgium). Inter-assay
coefficients of variation for these assays were 3.8 – 8.4%.[27] CSF Aβ40 was analysed by using a commercial assay based on the Luminex technology (BioSource, Invitrogen Ltd, Paisley, UK). Inter-assay coefficient of variation for Aβ40 was 5.4% (at 2875 pg/ml; n=32). The lower limit of detection was for Aβ42 50 pg/ml and for Aβ40 22 pg/ml.

**Statistical analysis**

Since p-tau181, t-tau, Aβ42, Aβ40, and the Aβ42/Aβ40 ratio were not all normally distributed, they were log-transformed. Differences in p-tau181, t-tau, Aβ42, Aβ40 and the Aβ42/Aβ40 ratio were analysed using 2-way ANCOVA. Since sex and age did not contribute to the differences in Aβ42, Aβ40 and the Aβ42/Aβ40 ratio between dementia groups and controls, both (sex and age) were removed from the model and the ANCOVA was thereafter rerun. Differences between AD and the other groups were further explored using Dunnett’s post-hoc test.

We used logistic regression analysis to assess the value of the Aβ42/Aβ40 ratio compared to other combinations of CSF biomarkers in differentiating AD from controls, from VaD, FTD, DLB, respectively, and from these three groups combined (‘non-AD dementia’). Sex and age contributed significantly to the logistic regression models and therefore the models were corrected for these factors. Receiver operating characteristic (ROC) curves were calculated and the areas under the ROC curves were compared using MedCalc (Mariakerke, Belgium). Sensitivity and specificity were determined based on the highest Youden index, i.e. the point on the ROC curve at which sensitivity + specificity – 1 is maximized. All other statistical analyses were carried out using SPSS, version 16.0.
Results

The mean level of CSF Aβ40 was significantly lower in VaD patients than in AD patients (p<0.001), as well as in DLB patients compared to AD patients (p=0.008) (see Table 1 and Fig. (1)). There was no significant difference in Aβ40 levels between AD patients and FTD patients (p=0.981) or controls (p=0.384). In AD patients, the concentration of CSF Aβ42 was significantly lower than in VaD and FTD patients and controls (p<0.001), whereas the concentration of p-tau181 and t-tau was significantly higher than in all other groups (p<0.001). The Aβ42/Aβ40 ratio was significantly lower in AD patients than in all other groups (p <0.001) (see Table 1 and Fig. (1)).

We investigated the diagnostic value of the Aβ42/Aβ40 ratio in several comparisons. First, we investigated if the use of the Aβ42/Aβ40 ratio would be superior to the use of Aβ42 alone. Differentiation of AD from either VaD, DLB or non-AD dementia significantly improved when using the Aβ42/Aβ40 ratio (p<0.01). In contrast, differentiation of AD from either FTD or controls did not improve (p> 0.05). Second, we analysed the diagnostic value of the Aβ42/Aβ40 ratio compared to the combination of Aβ42/Aβ40 ratio p-tau181 and t-tau, which is a frequently used combination of CSF biomarkers in AD research. Differentiation of AD from either FTD or non-AD dementia was equally good for the Aβ42/Aβ40 ratio or the combination of Aβ42, p-tau181 and t-tau (p >0.05). Differentiation of AD from either controls, VaD or DLB was better using the combination of Aβ42, p-tau181 and t-tau than using the Aβ42/Aβ40 ratio (p<0.05). Third, we analysed if replacement of Aβ42 by the Aβ42/Aβ40 ratio in the combination with p-tau181 and t-tau would improve results. Differentiation of AD from both controls and from all dementia groups was equally good for both combinations (p >0.05). ROC curves are shown in Fig. (2) and Fig. (3). Sensitivity and specificity, AUC and likelihood ratios of each parameter are shown in Table 2.
Discussion

We explored the CSF Aβ_{40} concentrations in patients with different types of dementia and in controls, and examined the value the Aβ_{42}/Aβ_{40} ratio in differentiating AD from controls, from FTD, DLB, VaD, and from these latter three groups combined. The observed patterns of Aβ_{40} and Aβ_{42} in the various dementia groups are remarkable. As expected, the AD group was characterized by normal Aβ_{40} and low Aβ_{42} levels, but contrary to our expectations, the VaD group had low Aβ_{40} and intermediate Aβ_{42} levels, whereas the DLB group was characterized by low concentrations of both Aβ_{40} and Aβ_{42} levels. The FTD group had normal Aβ_{40} and Aβ_{42} levels.

Only one study has reported the CSF Aβ_{40} concentration in patients with VaD. In accordance with our results, a lower Aβ_{40} concentration in VaD patients compared to AD patients was found.[28] Multiple explanations for this low Aβ_{40} concentration are possible. For example, it may be caused by the ischemic damage that has occurred in VaD patients, since cerebral ischemia has been shown to result in plaque formation and accumulation of Aβ_{40} and Aβ_{42} [29-31] and, consequently, leads to a reduced CSF concentration. In addition, atherosclerosis, one of the risk factors for VaD, may inhibit the clearance of Aβ_{40} across the blood-brain barrier, leading to vascular deposits of Aβ_{40}.[32]

Our finding of a lower Aβ_{40} concentration in DLB patients compared to AD is in accordance with the literature.[12] Possibly, the intraneuronal α-synuclein aggregates that are found in DLB affect Aβ metabolism, leading to an overall decrease in Aβ synthesis. Results from in vitro research indicate an interaction between α-synuclein and Aβ.[33, 34] Neuropathological studies found a positive correlation between Aβ plaque burden and α-synuclein load.[35, 36] Aβ_{40} plaque level was greater in cases with α-synuclein aggregates compared to cases lacking α-synuclein aggregates, while no difference was found in Aβ_{42} plaque burden.[35] A greater Aβ_{40} plaque burden in DLB might explain the decreased Aβ_{40} concentration in CSF that we found.

The few studies that measured Aβ_{40} concentration in FTD patients report varying results. Our results are supported by previous findings of similar concentrations of Aβ_{40} in FTD patients and AD patients.[37] In contrast with this, another group reported lower Aβ_{40} concentrations in FTD patients.
compared to AD patients. The varying results might be explained by the inclusion of heterogeneous FTD patient groups in research, comprising patients with clinically diagnosed FTD, semantic dementia and primary progressive aphasia, presumably with different neuropathological substrates.

We investigated the Ap42/Ap40 ratio under the assumption that Ap40 closely represents the total cerebral Aβ load. Since we found different Ap40 concentrations in the various dementia groups, it can be debated if the Ap42/Ap40 ratio is a good representation of the Ap42 fraction of the total Aβ load and thus eliminates inter-individual differences in total Aβ concentrations. Nevertheless, differentiating AD from VaD, DLB and non-AD dementia improved when we used this ratio compared to Ap42 alone, probably due to the differences in Ap40 concentrations. Results obtained by applying the Ap42/Ap40 ratio fulfilled the criteria for biomarkers as established by the Working Group on molecular and biochemical markers of Alzheimer’s disease in differentiating AD from VaD, FTD, DLB, and non-AD, since both sensitivity and specificity were >80%.

The Ap42/Ap40 ratio seems to be a good alternative for the combination of Ap42, p-tau181 and t-tau, to distinguish AD from either FTD or non-AD dementia. The Ap42/Ap40 ratio has the advantage that only two analyses are needed instead of three, and, consequently, the results are easier to interpret. The differentiation of AD from non-AD dementia is a frequently encountered problem in clinical practice, when dementia can be established, but the differential diagnosis encompasses AD and another type of dementia. Thus, the use of the CSF Ap42/Ap40 ratio may help in this clinical decision making. However, the use of four biomarkers, i.e. the Ap42/Ap40 ratio combined with p-tau181 and t-tau, did not improve differentiation when compared to the combination of the three currently used biomarkers Ap42, p-tau181 and t-tau.

Some bias may have occurred in our analysis since in less than 10% of the patients the results of the CSF analysis for Ap42, t-tau and p-tau181 were known to the clinicians. However, given the small fraction of patients this applies to, we believe that this did not affect our results, also since our sensitivity and specificity results for discriminating AD from other dementias using Ap42 are comparable with the literature. The number of patients in our non-AD groups were moderate, yet not very different from the numbers mentioned in other studies.
the significant results that we found had a p-value <0.01, suggesting that these results are not expected to change with an increasing number of patients.

In summary, the $A\beta_{42}/A\beta_{40}$ ratio is more accurate for differentiating AD from other types of dementia than $A\beta_{42}$ alone, and can be a good and easier interpretable alternative for the combination of the established biomarkers $A\beta_{42}$, p-tau$_{181}$ and t-tau for the differentiation of AD from non-AD dementia, which may help to accept or refute the clinical diagnosis of AD.
Acknowledgements

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40 Riemenschneider M et al. Tau and Abeta42 protein in CSF of patients with frontotemporal
Table 1 Clinical characteristics and results of CSF analysis

<table>
<thead>
<tr>
<th></th>
<th>controls</th>
<th>AD</th>
<th>VaD</th>
<th>FTD</th>
<th>DLB</th>
</tr>
</thead>
<tbody>
<tr>
<td>males/females (n)</td>
<td>23/24</td>
<td>34/35</td>
<td>17/9</td>
<td>19/8</td>
<td>12/4</td>
</tr>
<tr>
<td>age (y)</td>
<td>61 ± 8</td>
<td>69 ± 8</td>
<td>72 ± 9</td>
<td>65 ± 7</td>
<td>76 ± 8</td>
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<td>disease duration (mo)</td>
<td>n.a.</td>
<td>29 ± 23</td>
<td>35 ± 29</td>
<td>34 ± 21</td>
<td>34 ± 27</td>
</tr>
<tr>
<td></td>
<td>n=60</td>
<td>n=20</td>
<td>n=26</td>
<td>n=8</td>
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<tr>
<td>t-tau (pg/ml)*</td>
<td>221 ± 80</td>
<td>710 ± 390</td>
<td>391 ± 526</td>
<td>448 ± 315</td>
<td>257 ± 98</td>
</tr>
<tr>
<td>p-tau181 (pg/ml)*</td>
<td>49 ± 16</td>
<td>111 ± 52</td>
<td>46 ± 16</td>
<td>70 ± 36</td>
<td>53 ± 17</td>
</tr>
<tr>
<td>Aβ42 (pg/ml)*</td>
<td>840 ± 260</td>
<td>428 ± 127</td>
<td>631 ± 270</td>
<td>786 ± 229</td>
<td>499 ± 179</td>
</tr>
<tr>
<td>Aβ40 (pg/ml)*</td>
<td>4035 ± 1177</td>
<td>3698 ± 1096</td>
<td>2850 ± 1031</td>
<td>3590 ± 1038</td>
<td>2830 ± 697</td>
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<tr>
<td>Aβ42/Aβ40 ratio*</td>
<td>0.21 ± 0.04</td>
<td>0.12 ± 0.04</td>
<td>0.23 ± 0.08</td>
<td>0.23 ± 0.06</td>
<td>0.18 ± 0.06</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD.

*, p-value <0.001 by ANOVA.

AD, Alzheimer disease; VaD, vascular dementia; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies; t-tau, total tau; p-tau181, phosphorylated tau181; n.a., not applicable
Table 2 Sensitivities and specificities, AUC and likelihood ratios for discriminating Alzheimer's disease from controls and from other types of dementia, using different combinations of CSF biomarkers

<table>
<thead>
<tr>
<th></th>
<th>AD vs controls</th>
<th>AD vs VaD</th>
<th>AD vs FTD</th>
<th>AD vs DLB</th>
<th>AD vs non-AD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sens. spec.</td>
<td>AUC</td>
<td>LR</td>
<td>sens. spec.</td>
<td>AUC</td>
</tr>
<tr>
<td>$\text{A} \beta_{42}$</td>
<td>93%</td>
<td>0.949</td>
<td>7.3</td>
<td>83%</td>
<td>0.785</td>
</tr>
<tr>
<td></td>
<td>87%</td>
<td></td>
<td></td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>$\text{A} \beta_{42}/\text{A} \beta_{40}$ ratio</td>
<td>93%</td>
<td>0.947</td>
<td>7.3</td>
<td>93%</td>
<td>0.900*</td>
</tr>
<tr>
<td></td>
<td>87%</td>
<td></td>
<td></td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>$\text{A} \beta_{42}$, p-tau, t-tau</td>
<td>97%</td>
<td>0.994$^\dagger$</td>
<td>45.6</td>
<td>93%</td>
<td>0.963$^\dagger$</td>
</tr>
<tr>
<td></td>
<td>98%</td>
<td></td>
<td></td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>$\text{A} \beta_{42}/\text{A} \beta_{40}$ ratio, p-tau, t-tau</td>
<td>93%</td>
<td>0.980</td>
<td>43.5</td>
<td>91%</td>
<td>0.957</td>
</tr>
<tr>
<td></td>
<td>98%</td>
<td></td>
<td></td>
<td>96%</td>
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</tbody>
</table>

AD, Alzheimer disease; VaD, vascular dementia; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies; non-AD, combined group of patients with VaD, FTD or DLB.

Sens., sensitivity; spec., specificity; AUC, area under the ROC curve; LR, likelihood ratio; n.c., not computable.

* $p<0.01$ compared to AUC for $\text{A} \beta_{42}$ level

$^\dagger$ $p<0.05$ compared to AUC for $\text{A} \beta_{42}/\text{A} \beta_{40}$ ratio
Figure 1 Cerebrospinal fluid $\text{A}\beta_{42}$ and $\text{A}\beta_{40}$ concentrations and $\text{A}\beta_{42}/\text{A}\beta_{40}$ ratio in controls and patients with various types of dementia

See text for statistical analyses.

Bold horizontal bar represents the median. Central box: 25th to 75th percentile (interquartile range).

Vertical bar bordered by highest and lowest value within 1.5 * interquartile range.

AD, Alzheimer disease; VaD, vascular dementia; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies
Figure 2 Receiver Operating Characteristic curves comparing $\text{A} \beta_{42}$, and the $\text{A} \beta_{42}/\text{A} \beta_{40}$ ratio in AD versus controls and versus various types of dementia.

AD, Alzheimer disease; VaD, vascular dementia; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies.
Figure 3 Receiver Operating Characteristic curves comparing the Aβ_{12}/Aβ_{42} ratio, the Aβ_{12}/Aβ_{40} ratio combined with p-tau_{181} and t-tau, and the combination of Aβ_{42}, p-tau_{181} and t-tau in AD versus controls and versus various types of dementia.

AD, Alzheimer disease; VaD, vascular dementia; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies.