Correlation of Cerebrospinal Fluid Levels of Tau Protein Phosphorylated at Threonine 231 With Rates of Hippocampal Atrophy in Alzheimer Disease

Harald Hampel, MD; Katharina Bürger, MD; Jens C. Pruessner, PhD; Raymond Zinkowski, PhD; John DeBernardis, PhD; Daniel Kerkman, PhD; Gerda Leinsinger, MD; Alan C. Evans, PhD; Peter Davies, PhD; Hans-Jürgen Möller, MD; Stefan J. Teipel, MD

Background: The microtubule-associated tau protein abnormally phosphorylated at threonine 231 (p-tau231) has been investigated as a potential marker of Alzheimer disease. Levels of cerebrospinal fluid (CSF) p-tau231 vary across patients with Alzheimer disease. We hypothesized that these variations partially reflect differences in the degree of neuronal damage and therefore may be used to predict structural disease progression. 

Objective: To investigate whether CSF p-tau231 levels correlate with rates of hippocampal atrophy as an in vivo marker of regional neuronal loss. 

Design and Patients: We measured hippocampal volumes on the basis of serial magnetic resonance image examinations in 22 patients with Alzheimer disease. In addition, we determined CSF p-tau231 levels at baseline. 

Results: Levels of CSF p-tau231 were significantly correlated with baseline hippocampal volumes (P<.001) and rates of hippocampal atrophy (left hippocampus, P<.001; right hippocampus, P=.02), independent of disease duration and severity. 

Conclusion: These findings suggest that variations in p-tau231 levels may be used to predict progression of brain atrophy in patients with Alzheimer disease.

Arch Neurol. 2005;62:770-773

IN A SERIES OF STUDIES, THE MICRO-TUBE-ASSOCIATED TAU PROTEIN ABNORMAL PHOSPHORYLATED AT THREONINE 231 (P-TAU231) HAS BEEN INVESTIGATED AS A POTENTIAL MARKER OF ALZHEIMER DISEASE (AD). CEREBROSPINAL FLUID (CSF) P-TAU231 LEVELS CORRELATE WITH BASELINE HIPPOCAMPAL VOLUMES (% H11021 P<.001) AND RATES OF HIPPOCAMPAL ATROPHY (LEFT HIPPOCAMPUS, % H11021 P<.001; RIGHT HIPPOCAMPUS, P=.02), INDEPENDENT OF DISEASE DURATION AND SEVERITY.

METHODS

We studied 22 patients (13 women and 9 men) with the clinical diagnosis of probable AD according to the criteria of National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association. After describing the study to each subject, the holder of a durable power of attorney, or a legal guardian, written informed consent was obtained. Mean age was 67.8 years (SD, 7.9 years). Global cognitive functioning was assessed with the Mini-Mental State Examination (MMSE). The mean MMSE score was 23.1 (SD, 4.0). Twenty AD patients underwent MRI twice, and 2 underwent MRI 3 times. Length of observation time ranged from 11.3 to 41.0 months (mean, 18.4 months [SD, 14.8 months]). Originally, 15 patients had mild AD; for 2 patients the second and for 1 patient the first MRI from the series could not be used. The MRIs were acquired on the same 1.5-T scanner (Magneto Vision; Siemens AG, Ern...
In AD patients, higher CSF p-tau231 levels were significantly correlated with higher rates of hippocampal atrophy progression, even after controlling for disease duration and severity. This finding is consistent with the hypothesis that increased levels of CSF p-tau231 reflect more extensive neuronal damage, leading to higher rates of hippocampal atrophy.

Rates of hippocampal atrophy may reflect reduction of hippocampal neuron density as found in postmortem studies of AD. The significant correlations between p-tau231 and t-tau levels on hippocampal volumes and on rates of hippocampal atrophy (interaction effect). In addition, we examined the main effect of p-tau231 and t-tau levels on baseline hippocampal volumes. We determined correlations between rates of hippocampal atrophy and baseline hippocampal volumes (F1,20=0.16 [P=0.24], respectively) or on rate of point loss in MMSE scores (F1,22=1.81 [P=0.19]).

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**RESULTS**

Mean levels of p-tau231 were 729.6 pg/mL (SD, 404.3 pg/mL). Hippocampal volumes were 2267 mm³ (SD, 640 mm³) for the left and 2263 mm³ (SD, 651 mm³) for the right side.

As shown in the Table, the mixed general linear model yielded a significant effect of interaction on rates of hippocampal atrophy and left and right hippocampal volumes. Higher p-tau231 levels corresponded to higher rates of atrophy and baseline hippocampal volumes. There was no significant effect of t-tau levels on rates of left and right hippocampal atrophy (β=0.27 [P=0.14] and β=−0.10 [P=0.51], respectively).

The statistical significance of these findings remained unchanged when main and interaction effect terms for MMSE and disease duration were added to the model.

There was no significant correlation between p-tau231 and t-tau levels and CSF volume (Pearson r21=0.10 [P=0.68] and r21=0.06 [P=0.78], respectively), gray matter volume (r21=−0.13 [P=0.58] and r21=−0.26 [P=0.26], respectively), or white matter volume (r21=0.27 [P=0.24] and r21=0.16 [P=0.48], respectively).

Higher rates of MMSE score decline correlated significantly with higher rates of atrophy of left and right hippocampal volumes (p=0.52 [P=0.02] and p=0.47 [P=0.03], respectively) (Figure 2). There was, however, no effect of p-tau231 levels on MMSE scores at baseline (F1,20=1.57 [P=0.22]) or on rate of point loss in MMSE scores (F1,22=1.81 [P=0.19]).

**COMMENT**

In AD patients, higher CSF p-tau231 levels were significantly correlated with higher rates of hippocampal atrophy progression, even after controlling for disease duration and severity. This finding is consistent with the hypothesis that increased levels of CSF p-tau231 reflect more extensive neuronal damage, leading to higher rates of hippocampal atrophy.

Rates of hippocampal atrophy may reflect reduction of hippocampal neuron density as found in postmortem studies of AD. The significant correlations between p-

| Table. Effects of CSF p-tau231 Levels on Hippocampal Volumes* |
|---------------|------------------|-----------------|---------------|------------------|-----------------|
| Region        | β Value†         | F 1,20          | P Value       | β Value†         | F 1,20          | P Value       |
| Left hippocampus | 0.65            | 19.8            | <.001         | −0.36           | 15.3            | <.001         |
| Right hippocampus | 0.63           | 15.1            | .001          | −0.31           | 7.1             | .02           |

Abbreviations. CSF, cerebrospinal fluid; p-tau231, tau protein abnormally phosphorylated at threonine 231.

*Analysis of variance table of results from the mixed-effects general models for left and right hippocampus, investigating the effect of p-tau231 levels on hippocampal volumes at baseline (main effect) and on rates of hippocampal atrophy (interaction effect).

†Indicates the standardized regression weight for the main and interaction effects, respectively.

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tau\textsubscript{231} levels and rates of hippocampal atrophy suggest that CSF levels of p-tau\textsubscript{231} can serve as a marker for the degree of neuronal destruction and may be used to predict structural disease progression. The results were independent from disease duration and severity, indicating that the correlations do not reflect the effects of disease stage on rates of atrophy and p-tau\textsubscript{231} levels.

Levels of p-tau\textsubscript{231} and t-tau were positively correlated with baseline hippocampal volumes. There is no conclusive interpretation of this correlation at present. In a study of 8 patients with mild cognitive impairment, CSF p-tau\textsubscript{231} levels were decreased with larger ventricle size, suggesting a dilution of p-tau\textsubscript{231}. In our patients, however, p-tau\textsubscript{231} levels were not correlated with CSF volume, indicating that tau proteins are not simply diluted in CSF with larger ventricle size (which is inversely correlated with hippocampal volume). The baseline effect, however, was modeled in the mixed-effect regression analysis to ensure that the correlations between p-tau\textsubscript{231} and rates of hippocampal atrophy were independent of the p-tau\textsubscript{231} effects on baseline volumes. Our study did not examine the rate of delivery of p-tau\textsubscript{231} into the CSF and did not address any changes in the rate of CSF turnover. It is expected that these factors may contribute to the interpretation of the results, and further studies are warranted.

Rates of hippocampal atrophy were correlated with rates of change in MMSE scores, suggesting a functional consequence of progressive hippocampal atrophy. Levels of p-tau\textsubscript{231} were not correlated with rates of change in MMSE scores, suggesting that the significant correlations between p-tau\textsubscript{231} levels and hippocampal volume are related with hippocampal volume).
do not reflect an effect of \( \text{p-tau}_{231} \) levels on rates of clinical deterioration, but may reflect a more specific pathophysiological link between regional brain atrophy and expression of \( \text{p-tau}_{231} \) levels in CSF.

There was no significant effect of tau levels on rates of hippocampal atrophy. This suggests that the observed correlations between \( \text{p-tau}_{231} \) levels and rates of hippocampal atrophy are not merely a global effect of tau levels. It remains to be investigated whether these correlations are specific for the threonine 231 epitope or may be found with other phosphoepitopes also. There is evidence of a stage-specific sequence of tau phosphorylation in AD.\(^{18}\) It may be possible that correlations between rates of brain atrophy and levels of subtypes of phosphorylated tau differ across the clinical stages of AD.

Our data agree with the notion that variations in \( \text{p-tau}_{231} \) levels reflect differences in the degree of neuronal damage across AD patients. Although the strength of the correlations presently suggests no sufficient clinical utility to individual patients, \( \text{p-tau}_{231} \) levels may be used to predict progression of brain atrophy in AD. To draw more definite conclusions, replication of our findings is needed in larger studies.

Accepted for Publication: September 14, 2004.

Correspondence: Stefan J. Teipel, MD, Alzheimer Memorial Center and Geriatric Psychiatry Branch, Dementia and Neuroimaging Section, Department of Psychiatry, Ludwig-Maximilian University, Nussbaumstrasse 7, 80336 Munich, Germany (stefan.teipel@med.uni-muenchen.de).


Funding/Support: This study was supported in part by grants from the Medical Faculty of the Ludwig-Maximilian University, Munich, Germany (Drs Burger and Teipel); the Hirnliga eV, Nürmbrecht, Germany (Drs Teipel and Hampel); Eisai Co, Frankfurt, Germany (Drs Hampel and Teipel); Pfizer, Karlsruhe, Germany (Drs Hampel and Teipel); and the German Competency Network on Dementias (Kompetenznetz Demenzen) funded by the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung), Bonn, Germany (Drs Hampel and Teipel).

Previous Presentation: Part of this work originates from the doctoral thesis in preparation of Romea Mergner, Department of Psychiatry, Ludwig-Maximilian University.

Acknowledgment: We thank Felician Jancu, Bea Riemenschneider, and Christine Sänger, Department of Psychiatry, Ludwig-Maximilian University, for technical support.

CONCLUSIONS

REFERENCES