Cerebrospinal fluid tau levels in Alzheimer’s disease are elevated when compared with vascular dementia but do not correlate with measures of cerebral atrophy

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Abstract

Increased tau levels are a well-established finding in Alzheimer’s disease (AD). In contrast, the potential value of tau levels in the differential diagnosis of AD, vascular dementia (VD) and major depression warrants further investigation. The potential impact of psychotropic medication also needs to be established. We investigated cerebrospinal fluid (CSF) tau protein concentrations in 88 patients with AD, 23 patients with VD, 25 patients with major depression and 17 age-paralleled controls without cognitive impairment with respect to important clinical variables, type and dosage of psychotropic medication and cerebral changes as assessed by magnetic resonance imaging (MRI). The AD patients showed significantly elevated tau levels compared with patients with VD or major depression and controls. Tau levels obtained in the VD group were intermediate, with significant differences from both AD patients and patients with major depression and controls. Within the AD group, no significant correlation between tau levels, severity of dementia, age, duration of disease, type and dosage of psychotropic medication or MRI volumetric changes arose. A subgroup of AD patients without increased tau levels was characterized by a significantly larger percentage of patients with presenile onset.  

Keywords: Dementia; Differential diagnosis; CSF tau; Volumetric MRI

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1. Introduction

Tau is a microtubule-associated protein that is released into the cerebrospinal fluid (CSF) during neurofibrillary tangle formation in Alzheimer’s disease (AD). It is a protein with an apparent molecular mass of 46 kDa, measurable by enzyme-linked immunosorbent assay (ELISA) in the CSF. Recent studies found significantly increased CSF tau levels in patients with AD in comparison with healthy controls (Hulstaert et al., 1999; Andreasen et al., 1999; Kahle et al., 2000). This finding also applied to patients with mild cognitive impairment or mild AD and was not correlated with age, duration of dementia or gender. Furthermore, increased tau levels have been found in AD compared with vascular dementia (VD) (Blennow et al., 1995; Tato et al., 1995; Mori et al., 1995; Arai et al., 1998; Mecocci et al., 1998); this finding has been confirmed by most but not all studies.

Little is known about the potential effects of psychotropic medication on tau concentrations or the potential relation between tau levels and cerebral atrophy. Potential medication effects were mainly investigated for beta amyloid 1–40 and 1–42 levels (Schröder et al., 1997); with respect to cerebral changes, one may expect tau levels to be correlated with measures of hippocampal atrophy, which is generally considered to be a surrogate marker for AD-related brain pathology (Pantel et al., 1997, 1998; Schröder and Pantel, 1999).

In the present study, we investigated the potential value of tau levels in the differential diagnosis of AD, VD and major depression. Within the AD patients, tau levels were analyzed with respect to some important clinical characteristics of the disease as well as potential medication effects. In a second step, a subgroup of AD patients with tau levels in the normal range was identified.

2. Methods

Eighty-eight patients (57 females and 31 males) with probable (n = 38) and possible (n = 50) AD (NINCDS-ADRSA criteria; McKhann et al., 1984), 23 patients with probable VD (NINDS-AIREN criteria; Roman et al., 1993) and 25 patients with major depression (DSM-III-R criteria; American Psychiatric Association, 1987) were included. The VD patients showed focal signs on neurological examination and/or evidence of relevant cerebrovascular changes on brain imaging (computed tomography or magnetic resonance imaging). Patients were consecutively admitted inpatients under the care of the Section of Geriatric Psychiatry, University of Heidelberg. The Hachinski Ischemic Score modified by Loeb and Gandolf (1983) of the AD patients was below 3. Patients with onset before age 65 years were defined as suffering from AD with presenile onset (n = 23). Clinical diagnosis was based on all relevant information, including history, clinical examination, and neuropsychological and neuroradiological findings. At the time of investigation, all patients were free of choline esterase inhibitors. Patients with major depression were carefully screened for any indication of dementia by repeated clinical and thorough neuropsychological examinations. The control group consisted of 17 individuals without cognitive impairment or psychiatric disease, paralleled to the patients in age and gender. CSF samples were obtained from the controls during spinal anaesthesia at the Department of Anaesthesia, University Hospital Heidelberg. The degree of cognitive impairment was rated on the Mini-Mental State Examination (MMSE; Folstein et al., 1975). In all patients, lumbar puncture was performed at a fixed time of the day (between 10:00 and 12:00 h) as part of the routine diagnostic procedure to exclude inflammatory disease. The resultant CSF samples were immediately aliquoted into non-adsorbent tubes and frozen at −80 °C. Tau was measured using the Innotest tau antigen kit (Innogenetics, Zwijndrecht, Belgium), an ELISA constructed to measure the total amount of tau, i.e. both unphosphorylated and phosphorylated fraction (Vandermeeren et al., 1993).

In addition, volumetric magnetic resonance imaging (MRI) was performed in 36 AD patients on a 1.5-Tesla MAGNETOM 63/84 SP Siemens scanner using a three-dimensional (3D) MP-RAGE (magnetization-prepared rapid gradient echo) sequence (repetition time = 10 ms, echo time = 4 ms) for the T1 and a 3D PSIF (fast imaging with steady-state precession) sequence (repetition time = 17 ms, echo time = 7 ms) for the
Table 1
Means (± standard deviations) of clinical characteristics in patients and controls with the results of a Duncan’s test at the 5% level

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>VD</th>
<th>Depression</th>
<th>Controls</th>
<th>Duncan-Test (P &lt; 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-g1-</td>
<td>-g2-</td>
<td>-g3-</td>
<td>-g4-</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>88</td>
<td>23</td>
<td>25</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>74.2 (± 9.6)</td>
<td>79.4 (± 8.9)</td>
<td>68.4 (± 9.0)</td>
<td>66.2 (± 9.1)</td>
<td>g2 &gt; g1 &gt; g3, g4</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>71.0 (± 10.1)</td>
<td>73.7 (± 9.0)</td>
<td>61.7 (± 11.7)</td>
<td>Not applicable</td>
<td>g2, g1 &gt; g3</td>
</tr>
<tr>
<td>MMSE score</td>
<td>17.1 (± 6.4)</td>
<td>15.4 (± 6.1)</td>
<td>27.1 (± 3.0)</td>
<td>29.1 (± 0.7)</td>
<td>g1, g2 &lt; g3, g4</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>38.1 (± 34.6)</td>
<td>63.6 (± 66.9)</td>
<td>73.9 (± 81.8)</td>
<td>Not applicable</td>
<td>g3 &gt; g1</td>
</tr>
<tr>
<td>Tau protein (pg/ml)</td>
<td>550.9 (± 268)</td>
<td>417.9 (± 265.2)</td>
<td>202.6 (± 96.2)</td>
<td>246.6 (± 111.4)</td>
<td>g1 &gt; g2 &gt; g4, g3</td>
</tr>
</tbody>
</table>

T2 weighted image data cubes. Both 3D image data cubes with a slab thickness of 160 mm consisted of 128 sagittal image slices, resulting in a slice thickness of 1.25 mm. The slices had an in-plane field of view of 260 mm and the volume pixels were of the size 1.02 × 1.02 × 1.25 mm³. Image data processing was performed using the software NMRwin (Pantel et al., 1997). Intracranial and whole brain volume, frontal and temporal lobe volumes and the volumes of the amygdala–hippocampus complexes were measured as described previously (Pantel et al., 1998). To address potential interindividual differences in premorbid brain size, all volumetric measures were normalized by dividing them by the subject’s intracranial volume.

Potential psychotropic medication effects on tau in AD have not been investigated in previous studies, and to this end the AD group was subdivided according to medication status. Medication breakdown was as follows: 40 AD patients did not receive any psychotropic medication; 15 received antidepressants; and 33 received neuroleptic drugs.

For data analysis, Pearson correlation coefficients, analyses of variance (Duncan’s test) and/or covariance and \( \chi^2 \) tests were calculated. The study was approved by the ethics committee of the University of Heidelberg.

3. Results

Table 1 presents the means and standard deviations of the clinical variables. According to the results of a Duncan’s test at the 5% level, the AD patients were significantly older than the controls. Patients with VD were older than patients with AD, depressed patients or controls. As expected, MMSE scores were significantly lower in both AD and VD patients than in patients with depression. Patients with AD or VD were significantly older at onset of disease than the depressed patients. Duration of illness differed significantly between patients with depression and AD patients. Tau protein concentrations in patients with AD were significantly from levels in both AD patients, and patients with major depression and levels in controls, but did not significantly differ between controls and patients with depression (Fig. 1). Tau levels in VD patients were intermediate, differing significantly from levels in both AD patients, and patients with major depression and levels in controls. Corresponding results were obtained when age was entered as a covariate. In the AD patients, no significant correlation between tau levels and severity of dementia (MMSE scores), age or duration of disease arose. Furthermore, no significant correlations between morphometric measures (whole brain volume, frontal and temporal lobe volumes, volumes of the amygdala–hippocampus complex; Table 2) and tau protein levels were found. Analyses repeated with age partialled out revealed consistent results.

Within the AD group, tau levels ranged widely from 163.2 to 1200 pg/ml and thus showed a broad overlap with those obtained in patients with depression and controls. In particular, AD patients with tau levels below the 25th percentile (i.e. 343.5 pg/ml) of the distribution were similar to patients with depression and healthy controls.
Table 2
Volumes of different brain structures in patients with Alzheimer’s disease (n=36)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total intracranial volume</td>
<td>1260.8</td>
<td>146</td>
</tr>
<tr>
<td>Whole brain volume</td>
<td>823.1</td>
<td>126</td>
</tr>
<tr>
<td>Whole brain volume/TIV</td>
<td>0.651</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Frontal lobe
- Right: 44.83, 9.3
- Left: 44.10, 8.4
- Right/TIV: 0.036, 0.007
- Left/TIV: 0.035, 0.005

Temporal lobe
- Right: 39.99, 5.8
- Left: 39.99, 7.6
- Right/TIV: 0.03, 0.004
- Left/TIV: 0.03, 0.005

Amygdala–hippocampus
- Right: 3.43, 0.84
- Left: 3.33, 0.65
- Right/TIV: 0.0027, 0.0006
- Left/TIV: 0.0027, 0.0005

Absolute and normalized values are given (volumes in cm³). TIV, total intracranial volume.

Compared with the AD patients with increased tau levels, those without elevated tau levels tended to be younger. Duration of disease, MMSE scores, gender distribution and medication status did not significantly differ between these two groups. However, the subgroup without increased tau levels showed a significantly larger percentage of patients with a presenile onset (12 patients with presenile onset vs. 10 patients with senile onset) than the subgroup with increased tau levels (11 patients with presenile onset vs. 55 patients with senile onset) (Table 3). Within the AD group, tau levels showed only minor, non-significant differences between patients receiving neuroleptics, antidepressants or no psychotropic medication.

4. Discussion

This study provides three major findings: (1) significantly elevated tau protein concentrations were found in AD patients compared with patients with VD, depressed patients and controls. (2) Elevated tau levels were not found in a subgroup of AD patients characterised by a higher proportion of younger patients with presenile onset. (3) In AD, tau levels were neither correlated with clinical variables such as severity of dementia, MRI measures of cerebral atrophy nor type or dosage of psychotropic medication.

Our results confirm previous studies demonstrating increased tau levels in AD compared with
controls without cognitive deficits (Arai et al., 1995; Blennow et al., 1995; Jensen et al., 1995; Mori et al., 1995; Motter et al., 1995; Skoog et al., 1995; Tato et al., 1995; Vigo-Pelfrey et al., 1995; Munroe et al., 1995; Hock et al., 1995; RiemenSchneider et al., 1997; Golombowski et al., 1997; Galasko et al., 1998; Kanai et al., 1998; Mecocci et al., 1998; Nishimura et al., 1998; Shoji et al., 1998; Hulstaert et al., 1999; Andreasen et al., 1999; Kahle et al., 2000). These studies included between 14 and 407 AD patients and 12 and 100 controls. In AD patients, MMSE scores ranged from 7 to 28. In accordance with other studies, we also found significantly elevated tau levels in patients with AD compared with depressed patients (Blennow et al., 1995; Golombowski et al., 1997). This result could contribute to the differential diagnosis of dementia and geriatric depression insofar as elevated tau protein levels would not be expected in affective disorders.

Others have reported significantly elevated tau levels in AD compared with VD (Blennow et al., 1995; Tato et al., 1995; Mori et al., 1995; Arai et al., 1998; Mecocci et al., 1998), a result that was not confirmed in all studies (Skoog et al., 1995; Andreasen et al., 1998; Tapiola et al., 1998). However, in accordance with our findings, most of these studies found the highest tau levels in the AD group (Tapiola et al., 1998; Andreasen et al., 1998). A possible explanation for significantly elevated tau levels in VD might be the acute damage to cerebral tissue induced by an ischemic event. The temporal relationship between an ischemic episode and the CSF examination could thus explain part of the variance of tau levels observed in VD patients. This assumption is in line with the finding by Arai et al. (1998), who observed tau levels in patients with acute cerebral infarction to be increased 2–3 weeks after the event, but to normalize several months later. Hesse et al. (2001) reported a marked increase of tau levels in patients with acute ischemic stroke, peaking at 3 weeks and returning to normal after 3 months. In accordance with this observation, in our study, patients with the highest tau values of the VD group (Fig. 1) had recently suffered acute stroke (1018.2 and 959.2 pg/ml), lacunar thalamic infarction (950 pg/ml) or severe subcortical arteriosclerotic encephalopathy (882.6 pg/ml). Clinically, there was no concomitant degenerative pathology to be supposed.

Alternatively, the divergent results of studies comparing tau levels between AD and VD patients may refer to the presence of a concomitant degenerative pathology rather than pure vascular changes in many patients diagnosed with VD. Andreasen et al. (1998) found higher tau concentrations in a subgroup of VD patients without progressive leukoaraiosis. It might be speculated whether this group mainly comprises patients with concomitant Alzheimer’s pathology. Several neuropathological studies have shown that a high proportion of clinically diagnosed VD patients have notable concomitant AD pathology (Jellinger, 1996; KossuNen et al., 1996). These results, as well as our findings, emphasize the importance of a careful clinical differential diagnosis when comparing tau levels between AD and VD patients in clinical studies. They demonstrate that recent cerebrovascular events need to be considered when CSF tau levels in VD patients are interpreted.

In the AD group, no significant correlation between tau levels and severity of disease arose. Several studies reported similar results (Munroe et al., 1995; Jensen et al., 1995; Buch et al., 1998; Hulstaert et al., 1999; Sunderland et al., 1999; 

### Table 3

<table>
<thead>
<tr>
<th>Tau level (pg/ml)</th>
<th>MMSE score</th>
<th>Presenile/senile</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD tau positive</td>
<td>648.2 (238.5)</td>
<td>16.9 (6.3)</td>
</tr>
<tr>
<td>AD tau negative</td>
<td>259.1 (51.9)</td>
<td>17.5 (7.0)</td>
</tr>
<tr>
<td>Controls</td>
<td>246.6 (111.4)</td>
<td>29.1 (0.7)</td>
</tr>
</tbody>
</table>

*Values presented are means (S.D.). MMSE, Mini-Mental State Examination. AD, Alzheimer’s disease.*

AD tau positive vs. AD tau negative: $P^2 = 12.3$, $P < 0.005$. 

**References:**
- Arai et al., 1995
- Blennow et al., 1995
- Golombowski et al., 1997
- Hock et al., 1995
- Hulstaert et al., 1999
- Andreasen et al., 1998
- Tapiola et al., 1998
- Andreasen et al., 1999
- Kahle et al., 2000
- Skoog et al., 1995
- Jensen et al., 1995
- Buch et al., 1998
- Hulstaert et al., 1999
- Sunderland et al., 1999
- Andreasen et al., 1998
- Tapiola et al., 1998
- Andreasen et al., 2000
- Hulstaert et al., 1999
- Andreasen et al., 1999
- Kahle et al., 2000
Green et al., 1999; Kahle et al., 2000). A possible explanation might be that elevated tau levels in AD patients reflect the continuous degeneration of neurons resulting in a progressive impairment of cognitive functioning. However, recent studies have found that CSF tau levels are stable over an extended period of time in mild to moderately cognitively impaired AD patients, and that CSF tau levels predict neither the severity nor the rate of progression of AD (Sunderland et al., 1999; Andreasen et al., 1999; Tapiola and Pirttil, 2000).

In addition, tau levels in the AD group showed a high variability: patients with tau levels below the 25th percentile—among them a high percentage of severely demented patients—showed tau levels similar to those measured in patients with depression or healthy controls. This result cannot be explained by the limited accuracy of clinical diagnosis alone. The heterogeneity of AD may provide an alternative explanation. Indeed, the group of AD patients without elevated tau levels was characterised by a significantly higher percentage of patients with presenile onset. In these patients, other types of dementia that are characterised by lower tau levels such as Lewy body dementia could be excluded.

The potential impact of psychotropic medication on tau concentration has not been addressed in previous studies. In the present study, neither treatment with neuroleptics nor with antidepressants affected tau protein concentrations in AD. Similarly, a previous study did not find any significant medication effects on CSF beta-amyloid 1–42 levels (Schröder et al., 1997).

A recent study found a significant correlation between beta-amyloid 1–42 CSF levels—another putative CSF marker of AD—and cerebral volume changes as revealed by MRI (Schröder et al., 1997). The present study is the first to investigate the relationship between CSF tau levels and measures of cerebral atrophy using volumetric MRI. In contrast to Skoog et al. (1995), who investigated tau levels with respect to cerebral atrophy in 11 AD patients, no significant correlation between measures of global and regional cerebral changes and tau levels arose. This discrepancy may be attributed to differences in sample size; moreover, Skoog et al. used computed tomography and linear measures to assess cerebral atrophy. Our results are in line with Buch et al. (1998), who did not find a significant relationship between tau levels and cerebral perfusion using single photon emission computed tomography.

In conclusion, our results underline the importance of CSF tau protein concentrations in the differential diagnosis of AD. In accordance with other studies, we found significantly elevated tau levels in AD patients compared with controls and depressed patients. With respect to VD, our results support the hypothesis that a close temporal relationship between ischemic episodes and CSF examination may be responsible for elevated tau protein concentrations. Elevated tau levels were not found in a subgroup of AD patients characterized by a higher percentage of younger, presenile demented patients. From a clinical point of view, one may summarize that increased tau levels confirm the clinical diagnosis of AD, while normal values do not exclude the diagnosis.

References


MRI based study. Dementia and Geriatric Cognitive Disorders 9, 309–316.