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# Cerebrospinal Fluid Tau and Amyloid $\beta$ Proteins Do Not Correlate With Cognitive Functioning in Cognitively Impaired Memory Clinic Patients

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## ABSTRACT

**Objective:** The aim of this study was to investigate the influence of cerebrospinal fluid (CSF), amyloid  $\beta_{42}$  ( $A\beta_{42}$ ), phosphorylated tau<sub>181</sub> (p-tau), and total tau (t-tau) on cognitive functioning.

**Methods:** We analyzed the ability of the CSF biomarkers  $A\beta_{42}$ , p-tau, and t-tau to predict the results on the Cambridge Cognitive Examination–Revised (CAMCOG-R), a cognitive screening test that assesses multiple cognitive domains, in 65 memory clinic patients (73.1 $\pm$ 8.2 years) (n=30 probable Alzheimer’s disease [AD], n=7 possible AD, n=12 non-AD dementia, n=16 mild cognitive impairment).

**Results:** We found no correlations between CSF biomarkers and CAMCOG-R performance in the whole group, nor in subgroups based on

## FOCUS POINTS

- Cerebrospinal fluid (CSF)  $A\beta_{42}$ , p-tau, and t-tau do not correlate with cognitive functioning in a heterogeneous older population with cognitive impairment.
- Abnormal CSF biomarker concentrations may not reflect the absolute amount of neuronal damage, but merely serve as an indicator of AD pathology.
- Clinicians should be cautious that CSF biomarkers cannot be used in isolation to predict the severity of cognitive impairment.

aberrant biomarker concentrations.

**Discussion:** Changed concentrations of CSF amyloid  $\beta_{42}$ , p-tau, and t-tau cannot be directly linked to cognitive function in our sample of patients with cognitive impairment. Possibly, compensatory mechanisms such as cognitive reserve determine cognitive performance,

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rather than the absolute amount of damage caused by A $\beta$  deposition and tangle formation. In addition, abnormal CSF biomarker concentrations may not be a direct reflection of the amount of neuronal damage, but merely serve as an indicator of AD pathology.

**Conclusion:** While CSF biomarkers are valuable in establishing AD pathology, they cannot be used to predict severity of cognitive impairment.

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## INTRODUCTION

Cerebrospinal fluid (CSF) biomarkers amyloid  $\beta_{42}$  (A $\beta_{42}$ ), phosphorylated tau<sub>181</sub> (p-tau) and total tau (t-tau) concentrations are altered in Alzheimer's disease (AD) patients compared to controls. In other types of dementia and also in part of the patients with mild cognitive impairment (MCI), changes in these biomarker concentrations, although less specific, have been reported.<sup>1-3</sup> A $\beta$  is said to be neurotoxic,<sup>4</sup> while CSF tau and p-tau are suggested to reflect neurodegeneration.<sup>5</sup> Likely, pathological concentrations of these proteins induce or signal neuronal damage, resulting in cognitive impairment.

To date, research on the correlation between CSF biomarkers and cognitive functions shows contradicting results. In AD patients, inconsistent correlations between the Mini Mental State Examination (MMSE) and A $\beta_{42}$  have been reported.<sup>6-9</sup> A correlation between the MMSE and tau was often lacking,<sup>6,7</sup> but sometimes present.<sup>9</sup> The MMSE is a cognitive screening test that is easily applicable in clinical practice, but lacks sensitivity and specificity and may be biased by lack of correction for educational level.<sup>10,11</sup> This possibly explains these inconsistent results. A more extensive assessment of cognitive functioning may be a more valid approach to study the relation between CSF biomarkers and cognitive functioning. The few studies that have used such an extensive assessment again showed inconsistent results. In AD patients, a weak correlation between a paired-associate memory test and CSF p-tau and t-tau, but not A $\beta_{42}$ , has been reported,<sup>12</sup> while others failed to find a correlation between the CAMCOG, a cognitive measure that covers multiple domains, and CSF tau.<sup>13</sup> In a heterogeneous group of MCI and dementia patients (both AD and non-AD), a

correlation was found between false recognition and levels of CSF A $\beta_{42}$ , but not t-tau.<sup>14</sup>

We aimed to investigate the influence of CSF A $\beta_{42}$ , p-tau, and t-tau concentrations on cognitive functioning. We hypothesized that changes in these CSF biomarkers reflect neuronal damage and directly underlie cognitive impairment. Therefore, we expect a correlation between CSF biomarkers and cognitive performance, irrespective of the clinical diagnosis. To test this hypothesis, we retrospectively investigated a heterogeneous group of memory clinic outpatients, using the CAMCOG-R as a multiple-domain cognitive assessment.

## METHODS

This retrospective study used the database of the memory clinic of the Radboud University Nijmegen Medical Centre/Alzheimer Centre Nijmegen. We included all outpatients who visited our memory clinic between 2005 and October 2009 and underwent lumbar puncture as part of their diagnostic work up. All patients had a diagnosis of either MCI or a type of dementia (note that no lumbar punctures have been performed in participants without impairment on cognitive screening tests at admission to the memory clinic). We used the Revised Cambridge Cognitive Examination (CAMCOG-R) as a measure of cognitive functioning.<sup>15</sup> Its score ranges from 0–104, with a higher score indicating a better performance. Cut-off scores adjusted for age and education level have been established. Performance can be divided into a memory and a non-memory section (maximum score 37 and 67, respectively). These sections have been shown to discriminate between normal aging and early AD.<sup>16</sup> Time between lumbar puncture and CAMCOG-R had to be <3 months. CSF was collected in polypropylene tubes, transported at room temperature to the adjacent laboratory within 30 minutes, centrifuged after routine investigations, and immediately aliquoted and stored at -80 °C until analysis. Levels of A $\beta_{42}$ , t-tau, and p-tau in CSF were measured using enzyme linked immunosorbent assays (Innogenetics, Ghent, Belgium).

Sixty-five patients (32 males) were included. Of these, 30 were eventually diagnosed with probable AD and 7 with possible AD according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria,<sup>17</sup> 16 were diagnosed with MCI according to the criteria of the

International Working Group on Mild Cognitive Impairment,<sup>18</sup> and 12 with another type of dementia (5 vascular dementia, 2 frontotemporal dementia, 3 dementia with Lewy bodies, 2 dementia of unknown cause) (Table 1). Mean age ( $\pm$ SD) was 73.1 ( $\pm$ 8.2) years.

We used linear regression to examine the relation between CSF biomarkers and the performance on the CAMCOG-R. As dependent variable we used the CAMCOG-R score, related to the cut-off value, since this cut-off is adjusted for age and education. This relative score was calculated using the following formula: total score/cut-off  $\times$  100, and: (non-)memory score  $\times$  (cut-off/maximum score).  $A\beta_{42}$ , p-tau, and t-tau concentrations were not normally distributed and were log-transformed. Analyses were corrected for sex. Primary analyses included the total sample of 65 patients, predicting the CAMCOG-R total score and the scores on the memory and non-memory sections using CSF biomarkers. For secondary analyses, we divided the sample into subgroups based on their biomarker results to increase the likelihood of a neurodegenerative disorder being present. We used previously established cut-off values<sup>2</sup> (Table 2) and reran our linear regression models. We did not use the clinical diagnoses for subgroup analyses, since both CAMCOG-R and results of CSF analyses may have influenced the diagnostic decision making, whereas CSF biomarker concentrations

are an objective measure and therefore subgroup analyses based on these concentrations are more likely to yield valid results.

## RESULTS

The Figure shows the correlation between each of the CSF biomarkers and the total CAMCOG-R score. In the total sample including all 65 patients, neither CSF  $A\beta_{42}$ , p-tau, t-tau, nor the p-tau/ $A\beta_{42}$  ratio was a significant predictor of the total score on the CAMCOG-R. Using the memory score and non-memory score as dependent variables in the linear regression model did not change these results.

With respect to the secondary analyses, only three models of the 36 models tested showed a statistically significant outcome. First, in the group with an aberrant  $A\beta_{42}$  concentration, a higher  $A\beta_{42}$  was related to a higher total CAMCOG-R score (B 34.8,  $P=.040$ ). Second, in the group with an aberrant p-tau concentration, a higher t-tau was related to a lower total CAMCOG-R score (B -24.9,  $P=.015$ ). Last, in the group with an aberrant t-tau concentration, a higher t-tau was related to a lower non-memory score (B -5.9,  $P=.046$ ). All other secondary analyses ( $k=33$ ) were not significant (data not shown).

## DISCUSSION

We investigated the correlation between CSF

**TABLE 1.**  
**Characteristics of Total Sample and of Subgroups Based on Clinical Diagnosis**

|                                  | <i>Total Sample</i> | <i>Probable AD</i> | <i>Possible AD</i> | <i>Other Types of Dementia</i> | <i>MCI</i>     |
|----------------------------------|---------------------|--------------------|--------------------|--------------------------------|----------------|
| Male/Female                      | 32/33               | 11/19              | 4/3                | 6/6                            | 11/5           |
| Age (years)                      | 73.1 $\pm$ 8.2      | 71.5 $\pm$ 8.8     | 74.3 $\pm$ 8.5     | 76.1 $\pm$ 7.5                 | 73.1 $\pm$ 7.5 |
| Years of education               | 10.6 $\pm$ 3.8      | 10.4 $\pm$ 3.9     | 12.0 $\pm$ 4.2     | 11.9 $\pm$ 4.3                 | 9.6 $\pm$ 2.8  |
| MMSE                             | 21.3 $\pm$ 5.2      | 19.2 $\pm$ 3.9     | 23.6 $\pm$ 6.5     | 19.7 $\pm$ 6.2                 | 25.7 $\pm$ 2.9 |
| CAMCOG-R total                   | 67.9 $\pm$ 15.8     | 60.5 $\pm$ 11.7    | 73.6 $\pm$ 18.4    | 64.3 $\pm$ 18.8                | 82.0 $\pm$ 7.7 |
| CAMCOG-R memory                  | 20.2 $\pm$ 6.8      | 17.0 $\pm$ 4.8     | 22.4 $\pm$ 8.4     | 20.4 $\pm$ 7.7                 | 25.2 $\pm$ 5.5 |
| CAMCOG-R non-memory              | 47.7 $\pm$ 10.7     | 43.5 $\pm$ 8.9     | 51.1 $\pm$ 11.6    | 43.8 $\pm$ 12.4                | 56.8 $\pm$ 5.2 |
| CSF $A\beta_{42}$ (pg/ml)        | 571 $\pm$ 225       | 514 $\pm$ 210      | 506 $\pm$ 66       | 636 $\pm$ 232                  | 657 $\pm$ 264  |
| CSF t-tau (pg/ml)                | 570 $\pm$ 399       | 706 $\pm$ 464      | 739 $\pm$ 340      | 334 $\pm$ 214                  | 416 $\pm$ 250  |
| CSF p-tau <sub>181</sub> (pg/ml) | 91 $\pm$ 47         | 110 $\pm$ 52       | 110 $\pm$ 27       | 55 $\pm$ 30                    | 75 $\pm$ 33    |

Values are expressed as means $\pm$ SD.

AD=Alzheimer's disease; MCI=mild cognitive impairment; MMSE=Mini Mental State Examination; CAMCOG-R=Cambridge Cognitive Examination-Revised; CSF=cerebrospinal fluid;  $A\beta_{42}$ =amyloid  $\beta_{42}$ ; t-tau=total tau; p-tau<sub>181</sub>=phosphorylated tau<sub>181</sub>.

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biomarkers and cognitive functioning as measured with an extensive cognitive screening instrument that covers all major cognitive domains. We did not find such a correlation in a heterogeneous group of patients with cognitive impairment. Secondary analyses in subgroups characterized by abnormal biomarker profiles did not convincingly change this finding.

Our results are in agreement with previous research that reported no correlation between the CAMCOG and CSF tau in AD patients.<sup>13</sup> However, we did not replicate previously reported findings between CSF biomarkers and memory function.<sup>12,14</sup> Memory function is validly assessed by the memory section of the CAMCOG-R,<sup>16</sup> indicating that a correlation, if present, should have been detected in our study. Moreover, it is remarkable that previous studies found correlations in the same cognitive domain but with different CSF biomarkers. That is, one found a correlation with p-tau and t-tau, but not with A $\beta_{42}$ ,<sup>12</sup> while another found a correlation with A $\beta_{42}$ , but not with tau.<sup>14</sup> It is difficult to explain this discrepancy; it is unlikely that this discrepancy can be attributed to differences in

patient samples—only AD patients, versus a heterogeneous group of MCI and dementia patients. Furthermore, this cannot explain why we did not find a correlation with A $\beta_{42}$  in our heterogeneous group. In addition, a large number of tests and analyses have been performed in these previous studies that had not been corrected for multiple comparisons. The reported correlations were weak to moderate at best and in one study possibly driven by a cluster of patients with extreme values of p-tau and t-tau.<sup>12</sup> Consequently, it is possible that these previous findings are the result of a Type I error (ie, false positive results).

We hypothesized that changes in A $\beta_{42}$  and p-tau and t-tau, as measured in CSF, would reflect neuronal damage leading to impaired cognitive functioning. The present findings indicate that these changed concentrations in CSF cannot be directly linked to cognitive functioning. There are several explanations for this. First, it may not only be the absolute amount of damage caused by A $\beta$  deposition and tangle formation that determines cognitive performance, but also compensatory mechanisms, such as inter-individual differences

**TABLE 2.**  
**Characteristics of Subgroups Based on CSF Biomarker Results**

|                                  | <i>Aberrant A<math>\beta_{42}</math>*</i> | <i>Aberrant p-tau<sub>181</sub>*</i> | <i>Aberrant t-tau*</i> | <i>All 3 Biomarkers Aberrant*</i> |
|----------------------------------|---|--------------------------------------|------------------------|-----------------------------------|
| <b>Diagnoses</b>                 |   |                                      |                        |                                   |
| Probable AD                      | 19  | 17                                   | 23                     | 13                                |
| Possible AD                      | 3   | 6                                    | 6                      | 3                                 |
| Other dementia                   | 4   | 2                                    | 4                      | 1                                 |
| MCI                              | 7   | 6                                    | 8                      | 4                                 |
| Male/Female                      | 14/19                                     | 16/15                                | 21/20                  | 10/11                             |
| Age (years)                      | 71.3 $\pm$ 8.0                            | 71.8 $\pm$ 8.4                       | 71.7 $\pm$ 8.0         | 70.5 $\pm$ 8.8                    |
| Years of education               | 11.3 $\pm$ 3.9                            | 10.8 $\pm$ 3.9                       | 10.9 $\pm$ 3.8         | 11 $\pm$ 3.9                      |
| MMSE                             | 20.8 $\pm$ 5.5                            | 21.3 $\pm$ 6.0                       | 21.2 $\pm$ 5.7         | 20.9 $\pm$ 6.1                    |
| CAMCOG-R total                   | 65.6 $\pm$ 16.4                           | 68.3 $\pm$ 17.5                      | 68.2 $\pm$ 16.6        | 67.1 $\pm$ 17.6                   |
| CAMCOG-R memory                  | 19.5 $\pm$ 6.4                            | 20.2 $\pm$ 7.0                       | 19.6 $\pm$ 7.0         | 19.7 $\pm$ 7.0                    |
| CAMCOG-R non-memory              | 46.4 $\pm$ 11.5                           | 48.2 $\pm$ 11.8                      | 48.6 $\pm$ 11.0        | 47.4 $\pm$ 11.9                   |
| CSF A $\beta_{42}$ (pg/ml)       | 410 $\pm$ 73                              | 478 $\pm$ 132                        | 515 $\pm$ 185          | 412 $\pm$ 70                      |
| CSF t-tau (pg/ml)                | 659 $\pm$ 415                             | 881 $\pm$ 366                        | 771 $\pm$ 374          | 876 $\pm$ 359                     |
| CSF p-tau <sub>181</sub> (pg/ml) | 103 $\pm$ 50                              | 131 $\pm$ 36                         | 116 $\pm$ 42           | 132 $\pm$ 36                      |

\*Values are expressed as means $\pm$ SD. Aberrant A $\beta_{42}$ : <500 pg/ml; aberrant p-tau<sub>181</sub>: >85 pg/ml; aberrant t-tau: >350 pg/ml.

AD=Alzheimer's disease; MCI=mild cognitive impairment; MMSE=Mini Mental State Examination; CAMCOG-R=Cambridge Cognitive Examination-Revised; CSF=cerebrospinal fluid; A $\beta_{42}$ =amyloid  $\beta_{42}$ ; t-tau=total tau; p-tau<sub>181</sub>=phosphorylated tau<sub>181</sub>.

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in cognitive reserve. Plaques and tangles have indeed been found in individuals with no signs of cognitive impairment during life,<sup>19</sup> suggesting that these individuals could somehow compensate for the neuronal damage induced by the plaques and tangles. Moreover, it has been shown that plaque burden is a poor correlate of cognitive status at the time of death.<sup>20</sup>

Alternatively, abnormal CSF biomarker concentrations may not be a direct reflection of neuronal damage, but merely serve as an indicator of AD pathology. For example, in prodromal AD (ie, patients with MCI who developed AD at follow-up), aberrant concentrations of CSF biomarkers have been found.<sup>3,21</sup> Furthermore, in patients with established dementia, concentrations of CSF biomarkers remained stable during follow-up, while cognitive performance deteriorated.<sup>22-24</sup> A correlation between CSF A $\beta_{42}$  and post-mortem plaque burden has been reported to be present<sup>25</sup> as well as absent.<sup>26</sup>

In AD, it has been hypothesized that amyloid deposition reaches a plateau before clinical symptoms are apparent.<sup>5,27</sup> Increased tau is suggested to develop later and to continue to increase during disease progression.<sup>5</sup> According to this model, one would not expect a correlation between A $\beta_{42}$  and cognitive functioning in AD patients, but one would expect a correlation between p-tau and t-tau and cognitive functioning in AD patients, regardless of causality. To prevent ourselves from merely finding a correlation between two features of one disease, we examined a heterogeneous group of patients with cognitive impairment. We did not find a correlation between CSF biomarkers and cognitive functioning, showing that CSF biomarkers do not directly underlie cognitive impairment in a concentration-dependent way.

## CONCLUSION

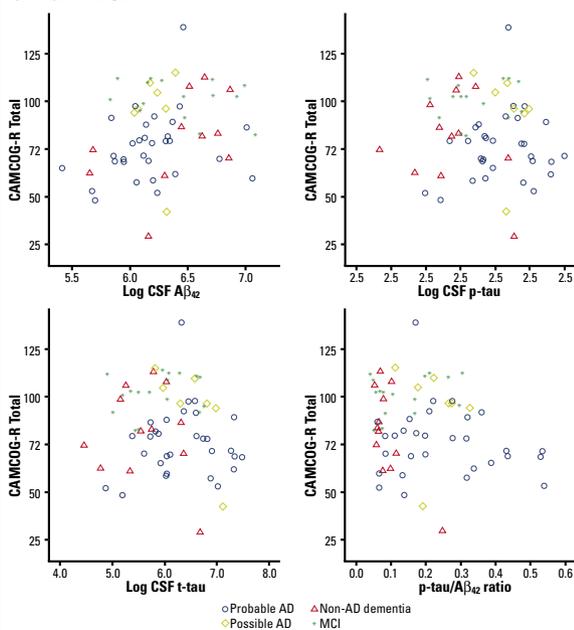
Concentrations of CSF amyloid  $\beta_{42}$ , p-tau, and t-tau have no clear relationship with cognitive functioning once cognitive decline has started. Severe cognitive impairment can be present in the absence of biomarker abnormality, and vice versa. Cognitive performance may be determined by other factors than the absolute amount of damage the brain has suffered, such as cognitive reserve. In addition, abnormal CSF biomarker concentrations may not reflect the amount of neuronal damage, but merely serve as an indicator of Alzheimer's disease. Clinicians should be cautious that CSF biomarkers can be valuable in establishing AD pathology, but they cannot be used to predict severity of cognitive impairment. Future studies on the relation between cognitive function and CSF biomarkers should focus on the rate of cognitive decline over time. **CNS**

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### FIGURE.

#### Scatter plots of CSF biomarkers versus total CAMCOG-R score (adjusted for age and education) in patients with probable AD, possible AD, non-AD dementia and MCI



CSF=cerebrospinal fluid; CAMCOG-R=Cambridge Cognitive Examination-Revised; AD=Alzheimer's disease; MCI=mild cognitive impairment; MMSE=Mini Mental State Examination; A $\beta_{42}$ =amyloid  $\beta_{42}$ ; t-tau=total tau; p-tau<sub>181</sub>=phosphorylated tau<sub>181</sub>.

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