Increased total tau (t-tau) protein levels and phosphorylated at threonine 181 tau (p-tau) levels were consistently found in the cerebrospinal fluid (CSF) of patients with mild cognitive impairment (MCI) compared to controls (for review see [3,20]). These findings are associated with slight atrophic changes in MCI within the medial temporal lobe which are closely correlated with declarative memory deficits characteristic for this condition [3,15,19]. Moreover, the neurobiological changes are generally considered to predict conversion of MCI to manifest Alzheimer’s disease (AD). Though MCI often overlaps with depressive symptoms making early diagnosis difficult, to date no CSF marker has been probed to support the differential diagnosis of geriatric major depressive disorder and MCI eventually converting to AD. Therefore, CSF t-tau and p-tau levels were compared between patients with MCI, geriatric major depressive disorder, and cognitively healthy controls. We expected that (i) cross-sectionally, MCI patients would show higher t-tau and p-tau levels compared to patients with geriatric major depressive disorder and controls; and (ii) that this finding would be more pronounced in those MCI patients who convert to AD during follow-up.

Data from 134 patients and 24 controls consecutively recruited through the Section of Geriatric Psychiatry were included (P.S., J.P., E.K., P.T.). All patients and controls had at least eight years of education and were older than 50 years. Eighty patients met MCI criteria according to aging-associated cognitive decline (AACD) [12] comprising: (i) subjective complaints; (ii) deficits in memory and learning, attention, and concentration, abstract thinking (problem solving, abstraction), language, or visuospatial functioning, as established by neuropsychological testing; (iii) normal activities of daily living. Moreover, other conditions sufficient to explain the respective cognitive deficits were excluded by thorough medical and psychiatric examination as described elsewhere [18]. Fifty-four
patients fulfilled DSM-IV diagnostic criteria for major depressive disorder [1]. Thirty-seven patients had a recurrent major depressive disorder while 17 presented with the first depressive episode. All patients with major depressive disorder were treated with antidepressants; 22 patients additionally received neuroleptic treatment. Exclusion criteria were dementia, alcohol or substance abuse, or previous electro-convulsive therapy. Patients were reassessed after a follow-up period of at least 12 months. Conversion to manifest AD was diagnosed based on clinical judgment particularly taking into account evidence of a significant impairment in any activity of daily living, corresponding to a clinical dementia rating score of more than 0.5.

Diagnoses were object to a clinical consensus diagnostic conference under supervision of a board certified geriatric psychiatrist (P.S, J.P., or J.S.) on basis of all relevant information including history, clinical examination, laboratory findings, neuropsychological, and neuroradiological but not t-tau nor p-tau values. The modified Hachinski ischemic score [13] of patients and controls was less than three; the severity of cognitive deficits was assessed on the Mini Mental State Examination (MMSE) [8].

The control group consisted of 24 individuals without cognitive impairment, psychiatric or neurological diseases from whom CSF samples were obtained during spinal anesthesia after thorough neuropsychological testing as described elsewhere [16]. In all patients lumbar puncture was performed between 10 and 12 am, as part of the routine diagnostic procedure. CSF samples were immediately aliquoted into non-absorbent tubes, frozen at −80 °C, and stored in polypropylene tubes until examination. T-tau and p-tau levels were determined using the INNOTEST-hTau-Ag-kit and the INNOTEST-Phospho-Tau(181P)-kit (Innogenetics, Ghent, Belgium) as described elsewhere [16]. For data analysis, we calculated one-way ANOVA with Duncan’s post hoc test for age, MMSE, CSF t-tau and CSF p-tau protein concentration as well as Pearson’s correlation coefficients. To test the predictive accuracy, positive predictive value and negative predictive value of t-tau and p-tau a logistic regression analysis was performed. The study was approved by the Ethical Committee of the University of Heidelberg.

Diagnostic groups (Table 1) differed significantly in MMSE scores ($F = 26.8, df = 2, 156, p < 0.0001$), CSF t-tau ($F = 26.9, df = 2, 156, p < 0.0001$), and CSF p-tau levels ($F = 26.4, df = 2, 156, p < 0.0001$) and age ($F = 3.3, df = 2, 156, p < 0.05$). According to a Duncan’s test on the 5%-level the MCI patients had significantly lower MMSE scores than the depressed who scored significantly lower on the MMSE than the controls. Moreover, the MCI patients showed significantly higher CSF t-tau and p-tau concentrations than both patients with depression and controls and were significantly older when compared to the controls, but these findings remained significant when age was partialed out as a covariate (t-tau: $F = 27.6, df = 3, 155, p < 0.0001$; p-tau: $F = 27.4, df = 3, 155, p < 0.0001$).

At follow-up, 23 (29%) MCI patients had developed AD (converters) while 57 did not convert to AD (non-converters) (Table 1). Converters presented with the highest CSF t-tau levels at baseline ($F = 33.1, df = 3, 155, p < 0.0001$) followed by the non-converters, while both differed significantly from controls and from patients with depression (Fig. 1). The same pattern of significant differences ($F = 24.4, df = 3, 155, p < 0.0001$) applied for p-tau protein levels (Fig. 2). Though the converters were significantly ($F = 3.5, df = 3, 155, p < 0.05$) older (72.0 ± 7.8

<table>
<thead>
<tr>
<th>Controls</th>
<th>Geriatric major depressive disorder</th>
<th>MCI total</th>
<th>MCI Non-converter</th>
<th>Converter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients no.</td>
<td>24</td>
<td>54</td>
<td>80</td>
<td>57</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>11/13</td>
<td>23/31</td>
<td>40/40</td>
<td>31/26</td>
</tr>
<tr>
<td>Age, y</td>
<td>65.3 ± 7.2</td>
<td>66.6 ± 8.2</td>
<td>69.3 ± 7.8</td>
<td>68.2 ± 7.6</td>
</tr>
<tr>
<td>MMSE score</td>
<td>29.3 ± 0.8</td>
<td>27.4 ± 1.9</td>
<td>26.6 ± 1.6</td>
<td>26.9 ± 1.6</td>
</tr>
<tr>
<td>Total tau (pg/ml)</td>
<td>230.8 ± 72.9</td>
<td>210.3 ± 79.3</td>
<td>406.0 ± 215.0</td>
<td>343.2 ± 175.6</td>
</tr>
<tr>
<td>p-tauThr181 (pg/ml)</td>
<td>49.7 ± 9.4</td>
<td>40.6 ± 14.8</td>
<td>66.9 ± 26.2</td>
<td>61.3 ± 23.7</td>
</tr>
</tbody>
</table>

MMSE: mini mental state examination; MCI: mild cognitive impairment.

Significant according to a Duncan’s test at the 5% level:

a MCI > controls (converter > non-converter, geriatric major depressive disorder, controls).
b MCI < geriatric major depressive disorder < controls (converter < non-converter, geriatric major depressive disorder < controls).
c geriatric major depressive disorder, controls < MCI (geriatric major depressive disorder, controls < non-converter < converter).
d geriatric major depressive disorder, controls < MCI (geriatric major depressive disorder, controls < non-converter < converter).

Fig. 1. CSF total-tau protein concentrations (pg/ml). Results of a Duncan’s test at the 5% level: geriatric major depression, controls < non-converters < converters.
years) than non-converters (68.2 ± 7.6 years), patients with geriatric major depressive disorder (66.6 ± 8.2 years), and controls (65.3 ± 7.2 years), these findings remained significant when age was partialled out as a covariate (t-tau: \( F = 34.4, df = 3, 155, p < 0.0001 \); p-tau: \( F = 25.0, df = 3, 155, p < 0.0001 \)).

In the MCI group, CSF t-tau and p-tau levels were significantly intercorrelated \((r = 0.9, p < 0.0001)\). MMSE scores were inversely correlated with t-tau \((r = -0.3, p < 0.05)\) but not p-tau levels \((r = -0.2, p = 0.09)\). Moreover, age was significantly correlated with p-tau \((r = 0.3, p < 0.05)\) but not t-tau levels \((r = 0.2, p = 0.07)\).

In a logistic regression model of AD conversion \((n = 158)\) the predictive accuracy, positive predictive value, and negative predictive value for t-tau (p-tau) were 86% (84%), 53% (40%), and 90% (87%), respectively.

Our study revealed two major findings: (i) CSF t-tau and p-tau levels were significantly increased in patients with mild cognitive impairment when contrasted to patients with geriatric major depressive disorder and controls; and (ii) these findings may also help to predict the clinical course of MCI.

Increased CSF t-tau and p-tau levels are typically found in manifest AD and differentiate this condition from geriatric major depressive disorder. That this finding also applies for the preclinical phase of the disorder \([4,16]\) is further supported by our observation of increased t-tau and p-tau levels in MCI compared to both patients with geriatric major depressive disorder and controls. Patients with depression could be clearly separated from the MCI subjects on basis of t-tau and p-tau levels indicating that the latter facilitate the differentiation between preclinical AD and geriatric major depressive disorder.

The conversion rate of 29% found in the present sample is well in the range reported in the literature. In a large population based study, Busse et al. \([5]\) reported a conversion rate of app. 20% during the first 18 month follow-up interval which decreased to about 10% at each further point of assessment. The hypothesis that the risk of conversion to dementia may be state-dependent is indirectly corroborated by the present finding of the highest t-tau and p-tau values in those MCI patients in whom symptoms actually progressed to manifest AD. Already at baseline, the respective values obtained in these converters were well in the range of those typically observed in patients with manifest AD whereas those measured in non-converters took an intermediate position between converters and patients with depression or controls. A similar pattern of findings with the highest t-tau and p-tau values characterizing a subgroup of patients with MCI at especially high risk of developing AD was recently described in two longitudinal studies \([10,11]\). In addition, the fact that converters were slightly older than the non-converters indicates that in the latter the risk of progression may gradually increase with chronological age as the condition progresses. This process should be accompanied by a slow increase of t-tau and p-tau values \([6]\) as suggested by the low but significant correlations between age, MMSE scores and the respective measures reported in this and other studies \([16]\). Taken together, these findings support the notion that MCI involves an increased risk of developing AD \([3]\) and raise the question if those MCI patients who did not convert to dementia during follow-up are nonetheless at an increased risk of developing AD in the later course.

Differences in medication status have to be considered as potential confounding variables, since the patients with depression were receiving antidepressants at time of investigation. However, previous studies of our group did not reveal effects of psychotropic medication on t-tau and p-tau levels \([16,17]\). Increased t-tau levels are unspecific as such and may occur in any condition involving neural degeneration. Hence, increased t-tau levels can also be used to predict outcome in traumatic brain injury \([14]\). Decreased \(\beta\)-amyloid\(1-42\) concentrations are generally regarded to be more closely related to AD since \(\beta\)-amyloid\(1-42\) plays a central role in the pathogenesis of the disorder \([3,7]\). A population based study \([9]\) found decreased \(\beta\)-amyloid\(1-42\) but not t-tau or p-tau concentrations to predict cognitive decline in otherwise healthy elderly women. \(\beta\)-amyloid\(1-42\) levels were related to the age at manifestation in familial AD \([7]\) and were predictive for progression of MCI to AD in the longitudinal studies \([10,11]\) cited above. Moreover, the combination CSF tau and \(\beta\)-amyloid\(1-42\) measurements may improve diagnostic accuracy \([2]\), and combined analysis of CSF tau protein and \(\beta\)-amyloid\(1-42\) is warranted in further studies.

Taken together our results emphasize the use of CSF tau protein analysis in the early and differential diagnosis of AD. Future studies should include longitudinal investigation of CSF tau in order to learn more about the course of neurodegeneration in those individuals who eventually convert to dementia. It might be hypothesized that the dynamic of CSF tau changes can provide additional information to improve the sensitivity and specificity of preclinical AD diagnosis.

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References


