Mild Cognitive Impairment: Cerebrospinal Fluid Tau Biomarker Pathologic Levels and Longitudinal Changes in White Matter Integrity

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Purpose:
To evaluate the relationship between (a) pathologic levels of cerebrospinal fluid (CSF) total tau as an index of the intensity of ongoing neuronal degeneration and (b) longitudinal changes in white matter (WM) integrity in patients with mild cognitive impairment (MCI).

Materials and Methods:
Participants gave written informed consent, and the Norwegian committee for medical research ethics approved the study. Thirty patients with MCI and nonpathologic CSF total tau levels, nine patients with MCI and pathologic CSF total tau levels, and 16 age-matched healthy control subjects underwent diffusion-tensor imaging at baseline and after a mean follow-up of 2.6 years ± 0.54 (standard deviation), with range of 1.58–3.98 years. The effect of diagnosis (MCI vs no MCI) at baseline and CSF tau levels at fractional anisotropy (FA), mean diffusivity, radial diffusivity ($D_r$), and axial diffusivity were tested with tract-based spatial statistics. Differences in WM integrity at baseline and follow-up and change over time were compared among patients with pathologic CSF total tau levels (MCI high tau), patients with normal CSF total tau levels (MCI low tau), and healthy control subjects. Linear mixed-model between-group within-subject analyses were conducted to examine differences in rate of change over time in FA and $D_r$.

Results:
Longitudinal analysis of regional WM change revealed significant decrease in FA ($P = .038$) and increase in $D_r$ ($P = .018$) in the MCI high-tau group relative to control subjects. For $D_r$, the changes were regionally specific to the right cingulum and the right superior and inferior longitudinal fasciculi.

Conclusion:
Reduction in WM integrity was greater in patients with MCI who had the most intense neuronal degeneration as indexed by using CSF total tau, suggesting that these patients might represent a subgroup of MCI with more intense WM degeneration who are possibly at greater risk of developing Alzheimer disease.

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Increased cerebrospinal fluid (CSF) levels of the microtubule-associated protein tau are commonly found in mild cognitive impairment (MCI) and Alzheimer disease (AD) (1). Tau is primarily located in the axons. By binding to tubulin, tau plays an important role in stabilizing and promoting assembly of microtubules, which are involved in maintaining cell structure and serve as tracks for axonal transport (2). Heightened levels of CSF total tau are probably markers for ongoing axonal damage (3), and increased levels of CSF total tau are found in a range of neurodegenerative disorders in addition to AD, such as some cases of frontotemporal dementia and Creutzfeldt–Jakob disease (4), as well as after acute stroke (5).

The pathologic processes behind the increased levels of CSF total tau in AD also seem to affect white matter (WM) integrity. WM damage in AD-type dementia has long been known from postmortem studies (6), but only recently has in vivo quantification of WM integrity been possible by use of diffusion-tensor imaging (7). Researchers in several studies (8–10) have shown reduced WM integrity in MCI and AD, establishing diffusion-tensor imaging as a promising tool for early detection of AD. However, the relationship between pathologic CSF total tau levels (on the basis of age-dependent criteria) and WM integrity at predementia stages has been scarcely explored. Knowledge about this relationship would increase our understanding of the complexity of the mechanisms involved in MCI and early AD. In a previous cross-sectional region-of-interest–based study of the same patient population as in the present article, lower fractional anisotropy (FA) and higher radial diffusivity (D_r) were found in the posterior cingulum in patients with MCI with pathologic levels of CSF total tau compared with patients with normal levels and healthy control subjects (11). To our knowledge, in no other study have the researchers explicitly addressed the relationship between measures at diffusion-tensor imaging and established CSF biomarkers. Longitudinal data are required to determine whether pathologic CSF tau levels help in the prediction of further WM degeneration or instead are related to the burden of accumulated WM injury during years. Because increases in CSF tau are seen in acute conditions with neuronal and axonal damage (3,5), we hypothesized that patients with MCI who have the highest levels of CSF total tau (MCI high tau) would show greater reduction in WM integrity over time compared with patients who have normal levels (MCI low tau) and healthy control subjects. The purpose of the present study was to evaluate the relationship between (a) pathologic CSF total tau levels as an index of the intensity of ongoing neuronal degeneration and (b) longitudinal changes of WM integrity in patients with MCI.

**Materials and Methods**

**Sample**
This prospective study was approved by the Regional Committee for Medical and Health Research Ethics, Oslo, Southeast, Norway, and written informed consent was obtained (11–14). Thirty-nine patients with MCI (19 women, 20 men; mean age, 50.79 years ± 7.6 [standard deviation]) attending a university-based memory clinic and 16 control subjects (10 women, six men; mean age, 61.69 years ± 7.9) without deficits related to memory, emotionality, or cognitive tempo (primarily the patients’ spouses) were included in the study. Participants were recruited consecutively between 2005 and 2009, with planned reassessment 2–3 years later. The last examination was performed in February 2011.

Inclusion criteria for the patients were age of 40–79 years and subjective
memory impairment lasting 6 months or longer, preserved general intellectual function, none or very mild problems with activities of daily living, and Global Deterioration Scale (15) score of 2 or 3, as determined by clinical interview and screening tests. The screening tests consisted of parameters 13–20 (memory, disorientation, abstract thinking, visuospatial function, language, sensory aphasia, visual agnosia, and apraxia) from the Stepwise Comparative Status Analysis, or STEP (16), verbal fluency, interference, and number-letter elements from I-Flex, which is a short form of the executive interview (17). Also included were elements from the Neurobehavioral Cognitive Status Examination (18), Clinical Dementia Rating (19), and Mini-Mental State Examination (MMSE [20]). Patients with MMSE score of 28 or higher, Stepwise Comparative Status Analysis score of 0, I-Flex score of 1 or lower, and a score of 0.5 in a maximum of one Clinical Dementia Rating domain were classified as having a Global Deterioration Scale score of 2. Patients with an MMSE score of 26 or higher, a Stepwise Comparative Status Analysis score of 1 or lower, an I-Flex score of 2 or lower, and a score of 0.5 in more than one Clinical Dementia Rating domain were classified as having a Global Deterioration Scale score of 3. One patient with an MMSE score of 23 was included in the group with a Global Deterioration Scale score of 3 because the participant was self-supporting and employed.

Criteria for exclusion were established psychiatric disorder, anoxic brain damage, cancer, drug abuse, or cognitive symptoms related to solvent exposure. Between baseline and follow-up, seven control subjects objected to reexamination, and one died of unrelated causes. Four patients with MCI objected to reexamination, one died of unrelated causes, and five were excluded because of definite other diagnoses. Fourteen participants were excluded on the basis of missing CSF data or missing or suboptimal data from diffusion-tensor imaging. This left 55 participants with complete data sets for both baseline and follow-up at the time of study. Patients and control subjects were assessed and evaluated clinically by two authors (V.S. and P.S., with 2 and 3 years of experience, respectively). Neuropsychological testing was performed by one author (R.G., with 3 years of experience).

Lumbar Puncture and Laboratory Analyses

Patients underwent lumbar puncture as part of the clinical evaluation; it was not available for the control subjects. The CSF samples were examined for total tau levels with commercially available kits (Innogenetics, Ghent, Belgium). The age-dependent criteria for pathologic values were based on a large sample of healthy control subjects and were as follows: total tau of 300 ng/L or higher for age younger than 50 years, total tau of 450 ng/L or higher for age 50–69 years, and total tau of 500 ng/L or higher for age older than 70 years (21). The 0.90 fractile was estimated to establish reference values for CSF tau. CSF analyses were performed at Akershus University Hospital, Lørenskog, Norway. The MCI group was categorized with regard to CSF total tau levels into MCI low-tau and MCI high-tau groups.

Imaging Acquisition

For practical reasons, two magnetic resonance (MR) imaging devices were used. At baseline, 13 patients and eight control subjects underwent MR imaging at site I; and 26 patients and eight control subjects, at site II. All participants had imaging at site I at follow-up. Diffusion-tensor images were acquired by using two-dimensional spin-echo echo-planar imaging sequences, with diffusion weighting applied along 12 noncollinear directions. At site I, imaging unit A (Symphony; Siemens Medical Solutions, Erlangen, Germany), a 1.5-T MR imaging device with software version 4VA25A (Siemens Medical Solutions) was used with the following parameters: repetition time msec/echo time msec, 4300/131; b value, 700 sec/mm²; number of axial sections, 19; section thickness, 5 mm; spacing, 1.5 mm; matrix, 128 × 128; and in-plane resolution, 1.8 × 1.8 mm. The sequence was repeated twice, and two images with a b value of 0 sec/mm² were obtained per imaging session. At site II, imaging unit B (Espree; Siemens Medical Solutions), a 1.5-T MR imaging device with software version 4VB13A (Siemens Medical Solutions) was used with the following parameters: 6100/117; b value, 750 sec/mm²; number of axial sections, 30; section thickness, 3 mm; spacing, 0.9 mm; matrix, 192 × 192; and in-plane resolution, 1.2 × 1.2 mm. The sequence was repeated five times, and five images with a b value of 0 sec/mm² were obtained per imaging session. Mean duration between MR image acquisitions at baseline and at follow-up did not differ significantly among groups (control subjects, 2.68 years ± 0.64; MCI low-tau group, 2.56 years ± 0.47; MCI high-tau group, 2.61 years ± 0.61).

Diffusion-Tensor Imaging

Image data were processed and analyzed by using tools from the Oxford Centre for Functional MRI of the Brain Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl). Following the standard tract-based spatial statistics processing stream, maps of fractional anisotropy (FA), mean diffusivity (Dm), and axial diffusivity (Da) were calculated from the fitted diffusion tensors after eddy-current corrections and brain extraction (22). We analyzed images from both times by using tract-based spatial statistics (22) but applied a modified processing scheme designed to optimize intrasubject registration to account for change of MR imaging unit, varying head placement, and unit drift between sessions (Fig 1). We used a procedure as described by Engvig et al (23) in which a base FA map is created, representing an unbiased halfway point between the two times for each participant. Diffusion-tensor imaging maps from both times aligned to the base FA map were used to create skeletonized images at both baseline and follow-up. One author (I.K.A., with 4 years of experience) processed and analyzed all images.
Statistical Analysis
A software package (SPSS, version 19.0; SPSS, Chicago, Ill) was used for comparisons of clinical and demographic variables. The $\chi^2$ and Fisher exact tests were used to examine the differences in categorical variables, and one-way analysis of variance was used to examine the differences in continuous variables. The statistical analyses were performed by one author (I.A., with 4 years of experience).

Exploratory whole-brain voxel-wise analyses on all diffusion-tensor imaging indexes were performed between groups at both baseline and follow-up. Permutation-based nonparametric cluster inference (Randomize, a part of the FSL software suite) (24) was used, with controlling for effects of the imaging unit, sex, and age. A total of 5000 permutations were performed, and the results were corrected for multiple comparisons across space by threshold-free cluster enhancement (25). The threshold level for a significant difference was set at $P < .05$ (corrected).

On the basis of the hypothesis that the MCI group would have more intense neuronal degeneration over time than would control subjects and that the diffusion-tensor imaging differences at follow-up would in part reflect this degeneration, we created binary masks from the voxels where MCI was significantly different (ie, lower FA and higher $D_R$) from those of control subjects at follow-up. We extracted the mean FA and $D_R$ for all participants from both times in the voxels overlapping these regions of interest. Because $D_A$ did not show significant group differences at follow-up (see below) and $D_M$ was almost perfectly correlated with $D_R$ ($r = 0.995$), these were omitted from further analysis.

Linear mixed-model between-group within-subject analysis (on the basis of restricted maximum likelihood) was conducted to examine effect of group on rate of change over time in FA and $D_R$. Sex was entered as a covariate of no interest, and age and imaging site were entered as time-varying covariates of no interest. We first examined rate of change between the MCI group as a whole versus control subjects; next, we extended the analyses by comparing rate of change between the MCI subgroups (MCI high-tau group vs MCI low-tau group) and between each of these subgroups and the control subjects.

To characterize the effects according to WM region, we created binary masks that were based on the Johns Hopkins University International Consortium of Brain Mapping diffusion-tensor imaging-81 WM labels atlas (26) and Johns Hopkins University WM tractography atlas (27), with a probability threshold of 5% chosen to accommodate variation in WM structure. The intersections between the tract-based spatial statistics WM skeleton and anatomic masks were used for the regional labeling of the effects (Fig 2).
The following regions and tracts were chosen: corpus callosum (genu, body, splenium), anterior thalamic radiation, cingulum in the cingulate area, hippocampal area of the cingulum, corticospinal tract, inferior and superior longitudinal fasciculi, inferior occipitofrontal fasciculus, uncinate fasciculus, forceps major, and forceps minor.

**Results**

The MCI and control groups did not differ significantly for age, sex, or education. Analysis of the CSF samples revealed that nine patients had pathologic CSF total tau levels, leaving nine patients in the MCI high-tau group and 30 patients in the MCI low-tau group. After we classified subjects in the MCI group, the MCI high-tau and MCI low-tau groups and the control group did not differ significantly for age, sex, or education. MMSE scores did not differ significantly between the MCI high-tau and MCI low-tau groups. Demographic and clinical characteristics are summarized in Table 1.

The cross-sectional analyses revealed that MCI had significantly \( P < .05 \), corrected) lower FA and higher \( D_r \), \( D_{at} \), and \( D_A \) in widespread areas compared with control subjects \( F = 5.48; df = 1, 53.2; P = .023 \).

The MCI high-tau group showed a significantly higher rate of FA decrease \( F = 4.83; df = 1, 21.75; P = .038 \) and a higher rate of \( D_A \) increase \( F = 6.60; df = 1, 22.01; P = .018 \) than did control subjects. In comparing the rate of change between the MCI high-tau and MCI low-tau groups or between the MCI low-tau and control groups, no significant differences were seen, but a trend of progressively more intense WM degeneration across groups emerged. The MCI high-tau group displayed an almost significantly higher rate of change than did the MCI low-tau group for FA \( (F = 3.47; df = 1, 36.24; P = .071) \) and for \( D_{at} \) \( (F = 3.95; df = 1, 36.63; P = .054) \), and the MCI low-tau group had an almost significantly higher rate of \( D_A \) change than did control subjects \( (F = 3.85; df = 1, 44.00; P = .056) \).

Tables and figures were used to support the findings:

- **Table 1**: Demographic and Clinical Characteristics and CSF Biomarker Levels according to Group
- **Figure 2**: Selected regions of interest superimposed on the mean WM skeleton template (green). Binary masks based on the Johns Hopkins University WM atlases (26,27) are shown in blue. Mean diffusion-tensor imaging values were extracted from the intersections between these binary masks and the mean WM skeleton voxels, shown in red. \( A = \) anterior, \( L = \) left, \( P = \) posterior, \( R = \) right.

FA were not significant \( F = 2.63; df = 1, 52.06; P = .11 \), but significant differences were found between the MCI and control groups in rate of \( D_A \) change: The patients with MCI showed a higher rate of increase in \( D_A \) over time than did control subjects \( F = 5.48; df = 1, 53.2; P = .023 \).

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the analysis further, examining in which WM tracts the effects were strongest. WM tracts displaying significant interactions between groups (MCI tau vs control groups) and time (Fig 2) were the hippocampal area of the cingulum ($F = 6.69; df = 1, 22.13; P = .017$), right inferior longitudinal fasciculus ($F = 5.01; df = 1, 22.33; P = .035$), and the right superior longitudinal fasciculus ($F = 4.35; df = 1, 24.09; P = .048$) for $D_r$. When the same tracts were examined for FA, no comparison reached a significant difference.

**Discussion**

The results of the present study suggest that longitudinal changes in WM integrity may be related to intensity of neuronal degeneration as indexed by using pathologic CSF total tau levels. Patients with MCI who had pathologic levels of CSF total tau at baseline displayed greater subsequent declines in FA and greater increases in $D_r$ compared with control subjects. This finding indicates the existence of a subgroup of patients with MCI who have more intense neuronal degeneration and concurrent accelerated reductions in WM integrity. The findings support the CSF total tau level as an important early biomarker for predicting rate of disease progress and outcome.

The current findings extend previously reported cross-sectional results in an overlapping sample. With the use of a manually placed region of interest, Stenset et al (11) found reduced WM integrity in posterior cingulum fibers when comparing the MCI high-tau group with the control group. The results from the present study indicate that the previously reported cross-sectional differences between MCI high-tau and control groups were not merely preexisting differences between the groups but might reflect ongoing degenerative processes. The results thus demonstrate that pathologic CSF total tau levels can be used to distinguish patients with MCI who have ongoing WM degeneration from patients without this degeneration. In addition, the region-of-interest analyses combined with longitudinal data revealed
relations between pathologic CSF total tau level and WM degeneration in areas outside the cingulum area, including the right inferior and superior longitudinal fasciculus.

The present findings may help clarify previous longitudinal findings of no significant differences in WM change between MCI and control groups. Researchers in two longitudinal studies (9,10) failed to detect differences in change in WM integrity among patients with MCI, patients with AD, and control subjects. The lack of differences in WM change in one study (9) might be partially explained by the relatively short follow-up period. Teipel et al (10) did use a longer follow-up, and although their results show no significant differences in change across groups on FA measures, the authors omitted reporting other diffusion-tensor imaging measures. However, these former studies did not include CSF biomarkers; group differences might have been detected if the analyses had been restricted to patients with pathologic CSF total tau levels because the present results indicate that the most intense WM degeneration is a characteristic only of a subgroup of patients with MCI.

Investigators in several previous studies detected differences between patients with MCI or AD and control subjects in diffusion parameters at baseline. Cross-sectional comparisons probably reflect years of accumulated WM damage, amplifying group differences. Alternatively, low WM integrity may constitute a risk factor, which, combined with other risk factors (eg, increased total tau levels), may lead to MCI and AD. Longitudinal studies are necessary to solve such issues. Results of the present study suggest that reduced WM integrity is not merely a preexisting vulnerability factor toward developing MCI or AD but reflects characteristics of disease progression in patients who also have pathologic CSF total tau levels. This observation also

Figure 4: Regions with reduced WM integrity (increased $D_A$, $MD$, or $D_R$, $D_A$, and $D_R$ in blue) in patients with MCI compared with control subjects at baseline and follow-up (threshold-free cluster enhancement–corrected for multiple comparisons at $P < .05$). The effects are superimposed on axial sections of the mean WM skeleton template in Montreal Neurologic Institute space displayed in green and are filled for ease of viewing. A = anterior, L = left, P = posterior, R = right, Z = Montreal Neurological Institute coordinates of the section through the z-axis.
First, the use of different MR imaging units and acquisition protocols could have potentially introduced biases. Further, previous studies on parcellation methods and approaches that data collected from the imaging equipment at baseline was not biased (11,12). In addition, at present it is not well documented how neurodegeneration in the MCI high–total tau group relates to mechanisms of incipient AD disease. Finally, the sample size was limited with regard to the number of patients with pathologic levels of CSF total tau biomarkers. Because we were primarily interested in early mechanisms for AD, we focused on a heterogeneous group of patients with MCI, including patients manifesting both objective and subjective memory problems. Consequently, a lower proportion of patients had pathologic CSF total tau levels than might have been expected in a group consisting solely of, for instance, patients with amnestic MCI.

In conclusion, the results of the present study show that WM degeneration characterizes a subgroup of patients with MCI and is related to levels of CSF tau. This finding demonstrates the benefits of combining neuroimaging and established CSF biomarkers in research on early stages of the disease. An important task in future research will be to test disease progression in the subgroups of patients.

### Table 2

**Regional Distribution of Effects at Follow-up**

<table>
<thead>
<tr>
<th>Region</th>
<th>Total No. of Voxels</th>
<th>No. of Significant Voxel in MCI vs Control Groups</th>
<th>No. of Significant Voxel in MCI vs Control Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corpus callosum</td>
<td></td>
<td>Lower FA</td>
<td>Higher ( \Omega )</td>
</tr>
<tr>
<td>Genu</td>
<td>1789</td>
<td>95 (5)</td>
<td>270 (15)</td>
</tr>
<tr>
<td>Body</td>
<td>3200</td>
<td>1726 (54)</td>
<td>2223 (69)</td>
</tr>
<tr>
<td>Splenium</td>
<td>2445</td>
<td>919 (38)</td>
<td>1190 (49)</td>
</tr>
<tr>
<td>Anterior thalamic radiation</td>
<td></td>
<td>60 (1)</td>
<td>263 (5)</td>
</tr>
<tr>
<td>Left</td>
<td>5812</td>
<td>8 (0)</td>
<td>22 (0)</td>
</tr>
<tr>
<td>Right</td>
<td>4666</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cingulum in cingulate area</td>
<td></td>
<td>70 (7)</td>
<td>254 (26)</td>
</tr>
<tr>
<td>Left</td>
<td>996</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1195</td>
<td>211 (18)</td>
<td>418 (35)</td>
</tr>
<tr>
<td>Hippocampal area of cingulum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>1308</td>
<td>135 (10)</td>
<td>706 (54)</td>
</tr>
<tr>
<td>Right</td>
<td>1131</td>
<td>65 (6)</td>
<td>116 (10)</td>
</tr>
<tr>
<td>Corticospinal tract</td>
<td></td>
<td>222 (7)</td>
<td>399 (12)</td>
</tr>
<tr>
<td>Left</td>
<td>3390</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>3522</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forceps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>5318</td>
<td>302 (6)</td>
<td>676 (13)</td>
</tr>
<tr>
<td>Minor</td>
<td>5503</td>
<td>74 (1)</td>
<td>261 (5)</td>
</tr>
<tr>
<td>Inferior occipito</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal fasciculus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>7757</td>
<td>0</td>
<td>808 (10)</td>
</tr>
<tr>
<td>Right</td>
<td>8318</td>
<td>43 (1)</td>
<td>277 (3)</td>
</tr>
<tr>
<td>Inferior longitudinal fascicu</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>6279</td>
<td>0</td>
<td>1312 (21)</td>
</tr>
<tr>
<td>Right</td>
<td>4958</td>
<td>4 (0)</td>
<td>108 (2)</td>
</tr>
<tr>
<td>Superior longitudinal fascicu</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>8924</td>
<td>27 (0)</td>
<td>809 (9)</td>
</tr>
<tr>
<td>Right</td>
<td>8391</td>
<td>13 (0)</td>
<td>1277 (15)</td>
</tr>
<tr>
<td>Uncinate fasciculus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>3586</td>
<td>0</td>
<td>430 (12)</td>
</tr>
<tr>
<td>Right</td>
<td>2446</td>
<td>0</td>
<td>430 (12)</td>
</tr>
</tbody>
</table>

Note.—Data are number of skeleton voxels overlapping each tract or region of interest, displaying significantly lower FA and higher \( \Omega \) in patients with MCI versus healthy control subjects (\( P < .05 \), threshold-free cluster enhancement–corrected for multiple comparisons).

* Numbers in parentheses are percentages.

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