Cerebrospinal Fluid Tau Protein and Periventricular White Matter Lesions in Patients With Mild Cognitive Impairment

Implications for 2 Major Pathways

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Background: Mild cognitive impairment (MCI) may be a heterogeneous condition rather than a uniform disease entity.

Objective: To develop reliable tools that aid in identifying patients at risk of developing Alzheimer disease (AD) among heterogeneous populations with MCI to maximize the benefits of emerging therapies for AD.

Design: A 2-year prospective study.

Setting: Clinical follow-up in an outpatient memory clinic.

Patients: Seventy-two consecutive older patients with memory complaints.

Main Outcome Measures: Cerebrospinal fluid tau levels, severity of periventricular and deep white matter lesions, silent brain infarction on magnetic resonance imaging, plasma homocysteine levels, apolipoprotein E genotype, and other vascular risk factors were assessed at baseline.

Results: Fifty-seven patients were diagnosed as having amnestic MCI. Forty-one patients with (AD-converted MCI group) or without (progressive MCI group) conversion to dementia and AD progressed over time, whereas the other 16 patients remained cognitively stable (stable MCI group). The stable MCI group was characterized by normal cerebrospinal fluid tau levels and a high grade of periventricular white matter lesions (PWMLs). The progressive MCI and AD-converted MCI groups had increased cerebrospinal fluid tau levels and low grades of PWMLs. A logistic regression model showed that age was significantly associated with developing PWMLs (P = .03; odds ratio, 1.15; 95% confidence interval, 1.0-1.3).

Conclusions: Tau-related AD pathologic conditions and possibly ischemic PWMLs represent 2 major etiologies in the development of MCI, reflecting heterogeneity in the clinical progression. Because the progressive type of MCI may be a primary target of clinical trials that aim at secondary prevention of dementia, these patients should be identified by appropriate biomarkers and neuroimaging techniques.

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RECENTLY, A SUBGROUP OF older people has been recognized with memory failure but without dementia, described as having mild cognitive impairment (MCI).1,2 Although a substantial proportion of patients with MCI may progress and develop clinically diagnosable dementia and Alzheimer disease (AD),3 studies show that MCI may be etiologically more heterogeneous than previously reported and related to general health problems, including midlife hypertension4 and high serum cholesterol levels.5 In a previous study,6 19 of 27 patients with MCI progressed to AD during 4 years, but the other 8 patients did not worsen cognitively. However, there has been no explanation why a subset of patients with MCI remains stable in contrast to a progressive course in others. To maximize the benefits of emerging therapeutic strategies that aim not only to maintain cognitive and functional performance or delay the progression of dementia but also to target more fundamental processes, including brain amyloid deposits, it is essential to identify patients with AD and initiate therapies at MCI stages or earlier. To accomplish this goal, there is a need to develop reliable tools that aid in identifying patients at risk of developing AD within the heterogeneous population of patients with MCI. Herein, we demonstrate 2 distinct MCI subgroups based on results of cere-
brosplinal fluid tau (CSF-tau) measures and magnetic resonance imaging (MRI) findings.

**METHODS**

**PATIENT POPULATION**

We examined and prospectively followed up 72 consecutive individuals with memory complaints. These patients came to the Department of Geriatric Medicine at Tohoku University Hospital Outpatient Clinic on Dementia to seek medical advice about their memory problems. The memory complaints were subjective, observed by family members, or both. At baseline, the patients were functioning independently in the community and were not psychoactive drug users or excessive alcohol drinkers. Global cognitive function was assessed by the Mini-Mental State Examination. Memory function was evaluated using the Japanese version of the Wechsler Memory Scale—Revised (WMS-R). As described by Sugishita and Omura, the original WMS-R has been successfully translated into Japanese and validated for clinical use in an age-adjusted fashion. Because delayed episodic memory is compromised in MCI and thus likely to represent a sensitive indicator that discriminates persons with and without MCI among older people, scores of the logical memory II, visual reproduction II, verbal paired associates II, and visual paired associates II in the WMS-R subscales were summed and expressed as “delayed recall scores” after adjustment for age. A diagnosis of amnestic MCI was made if a patient met the following criteria: (1) complaint of defective memory function by the patient or informant, (2) normal activities of daily living, (3) normal general cognitive function, (4) impaired memory function as revealed by the delayed recall score on the WMS-R, (5) ability to recognize and classify lesions, and (6) no history of head trauma or other reliable collateral source. Small punctate hyperintensity lesions with a diameter of 1 to 2 mm are likely to represent dilated perivascular spaces and were not considered herein. Deep white matter lesions (DWMLs) were defined as high-intensity areas in the fluid-attenuated inversion recovery and T2-weighted images but nearly isointense with normal brain parenchyma in the T1-weighted images as described previously. The DWMLs were located subcortically but not adjacent to lateral ventricle. The other type of white matter lesions that were adjacent to lateral ventricle were periventricular white matter lesions (PWMLs). The severity of DWMLs was graded as 0 (absent), 1 (punctate), 2 (beginning confluent), and 3 (large confluent) and that of PWMLs as 0 (absent), 1 (thin lining or small foci), and 2 (smooth halo or thick lining) by a visual rating scale according to the method described by Fazekas et al. No fresh cerebrovascular lesions were confirmed in any patients with MCI during follow-up. Arterial hypertension was considered present if a patient had a history of blood pressure recordings greater than 160/95 mm Hg or was taking antihypertensive medication. Hypercholesterolemia was diagnosed when serum cholesterol levels exceeded 220 mg/dL (5.7 mmol/L) or the patient was taking statins. Diabetes mellitus was considered present if fasting plasma glucose levels were greater than 110 mg/dL (6.1 mmol/L) or the patient was receiving oral hypoglycemic agents or insulin therapy.

**MRI MEASURES**

On 1.5-T superconducting MRI, silent brain infarction was defined as follows: (1) spotty areas 3 mm or greater in diameter showing high intensity in the T2-weighted images and low intensity in the T1-weighted images, (2) lack of neurological signs or symptoms that can be explained by the MRI lesions, and (3) no medical history of clinical stroke confirmed by a family member or other reliable collateral source. Small punctate hyperintensity lesions with a diameter of 1 to 2 mm are likely to represent dilated perivascular spaces and were not considered herein. Deep white matter lesions (DWMLs) were defined as high-intensity areas in the fluid-attenuated inversion recovery and T2-weighted images but nearly isointense with normal brain parenchyma in the T1-weighted images as described previously. The DWMLs were located subcortically but not adjacent to lateral ventricle. The other type of white matter lesions that were adjacent to lateral ventricle were periventricular white matter lesions (PWMLs). The severity of DWMLs was graded as 0 (absent), 1 (punctate), 2 (beginning confluent), and 3 (large confluent) and that of PWMLs as 0 (absent), 1 (thin lining or small foci), and 2 (smooth halo or thick lining) by a visual rating scale according to the method described by Fazekas et al. No fresh cerebrovascular lesions were confirmed in any patients with MCI during follow-up. Arterial hypertension was considered present if a patient had a history of blood pressure recordings greater than 160/95 mm Hg or was taking antihypertensive medication. Hypercholesterolemia was diagnosed when serum cholesterol levels exceeded 220 mg/dL (5.7 mmol/L) or the patient was taking statins. Diabetes mellitus was considered present if fasting plasma glucose levels were greater than 110 mg/dL (6.1 mmol/L) or the patient was receiving oral hypoglycemic agents or insulin therapy.

**APOLIPOPROTEIN E GENOTYPING AND CSF-TAU AND PLASMA HOMOCYSTEINE DETERMINATIONS**

DNA was extracted from peripheral leukocytes, and genotyping of apolipoprotein E (APOE) alleles was performed by am-

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Normal</th>
<th>Stable MCI</th>
<th>Progressive MCI</th>
<th>AD-Converted MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (male-female ratio)</td>
<td>15 (7:8)</td>
<td>16 (7:9)</td>
<td>24 (7:17)</td>
<td>17 (3:14)</td>
</tr>
<tr>
<td>Age, y</td>
<td>71.9 ± 4.1</td>
<td>75.6 ± 7.1</td>
<td>73.9 ± 7.2</td>
<td>72.4 ± 3.9</td>
</tr>
<tr>
<td>Education, y</td>
<td>10.6 ± 1.7</td>
<td>10.5 ± 2.0</td>
<td>11.5 ± 2.0</td>
<td>12.8 ± 3.0</td>
</tr>
<tr>
<td>Baseline MMSE score</td>
<td>29.2 ± 0.8</td>
<td>25.6 ± 1.5</td>
<td>25.8 ± 1.4</td>
<td>25.5 ± 1.1</td>
</tr>
<tr>
<td>Delayed recall score on WMS-R</td>
<td>99.0 ± 9.1</td>
<td>60.8 ± 5.8</td>
<td>58.4 ± 7.5</td>
<td>55.6 ± 4.9</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>2.0 ± 0.3</td>
<td>2.0 ± 0.3</td>
<td>1.9 ± 0.4</td>
<td>2.0 ± 0.5</td>
</tr>
<tr>
<td>Change in MMSE score by the end of follow-up</td>
<td>0.2 ± 0.4</td>
<td>-0.7 ± 0.8</td>
<td>-2.7 ± 1.0</td>
<td>-5.5 ± 2.1</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; MMSE, Mini-Mental State Examination; WMS-R, Wechsler Memory Scale—Revised.

*Values are expressed as mean ± SD unless otherwise indicated.

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RESULTS

Figure 1. Differential evolution of cognitive impairment among patients with stable, progressive, and Alzheimer disease (AD)-converted mild cognitive impairment (MCI). Mini-Mental State Examination (MMSE) scores were monitored at baseline and every 6 months. There was a significant difference in the MMSE scores between the 3 subgroups at 12 months ($P<.001$), 18 months ($P=.002$), and 24 months ($P<.001$).

Figure 2. Cerebrospinal fluid tau (CSF-tau) values in the normal, stable, progressive, and Alzheimer disease (AD)-converted mild cognitive impairment (MCI) groups. There was a significant difference in the CSF-tau values between the stable and progressive MCI groups ($P<.001$), but these values did not differ significantly between the normal group and the stable MCI group ($P=.45$) or between the progressive MCI group and the AD-converted group ($P=.36$). Bars indicate mean values.

By the end of follow-up, the Mini-Mental State Examination scores declined from baseline by a mean $\pm$ SD of $2.7 \pm 1.0$ points in the progressive MCI group and by $5.5 \pm 2.1$ points in the AD-converted MCI group, whereas there was a 0.7-point change in the Mini-Mental State Examination score during the same period in the stable MCI group ($P<.001$). The differential evolution of cognitive impairment among the 3 MCI subgroups is depicted in Figure 1. The overall annual conversion rate to AD was 16.5%. As shown in Figure 2, the CSF-tau level was significantly higher ($P<.001$) in the progressive MCI group (64.3 $\pm$ 270.6 pg/mL) compared with the stable MCI group (278.3 $\pm$ 225.1 pg/mL) but did not differ significantly ($P=.36$) from that in the AD-converted MCI group (545.7 $\pm$ 269.8 pg/mL). There was no significant difference ($P=.45$) in the CSF-tau values between the stable MCI group (278.3 $\pm$ 225.1 pg/mL) and the normal group (215.1 $\pm$ 70.5 pg/mL). When the progressive MCI and the AD-converted MCI groups were combined, we achieved a sensitivity of 87.8% (36/41) and a specificity of 87.5% (14/16) to distinguish the progressive MCI and AD-converted group from the stable MCI group by using a cutoff value of 320.1 pg/mL (mean $+1.5$ SDs of the normal group). The positive predictive value was 94.7% (36/38), and the negative predictive value was 73.7% (14/19). Therefore, 87.7% (50/57) of the patients with amnestic MCI were correctly predicted for disease progression by CSF-tau measures.

As shown in Table 2, hypertension was most common in the stable MCI group (68.8%) compared with all other groups. The prevalence of diabetes mellitus and hypercholesterolemia did not differ significantly between the 4 comparison groups, nor did APOE allele frequency ($P=.12$) or plasma homocysteine levels ($P=.91$). The PWML grade in the stable MCI group (1.3 $\pm$ 0.9 points) significantly differed from that in the progressive MCI group (0.5 $\pm$ 0.7, $P<.001$) and the AD-converted MCI group (0.4 $\pm$ 0.7, $P<.001$). In contrast to the PWML grade, the DWML grade did not differ significantly between the 4 comparison groups ($P=.50$). Finally, silent brain infarction was noted in 42.9% of the normal group, 56.3% of the stable MCI group, 26.1% of the progressive MCI group, and 35.3% of the AD-converted group ($P=.28$).

Figure 3 demonstrates the plots of the CSF-tau values as a function of PWML grade. Eight (50%) of 16 subjects with stable MCI had grade 2 PWMLs, whereas grade 2 PWMLs were present only in 4 (10%) of the 39 subjects with progressive MCI and AD-converted MCI. On the other hand, 25 (64%) of the 39 had grade 0 PWMLs (MRI data were missing in 2 subjects from the combined group because they, according to their medical history, underwent implantation of a pacemaker), whereas grade 0 PWMLs were only seen in 3 (19%) of 16 of the subjects with stable MCI. Therefore, PWMLs were significantly more frequently detected in the stable MCI group compared with the progressive MCI and AD-converted MCI group ($\chi^2$ test, $P<.001$). Thirty-two (94%) of 34 patients with high CSF-tau levels ($>320.1$ pg/mL) and grade 0 or grade 1 PWMLs showed progression over time, whereas 12 (80%) of 15 patients with low CSF-tau levels ($\leq320.1$ pg/mL) and grade 1 or grade 2 PWMLs...
were in the stable MCI group. Finally, among potential variables, including age, sex, hypertension, diabetes mellitus, and hypercholesterolemia, a logistic regression model showed that age was the only risk factor that was significantly associated with developing PWMLs (P = .03; odds ratio, 1.15; 95% confidence interval, 1.0-1.3).

**COMMENT**

Our study demonstrates that amnestic MCI that is diagnosed by current clinical criteria is heterogeneous clinically and possibly pathologically. Approximately 70% of our patients with MCI showed progression, with rapid conversion to dementia in a subset, whereas cognition was nearly stable over time in the remaining 30%. This study is an extension of previous studies, that showed that CSF-tau measures helped predict progression from MCI to AD. Herein, we not only confirmed these earlier observations with a selected MCI cohort but also highlighted a subset of patients with MCI who remained cognitively stable, suggesting new insights into the clinical and biological heterogeneity of MCI. Indeed, the evolution of cognitive impairment differed among different MCI subgroups as shown in Figure 2. Our results were consistent with recent studies, that showed that MCI is not merely a prodromal stage of dementia but includes more complex conditions. For example, Palmer et al reported that 34% died, 35% progressed to dementia, and 31% remained stable or improved during follow-up for 3 years among community-dwelling individuals with cognitive impairment without dementia. Wahlund et al showed that, during a mean follow-up of 3 years, 11% improved, 53% remained stable, and 35% developed dementia among patients with MCI who had been referred to a memory clinic. The divergent results among different research groups regarding progression and the conversion from MCI to dementia may arise from different study designs, selection of study populations, and inclusion criteria for the diagnosis of MCI. Two indicators that aid in separating the stable type of MCI from the progressive type are the following: (1) The progressive type is characterized by high CSF-tau levels and a low grade of PWMLs. (2) Conversely, the stable type is characterized by normal CSF-tau levels and a high grade of PWMLs. Because the AD-converted MCI group also is characterized by high CSF-tau levels and a low grade of PWMLs, we assume that there is no essential difference between the progressive MCI group and the AD-converted group, despite a faster progression in the latter group. A change in cerebrospinal fluid tau levels may reflect a progressive loss of specific vulnerable neurons in AD and other neurological conditions. Two recent clinicopathological studies demonstrated that the presence of neurofibrillary pathologic conditions in the ventromedial temporal lobe was associated with impairment of episodic memory in MCI. Consistent with another recent prospective study, it is possible that MCI with high CSF-tau levels should be regarded as a precursor state of dementia and AD.

The etiology of white matter lesions remains largely unknown. The periventricular region contains numerous long projecting fibers that connect the cortex with sub-
cortical nuclei and more distant cortical areas, whereas the subcortical region has abundant short-looped U fibers that connect adjacent cortical areas. Therefore, it is likely that PWMLs may disrupt long associating fibers that connect distant cortical areas. Fazekas et al reported histopathological changes associated with incidental white matter signal abnormality on MRI and found that caps or a smooth halo of PWMLs is linked to disruption of the ependymal lining, subependymal gliosis, and concomitant loss of myelin due to altered periventricular fluid dynamics, whereas punctate to confluent DWMLs reflect increasing ischemic tissue damage. Irregular PWMLs extending into deep white matter also indicate a degree of atherosclerotic change similar to that of confluent DWMLs. A link between white matter lesions and vascular risk factors such as hypertension is well described in the literature. Despite an extensive evaluation of potential risk factors for PWMLs and despite the fact that the prevalences of hypertension and mean plasma homocysteine levels were highest in the stable MCI group, PWMLs were only predicted by age. Although this assumes that stable MCI may simply be a form of brain aging rather than a particular pathologic condition, the small sample size, with only 12 subjects with grade 2 PWMLs, and a lack of quantitative measures of white matter lesions, may be alternative explanations for the lack of association between PWMLs and vascular risk factors. A prospective study with a sufficient number of patients with stable MCI would address the issue if at least a subset of patients with stable MCI were to convert to a specific type of vascular dementia over time. In addition, it should be determined whether other novel but poorly recognized age-related risk factors may be associated with developing PWMLs and stabilizing MCI.

In conclusion, we described 2 major etiologies among a clinically defined population with MCI. This may explain, at least in part, why there is heterogeneity in progression among individuals with MCI. Because the progressive type of MCI may be a primary target of clinical trials that aim at secondary prevention of dementia, this group should be accurately identified by use of appropriate biomarkers and neuroimaging techniques.

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Author contributions: Study concept and design (Drs Maruyama, Arai, and Sasaki); acquisition of data (Drs Maruyama, Matsu, Tanji, Nemoto, and Tomita and Ms Ootsuki); analysis and interpretation of data (Drs Maruyama, Matsu, Nemoto, and Arai); drafting of the manuscript (Drs Maruyama, Matsu, Tomita, Nemoto, Tomita, and Arai and Ms Ootsuki); critical revision of the manuscript for important intellectual content (Drs Maruyama, Arai, and Sasaki); statistical expertise (Drs Maruyama and Matsu); administrative, technical, and material support (Drs Matsu, Tanji, Nemoto, Tomita, and Arai and Ms Ootsuki); study supervision (Drs Arai and Sasaki).

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