Differential Diagnosis of Alzheimer Disease With Cerebrospinal Fluid Levels of Tau Protein Phosphorylated at Threonine 231

Katharina Buerger, MD; Raymond Zinkowski, PhD; Stefan J. Teipel, MD; Tero Tapiola, MD; Hiroyuki Arai, MD, PhD; Kaj Blennow, MD, PhD; Niels Andreasen, MD, PhD; Klaus Hofmann-Kiefer, MD; John DeBernardis, PhD; Daniel Kerkman, PhD; Cheryl McCulloch, BS; Russell Kohnken, PhD; Frank Padberg, MD; Tuula Pirttila, MD, PhD; Marc B. Schapiro, MD; Stanley I. Rapoport, PhD; Hans-Jürgen Möller, MD; Peter Davies, PhD; Harald Hampel, MD

Background: Phosphorylation of tau protein at threonine 231 (using full-length tau, 441 amino acids, for the numbering scheme) (p-tau231) occurs specifically in post-mortem brain tissue of patients with Alzheimer disease (AD) and can be sensitively detected in cerebrospinal fluid (CSF).

Objectives: To determine to what extent CSF levels of p-tau231 distinguish patients with AD from control subjects and from patients with other dementias, and to investigate whether p-tau231 levels are a better diagnostic marker than levels of total tau protein (t-tau) in CSF.

Design and Setting: Cross-sectional, multicenter, memory clinic–based studies.

Participants: One hundred ninety-two patients with a clinical diagnosis of AD, frontotemporal dementia (FTD), vascular dementia, Lewy body dementia, or other neurological disorder and healthy controls.

Main Outcome Measures: Levels of CSF tau proteins as measured with enzyme-linked immunosorbent assays.

Results: Mean CSF levels of p-tau231 were significantly elevated in the AD group compared with all other groups. Levels of p-tau231 did not correlate with dementia severity in AD, and discriminated with a sensitivity of 90.2% and a specificity of 80.0% between AD and all non-AD disorders. Moreover, p-tau231 levels improved diagnostic accuracy compared with t-tau levels when patients with AD were compared with healthy controls (P = .03) and demented subjects (P < .001), particularly those with FTD (P < .001), but not those with vascular and Lewy body dementias. Sensitivity levels between AD and FTD were raised by p-tau231 compared with t-tau levels from 57.7% to 90.2% at a specificity level of 92.3% for both markers.

Conclusion: Increased levels of CSF p-tau231 may be a useful, clinically applicable biological marker for the differential diagnosis of AD, particularly for distinguishing AD from FTD.

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ABNORMAL hyperphosphorylation of the microtubule-associated tau protein and its incorporation into neurofibrillary tangles are major hallmarks of Alzheimer disease (AD). Until recently, only total tau protein (t-tau) as a marker of neuronal damage was detectable in cerebrospinal fluid (CSF). Elevated levels of CSF t-tau have been observed in patients with AD,1 even in those with mild dementia,2 compared with healthy elderly controls. However, CSF t-tau levels are of limited value in the differential diagnosis of AD, because they can be increased in other dementia disorders.3,4 Therefore, it appears likely that t-tau levels reflect neuronal degeneration rather than AD-specific pathophysiology. The use of antibodies to sites of tau that are specifically phosphorylated in AD may help to increase diagnostic accuracy, because the marker would be linked to a neuropathological hallmark of the disease. Detection of phosphorylated tau protein in the CSF therefore may provide a useful biomarker as outlined by the consensus report of the Working Group on Molecular and Biochemical Markers of Alzheimer’s Disease.9

Recently, 3 different immunoassays were developed that reliably detect phosphorylated tau (p-tau) in the CSF.10-12 These assays detect different sites of phosphorylation. Levels of CSF tau phosphorylated at threonine 181 were elevated in patients with AD compared with those with other dementias and healthy control subjects.13,14 Itoh and colleagues12 showed that CSF tau phosphorylated at serine 199 dis-
SUBJECTS, MATERIALS, AND METHODS

SUBJECT SELECTION

We enrolled a total of 192 subjects. Of these, 82 had probable AD (defined by criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association) [21], 26, FTD [18], 17, LBD [19], and 20, VD [20]. These patients had structural and functional imaging findings consistent with the diagnoses. Twenty-six patients with OND were diagnosed as having amyotrophic lateral sclerosis (n=2), human immunodeficiency virus infection (n=1), systemic lupus erythematosus (n=1), stroke syndrome (n=3), hereditary motor and sensory neuropathy type I (n=1), Lyme borreliosis (n=3), rheumatoid arthritis (n=1), polyneuropathy (n=2), sarcoidosis (n=1), Huntington disease (n=1), progressive spasticity of unknown etiology (n=1), bulbar syndrome of unknown etiology (n=2), other psychiatric disorder (n=2), myopathy (n=1), diplopia and nystagmus (n=1), palsy of the sixth cranial nerve (n=1), essential tremor (n=1), and extrapyramidal symptoms of unknown etiology (n=1). We also included 21 HC subjects. Study subjects were recruited at the following 5 academic expert centers: the Alzheimer Memorial Center, Department of Psychiatry, Ludwig-Maximilian University, Munich, Germany (38 AD, 6 FTD, 10 VD, 9 LBD, 19 OND, and 13 HC subjects); the Department of Neuroscience and Neurology, University of Kuopio, Kuopio, Finland (7 AD, 4 FTD, 6 VD, 5 LBD, and 7 OND subjects); the Department of Geriatric Medicine, Tohoku University School of Medicine, Sendai, Japan (12 AD, 7 FTD, 4 VD, and 3 LBD subjects); the Department of Rehabilitation, Pitea River Valley Hospital, Pitea, Sweden (5 FTD subjects); and the Brain Physiology and Metabolism Section, National Institute on Aging, National Institutes of Health, Bethesda, Md (25 AD, 4 FTD, and 8 HC subjects).

Characteristics of the patients and controls are given in Table 1. The protocol was approved by the local ethical committees and the institutional review boards of the participating centers. Informed consent was obtained from all subjects.

Eight of the 21 HC subjects were volunteers without any medical, neurological, or psychiatric disorder. Thirteen HC subjects were cognitively normal according to results of the battery of the Consortium to Establish a Registry for Alzheimer’s Disease [21] (results within ±1 SD in all subtests). The CSF was collected while the subjects underwent spinal anesthesia for surgery of the urinary tract or lower extremities. Three of these subjects had diabetes mellitus as a substantial somatic comorbidity.

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CSF SAMPLING AND ANALYSES OF TAU PROTEINS

The CSF samples were obtained by means of lumbar puncture, and aliquots were stored at -80°C until analysis. Mean ± SD length of CSF storage was 4.1 ± 4.4 years. Levels of p-tau231 were measured using an enzyme-linked immunosorbent assay (Molecular Geriatrics Corporation, Vernon Hills, Ill) that is specific for p-tau231. Results of experiments describing the specificity of the detection antibody CP9 for p-tau231 have been reported. The coefficients of variation calculated from the raw data were 13.6% (interassay) and 6.8% (intra-assay). For each patient, 80 µL of CSF was analyzed per well in duplicates. Repeated cycles of freezing and thawing of CSF samples did not affect the level of p-tau231 (data not shown). Length of CSF storage did not affect p-tau231 levels in any group (p > 0.15 to 0.30; P > 0.20).

A pool of AD CSF was made from samples of 40 individuals with clinically diagnosed AD who were unrelated to the study population. This AD CSF pool was used to produce a standard curve. Levels of p-tau231 in our subjects were expressed in terms of the volume of the AD CSF pool that gave an equivalent signal, termed microliters of CSF equivalents. The plot of the standard curve produced with the AD CSF pool did not pass through the origin, and consequently, extremely low p-tau231 signals produced negative values in terms of microliters of CSF equivalents. Levels of t-tau protein were measured in duplicate using a commercially available enzyme-linked immunosorbent assay (Innotest hTau, Art K-1032; Innogenetics, Gent, Belgium) according to the manufacturer’s instructions. The coefficients of variation were less than 13% (interassay) and 11% (intra-assay). Assay operators (R.Z. and C.M.) were masked to the diagnostic category of the samples.

STATISTICAL ANALYSES

Values for p-tau231 and t-tau differed significantly from a normal distribution by the Kolmogorov-Smirnov test. Differences in mean levels of CSF p-tau231 and t-tau across all groups were assessed with the Kruskal-Wallis nonparametric 1-way analysis of variance. Pairwise comparisons between the AD and the other groups were performed with the Mann-Whitney test. For p-tau231 and t-tau levels, sensitivity and specificity levels and numbers of correctly allocated cases were derived from receiver operating characteristic (ROC) curve analysis when the sum of specificity and sensitivity was maximized. Areas under the ROC curves (AUC) as measures of diagnostic accuracy were compared between p-tau231 and t-tau levels using the algorithm of Hanley and McNeil [22,23]. Correlations between p-tau231 and t-tau levels and group characteristics were assessed with the Spearman rank correlation. Differences between groups with regard to age were assessed with the Mann-Whitney test, and with regard to sex distribution with the χ² test.
Lewy body dementia (LBD) and between patients with AD and healthy controls (HC). To our knowledge, the potential of p-tau231 in CSF to differentiate AD from other dementias has not been studied. The discriminatory power of p-tau231 measurements was compared with that of measurements of t-tau, which has been studied as a diagnostic marker for AD.

RESULTS

CSF p-TAU231 AND t-TAU LEVELS

As illustrated in Figure 1, levels of p-tau231, and t-tau were significantly increased in the AD group compared with all other groups. Because the HC group was significantly younger than the AD group, we repeated our analysis on a subgroup of 21 patients with AD and 21 HC subjects matched for age (P=.69) and sex (P=.99). Differences between the AD and HC subgroups remained highly significant (P<.001) for p-tau231 and t-tau levels. Therefore, we included all patients with AD in our analyses. Levels of CSF p-tau231 and t-tau correlated significantly with each other in subjects with AD (Spearman ρ=0.82; P<.001), VD (Spearman ρ=0.78; P<.001), and LBD (Spearman ρ=0.77; P<.001).

CSF p-TAU231 LEVELS ACCORDING TO AGE, SEX, MINI-MENTAL STATE EXAMINATION SCORE, AND CENTER IN THE AD GROUP

We found no significant effect of sex (P=.86) or age (P=.05; P=.67) on levels of p-tau231. Levels of CSF p-tau231 did not correlate with the Mini-Mental State Examination score (Figure 2) (P=.02; P=.85). Levels of p-tau231 levels did not differ significantly between participating centers (Figure 3) (χ2=1.75; P=.63).

ROC ANALYSIS

Sensitivity and specificity levels as well as percentage and absolute numbers of correctly allocated cases are given in Table 2. Levels of p-tau231 discriminated with a high accuracy between AD and non-AD groups. At a specificity level of 80.0% (88/110), the p-tau231 level was 90.2% (74/82) sensitive and correctly allocated 162 (84.4%) of 192 subjects. In discriminating the AD from the non-demented groups (HC and OND), p-tau231 levels correctly classified more than 90% of subjects (101 of 103 and 102 of 108 subjects, respectively). Sensitivity (21/21 [100.0%]) and specificity (19/21 [90.5%]) levels remained stable for comparison of age- and sex-matched AD and HC sub-

Table 1. Characteristics of Patients and Control Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Age, Mean ± SD (Range), y</th>
<th>No. of F/M†</th>
<th>MMSE Score, Mean ± SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>69.3 ± 9.5 (35-86) (n = 82)</td>
<td>45/37</td>
<td>17.7 ± 6.1§ (1-28) (n = 80)</td>
</tr>
<tr>
<td>FTD</td>
<td>66.8 ± 10.5 (49-88) (n = 25)</td>
<td>16/10</td>
<td>20.1 ± 5.0§ (9-28) (n = 22)</td>
</tr>
<tr>
<td>VD</td>
<td>75.0 ± 5.3 (65-85) (n = 20)</td>
<td>10/10</td>
<td>19.6 ± 5.4§ (10-25) (n = 18)</td>
</tr>
<tr>
<td>LBD</td>
<td>73.1 ± 6.7 (63-84) (n = 17)</td>
<td>8/9</td>
<td>19.2 ± 6.5§ (9-29) (n = 14)</td>
</tr>
<tr>
<td>OND</td>
<td>61.4 ± 12.9 (41-89) (n = 26)</td>
<td>9/17</td>
<td>NA</td>
</tr>
<tr>
<td>HC</td>
<td>57.7 ± 14.2 (36-91) (n = 21)</td>
<td>8/13</td>
<td>29.0 ± 0.8 (27-30) (n = 13)</td>
</tr>
</tbody>
</table>

*MMSE indicates Mini-Mental State Examination; AD, Alzheimer disease; FTD, frontotemporal dementia; VD, vascular dementia; LBD, Lewy body dementia; OND, other neurological disorders; HC, healthy control subjects; and NA, not available.
†No significant difference was seen in sex distribution between groups (Pearson χ2 = 5.88; P = .32).
‡Significant differences in age between the AD and the other groups studied are as follows: AD vs VD, P<.05; AD vs OND, P<.05; and AD vs HC, P<.001.
§No significant differences were seen between AD, VD, LBD, and FTD groups in severity of dementia as established by the MMSE score (P = .36).

Figure 1. Levels of tau protein phosphorylated at threonine 231 (p-tau231) (A) and total tau protein (t-tau) (B) in the cerebrospinal fluid (CSF) of patients and control subjects. Dashed lines represent the cutoff level yielding the best sensitivity and specificity for discriminating patients with Alzheimer disease (AD) from those with non-AD disease and healthy control (HC) subjects (by means of receiver operating characteristic curves). Horizontal solid lines indicate means; FTD, frontotemporal dementia; VD, vascular dementia; LBD, Lewy body dementia; OND, other neurological disorders; asterisk, P<.05; dagger, P<.005; and double dagger, P<.001. All comparisons are with the AD group.

Figure 2. ROC ANALYSIS
In the present study, we investigated to what extent CSF p-tau231 levels discriminate between subjects with AD, those with other common causes of dementia, and nondemented controls. The p-tau231 levels discriminated with a specificity of 80.0% and a sensitivity of 90.2% between the group with clinically diagnosed AD and the combined non-AD groups. The phosphorylation of the threonine 231 epitope has been specifically implicated in the tau pathology of AD.15 The results of our study indicate that p-tau231 levels in CSF may be a clinically applicable biomarker for AD, reflecting an important feature of AD pathophysiology.9

The CSF p-tau231 levels showed an excellent discriminative power between the AD and control (HC and OND) groups, with sensitivity and specificity levels ranging from 90% to 100%. This finding, which was obtained in an independent sample, confirms previous results.10

In our first study, we had used an AD brain extract for construction of a standard curve.12 We subsequently found that serial dilutions of AD CSF produced a nonlinear response in the assay. To better mimic the response of patient CSF in the current assay, we used an AD CSF pool to generate a standard curve. We showed a parallelism between the AD brain extract and the AD CSF pool by performing ROC curve analysis for samples assayed with both of the standards and then comparing the AUC as a measure of diagnostic accuracy.24 The difference in the AUC between the 2 standards was statistically insignificant. Thus, in terms of diagnostic accuracy, the standards are equivalent.

Moreover, CSF p-tau231 levels correctly allocated 80.7% of subjects when AD was compared with other dementia disorders. Levels of p-tau231 in the CSF were found to clearly distinguish AD from FTD, with a sensitivity of 90.2% and a specificity of 92.3%. The high level of discrimination is likely due to the fact that the biochemical and molecular signatures of tau pathology are distinctly different between the two diseases.25 Thus, CSF p-tau231 levels appear to be particularly accurate in discrimination between AD and FTD and may also serve this differential diagnosis in clinical practice.

We found an increase of p-tau231 levels in some patients with VD and LBD. Concomitant AD pathology including neurofibrillary tangles has been described for a considerable number of patients with VD26 and LBD27 who are clinically indistinguishable from those with “pure” VD and LBD, respectively. Most likely, our VD and LBD
groups were heterogeneous with regard to underlying AD-pathology, resulting in an increase of p-tau231 levels in some of the patients with VD and LBD. This decreases the discriminative power of p-tau231 between AD and VD and between AD and LBD.

Our findings on the high discriminative power of CSF p-tau231 level as a single biomarker between the AD and non-AD groups are consistent with those of a report on CSF tau phosphorylated at serine 199.12 In addition, we show the potential of p-tau231 to discriminate patients with AD from those with other relevant dementia disorders and from subjects without dementia. We found no effect of age, sex, or clinical dementia severity on levels of p-tau231. Moreover, investigating the applicability of p-tau231 levels across several study sites, we found no effect of center on p-tau231 levels.

These findings indicate that p-tau231 levels may be a valuable marker for the clinical diagnosis of AD, irrespective of age, sex, dementia severity, and diagnostic center. We avoided a potential bias of our results because none of the diagnostic groups investigated herein was exclusively recruited by a single center.

The present study also investigated whether p-tau231 levels have a superior discriminative power compared with t-tau levels. Our CSF t-tau levels in AD and other disorders are consistent with those of previous reports.28 Compared with t-tau levels, CSF p-tau231 levels allowed a significantly better discrimination between the AD and the combined non-AD groups, between the AD and HC groups, and between the AD and non-AD dementia groups. In particular, p-tau231 levels were superior to t-tau levels for distinguishing AD from FTD.

**CONCLUSIONS**

Our data indicate that CSF p-tau231 levels may be a useful biological marker to differentiate patients with clinically diagnosed AD from those with OND and other dementia disorders, particularly FTD, and from HC subjects. We show that p-tau231 levels fulfill the core criteria of a useful biomarker of AD as outlined by the consensus report of the Working Group on Molecular and Biochemical Markers of Alzheimer’s Disease.9 The diagnostic accuracy of the various p-tau epitopes should be evaluated through a comparative study applying the immunosays of the different p-tau epitopes on the same set of patients. Part of our sample is enrolled in a neuropathological program designed to confirm diagnoses and to provide subjects with autopsy-confirmed disease. Neuropathological studies in clinically well-characterized patients are warranted to further establish CSF p-tau231 levels as a clinically applicable diagnostic tool. A biochemical marker to accurately discriminate patients with AD from healthy controls would be useful in the early diagnosis of AD. A biomarker for differential diagnosis of AD would be clinically relevant for therapeutic interventions, caregiver counseling, and prognosis. Our findings suggest that CSF p-tau231 levels might be such a marker.

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**Author contributions:** Study concept and design (Drs Buerger, Arai, Blennow, Andreasen, Kerkman, Zinkowski, Davies, and Hampel); acquisition of data (Drs Buerger, Zinkowski, Tapiola, Arai, Andreasen, Hofmann-Kiefer, Kohnken, Pirttila, Schapiro, and Rapoport and Ms McCulloch); analysis and interpretation of data (Drs Buerger, Zinkowski, Teipel, Arai, Blennow, Andreasen, DeBernardis, Kerkman, Padberg, Moller, and Hampel and Ms McCulloch); drafting of the manuscript (Drs Buerger, Arai, Andreasen, Zinkowski, and Hampel); critical revision of the manuscript for important intellectual content (Drs Buerger, Zinkowski, Teipel, Tapiola, Blennow, Andreasen, Hofmann-Kiefer, DeBernardis, Kerkman, Padberg, Pirrtilla, Schapiro, Rapoport, Moller, and Hampel and Ms McCulloch); statistical expertise (Drs Buerger and Teipel); obtained funding (Drs Andreasen and Hampel); administrative, technical, and material support (Drs Zinkowski, Tapiola, Arai, Blennow, Hofmann-Kiefer, DeBernardis, Kerkman, Kohnken, Schapiro, Rapoport, Moller, Davies, and Hampel and Ms McCulloch); and study supervision (Drs Zinkowski, Kerkman, Padberg, and Hampel).

From the Dementia Research Section and Memory Clinic, Alzheimer Memorial Center, Geriatric Psychiatry Branch, Department of Psychiatry (Drs Buerger, Teipel, Padberg, Moller, and Hampel), and the Department of Anesthesiology (Dr Hofmann-Kiefer), Ludwig-Maximillan University, Munich, Germany; the Molecular Geriatrics Corporation, Vernon Hills, Ill (Drs Zinkowski, DeBernardis, Kerkman, and Kohnken and Ms McCulloch); the Department of Neuroscience and Neurology, University Hospital, University of Kuopio, Kuopio, Finland (Drs Tapiola

Table 2. Sensitivity, Specificity, and Correctly Allocated Cases Using ROC Analysis for CSF p-Tau231 and t-Tau*

<table>
<thead>
<tr>
<th>Groups</th>
<th>CSF p-Tau231 Level</th>
<th>CSF t-Tau Level</th>
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<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>AD vs non-AD</td>
<td>74/82 (90.2)</td>
<td>88/110 (80.0)</td>
</tr>
<tr>
<td>AD vs OND</td>
<td>76/82 (92.7)</td>
<td>26/26 (100.0)</td>
</tr>
<tr>
<td>AD vs HC</td>
<td>82/82 (100.0)</td>
<td>19/21 (90.5)</td>
</tr>
<tr>
<td>AD vs other dementias</td>
<td>76/82 (92.7)</td>
<td>41/63 (65.1)</td>
</tr>
<tr>
<td>AD vs FTD</td>
<td>74/82 (90.2)</td>
<td>24/26 (92.3)</td>
</tr>
<tr>
<td>AD vs VD</td>
<td>76/82 (92.7)</td>
<td>13/20 (65.0)</td>
</tr>
<tr>
<td>AD vs LBD</td>
<td>63/82 (76.8)</td>
<td>13/17 (76.5)</td>
</tr>
</tbody>
</table>

*Data are given as number/total number (percentage) of cases. CSF indicates cerebrospinal fluid; p-tau231, tau protein phosphorylated at threonine 231; and t-tau, total tau protein. Other abbreviations are explained in the first footnote to Table 1.
and Pirrittilä); the Department of Geriatric Medicine, Tohoku University School of Medicine, Sendai, Japan (Dr Arai); the Unit of Neurochemistry, Department of Clinical Neuroscience, University of Göteborg, Sahlgren’s University Hospital, Mölndal, Sweden (Dr Blennow); the Department of Rehabilitation, Pitea River Valley Hospital, Pitea, Sweden (Dr Andreasen); the Division of Pediatric Neuropsychology, Children’s Hospital Medical Center, Cincinnati, Ohio (Dr Schapiro); the Brain Physiology and Metabolism Section, National Institute on Aging, National Institutes of Health, Bethesda, Md (Dr Rapoport); and the Department of Pathology, Albert Einstein College of Medicine, Bronx, NY (Dr Davies). Dr Andreasen is now affiliated with the Division of Geriatric Medicine, Karolinska Institutet, Neurotec, Huddinge University Hospital, Stockholm, Sweden.

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Corresponding authors: Katharina Buerger, MD, and Harald Hampel, MD, Dementia Research Section and Memory Clinic, Alzheimer Memorial Center, Geriatric Psychiatry Branch, Department of Psychiatry, Ludwig-Maximilian University, Nussbaumstrasse 7, 80336 Munich, Germany (e-mail: katharina.buerger@psy.med.uni-muenchen.de; hampel@psy.med.uni-muenchen.de).

Reprints: Raymond Zinkowski, PhD, Molecular Geriatrics Corporation, 50 Lakeview Pkwy, Vernon Hills, IL 60061 (e-mail: zinkowski@moleculargeriatrics.com).

REFERENCES


