Clinical and demographic predictors of mild cognitive impairment for converting to Alzheimer's disease and reverting to normal cognition

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Author's key words: Alzheimer's disease, Mild cognitive impairment, Reverter, Converter, Clinical and demographic predictors

Abbreviation: AD, Alzheimer's disease; ADNI, Alzheimer's disease neuroimaging initiative; APOE, apolipoprotein E; CDR, clinical dementia rating; DWMH, deep white matter hyperintensity; FLAIR, fluid attenuated inversion recovery; MCI, mild cognitive impairment; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; NINCDS / ADRDA, national institute of neurological and communicative disorders and stroke and Alzheimer's disease and related disorders association; PGA, parahippocampal gyrus atrophy; PVH, periventricular hyperintensity; VRFs, vascular risk factors; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease; WMLs, white matter lesions.
Abstract

Objective: To identify clinical and demographic predictors for converting to Alzheimer's disease (AD), sustaining mild cognitive impairment (MCI), or reverting to normal cognition from MCI.

Methods: We retrospectively investigated 74 baseline MCI subjects who were categorized into three subgroups those who converted to AD, sustained with MCI, or reverted to normal cognition in one year. The clinical and demographic characteristics assessed were age, gender, educational attainment, vascular risk factors (VRFs), white matter lesions (WMLs), and parahippocampal gyrus atrophy (PGA) on magnetic resonance imaging (MRI). PGA was analyzed using the Voxel-based Specific Regional analysis system for AD (VSRAD).

Results: Out of 74 MCI subjects, 29 (39.2%) were classified as “converters”, 39 (52.7%) as “sustained MCI”, and 6 (8.1%) as “reverters”. Among the three subgroups, there were significant differences in educational attainment (years) (*p=0.03), baseline mini-mental state examination (MMSE) scores (***p<0.001), and periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) grades (*p=0.02 and *p=0.03, respectively). Baseline PGA showed a significant increasing trend among the three subgroups (reverters < sustained MCI < converters, ###p<0.001). MCI subjects with higher educational attainment and a low VSRAD Z-score without WMLs were related to the reverter-to-normal cognitive function.

Conclusions: Risk factors of MCI for AD converters were a low educational attainment, a low baseline MMSE score, high grade WMLs, and a high VSRAD Z-score, while a high educational attainment, a low VSRAD Z-score, and no WMLs characterized reverters.

Keywords: Alzheimer's disease, Mild cognitive impairment, reverter, converter, Clinical and demographic predictors
Introduction

Mild cognitive impairment (MCI) has been defined as a transition state between healthy aging and dementia, such as Alzheimer's disease (AD)\(^1\). The annual rate of conversion from MCI to AD was from 8.3% to 33.6%\(^2,3\) with a high rate of MCI subjects with sustained MCI (64%)\(^4\) and the reversion to normal cognition varying from 2.0% to 53.0%\(^5-7\). Detecting predictors of MCI for converting to AD or for reverting to normal cognition is important to prevent or delay further cognitive decline and to promote reversion.

Previous studies have implicated a number of clinical and demographic predictive factors to AD or back to normal cognition: age, gender, educational attainment, the apolipoprotein E (APOE) \(\varepsilon4\) allele, cognitive status, vascular risk factors (VRFs), white matter lesions (WMLs), medial temporal lobe atrophy, and biomarkers of AD neuropathology\(^7-11\). Risk factors converting to AD were inversely associated with those reverting to normal cognition\(^4\). However, those previous reports studied only one direction of MCI for converting to AD or reverting to normal cognition. Here, we investigated MCI subjects with clinical and demographic predictors in both directions of MCI for converting to AD and reverting to normal cognition as well as with sustained MCI.

Patients and Methods

To carry out this observational study, we used the computerized database of the Okayama University Hospital, Japan. We retrospectively investigated 74 patients (age range 58-89 years old) with MCI based on the Alzheimer's disease neuroimaging initiative (ADNI) criteria, which consists of mini-mental state examination (MMSE) scores between 24-30 (inclusive), a memory complaint, a clinical dementia rating (CDR) of 0.5, essentially preserved activities of daily living, and the absence of dementia\(^12\). At the follow-up about one year later, cognitive status was reassessed and categorized into three types, i.e., converters to mild AD, sustained MCI, and reverters to normal cognition. There were three inclusion criteria for patients with mild AD: (1) an MMSE score between 20-26 (inclusive), (2) a CDR of 0.5 or 1.0, (3) National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS / ADRDA) criteria for probable AD\(^13\). Normal cognition met the following criteria: (1) MMSE scores between 24-30 (inclusive), (2) CDR of 0, (3) no MCI and no dementia.

The clinical and demographic characteristics assessed were age, gender, educational attainment, WMLs by magnetic resonance imaging (MRI),
parahippocampal gyrus atrophy (PGA) by MRI, and vascular risk factors (VRFs) such as hypertension, hyperlipidemia, diabetes mellitus, and smoking history. PGA was analyzed using the Voxel-based Specific Regional analysis system for Alzheimer's disease (VSRAD) 14. With this program, the T1 weighted image of the entire brain was taken with a 1.5 Tesla MRI device.

The location and severity of WMLs were estimated on T2 and fluid attenuated inversion recovery (FLAIR) scans by a trained neurologist using the Fazekas scale15. The Fazekas scale provides two different scores (periventricular hyperintensity, PVH, and deep white matter hyperintensity, DWMH), rated on a 0 to 3 point scale of increasing severity. Participants were classified as having no WMLs, mild, moderate, or severe (grade 0, 1, 2, or 3, respectively) in each location. We dichotomized our sample into low grade WMLs (participants with no or mild lesions) and high grade WMLs (participants with moderate or severe lesions). High grade PVH was thus defined as PVH $\geq 2$ and high grade DWMH as DWMH $\geq 2$.

Exclusion criteria

Participants were excluded if they had a previous diagnosis of psychotic symptoms, multiple sclerosis, motor neuron disease, Parkinson's disease, other major neurological diseases, or if they had medical or psychological conditions that prevented their assessment tasks.

Statistical analysis

Comparisons were performed using the Kruskal-Wallis test (post hoc test; Steel-Dwass test) and the Fisher's exact test, as appropriate. In addition, trends were analyzed with the Cochran-Armitage and Jonckheere-Terpstra tests. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing)16. More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. We selected $p< 0.05$ as the threshold of significance.

This study was approved by the Ethics Committee on Epidemiological Studies of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences No. 694. Written informed consent was obtained from all participants.

Results

The clinical and demographic characteristics of this study follow. As the data
did not show a normal distribution, statistical significance was assessed using nonparametric tests and thus the data are presented as median values. Seventy-four subjects with a median age of 79.0 years were enrolled in the present study. Of 74 subjects, 29 were male and 45 female. The median of years of education was 12.0 years, the median of test intervals was 371.0 days and the median MMSE score of all MCI subjects was 26.0 points.

As shown in Table 1, 29 subjects (39.2%) were classified as subgroup “converters”, 39 subjects (52.7%) as sustained MCI, and 6 subjects (8.1%) as “reverters”. The three subgroups were well matched for age (converters 79.0 years, sustained MCI 79.0 years, and reverters 78.5 years), gender, and test intervals (392.0, 371.0, and 358.0 days, respectively). However, educational attainment (12.0, 12.0, and 14.0 years, respectively, *p=0.03) and MMSE (baseline MMSE; 26.0, 27.0, and 28.0 points, respectively, ***p<0.001; follow-up MMSE; 23.0, 27.0, and 29.0 points, respectively, ***p<0.001) were significantly different among these three subgroups.

As shown in Table 2, there were no significant differences in VRFs among the three subgroups. However, the proportion of high grade PVH was 19/29 (65.5%) in the converters, 15/39 (38.5%) in the sustained MCI, and 1/6 (16.7%) in the reverters, in descending order. Similarly, the proportion of high grade DWMH was 20/29 (69.0%) in the “converters”, 18/39 (46.2%) in the sustained MCI, and 1/6 (16.7%) in the “reverters”, in descending order. There were significant differences between high grade PVH and DWMH proportions among the three subgroups (*p=0.02 and *p=0.03, respectively). The proportion of subjects with high grade PVH and DWMH increased gradually with a linear trend (###p<0.001 for the trend in both cases).

There was significant difference in educational attainment among the three subgroups (Table 1, *p=0.03). Compared with the reverters, the median period of education was significantly shorter in the converters (Fig. 1, 12.0 vs 14.0 years, *p=0.02), while that in sustained MCI was not significantly different. Furthermore, there was no significant difference between converters and sustained MCI (Fig. 1, 12.0 vs 12.0 years). Trend analysis showed a statistically significant decreasing trend among the three subgroups (Fig. 1, reverters > sustained MCI > converters, ###p<0.001 for the trend).

There were differences in baseline and follow-up MMSE scores among the three subgroups (Table 1, baseline MMSE; converters 26.0 points, sustained MCI 27.0 points, and reverters 28.0 points, ***p<0.001; follow-up MMSE; 23.0, 27.0, and 29.0 points, respectively, ***p<0.001). The scores of converters became significantly worse than those of the reverters (Fig. 2, 26.0 vs 28.0 points, **p<0.01 and 23.0 vs 29.0 points,
Moreover, the follow-up MMSE score of converters was significantly lower than that of sustained MCI (Fig. 2, 23.0 vs 27.0 points, ***p<0.001). Trend analysis showed a statistically significant decreasing trend among the three subgroups (Fig. 2, reverters > sustained MCI > converters, ###p<0.001 for the trend).

The results of Z scores by VSRAD are presented in Fig. 3. Z scores did not differ among the three subgroups. However, trend analysis showed a statistically significant increasing trend of the VSRAD value among the three subgroups (reverters < sustained MCI < converters, ###p<0.001 for the trend).

Discussion

Our study showed that the level of progression to dementia (converters) was 39.2%, and that of reverters to normal cognition was 8.1% (Table 1). The present age- and gender-matched study showed that lower educational attainment, lower baseline MMSE score, high grade WML and high Z-score of VSRAD were the risk factors for conversion to AD (Tables 1-2, Fig. 1-3). In contrast, higher educational attainment, higher baseline MMSE score, low grade WMLs and a low Z-score of VSRAD were the factors that characterized reverters (Tables 1-2, Fig. 1-3). Previous reports described an annual level of conversion that ranged from 8.3% to 33.6%2,3, and a level of reversion that varied from 2.0% to 53.0%5,6. Thus, compared to the literature, our study showed a slightly higher level of AD conversion and average reversion.

MMSE is a widely used and well validated assessment for global cognitive function17, 18, and a simple clinical tool for quantifying the risk of future cognitive decline in MCI19. As poorer cognitive performance is associated with converters20, a low MMSE score is a substantial predictor of AD21. In the present study, we found a significant difference in the baseline MMSE and follow-up MMSE scores among the three subgroups (Table 1). Similar to an epidemiologic study in which low educational attainment was significantly associated with an increasing risk of AD22, our present study also confirmed that a short educational period was also a risk of MCI to AD conversion (Fig. 1, Table 1), and that a cognitive reserve with high educational attainment could prevent the conversion to AD and promote the reversion of cognitive function.

Some reports showed that the severity of WMLs significantly affected cognitive performance in AD23,24, while others did not25,26. The present study showed a high grade WMLs (Fazekas grades 2 and 3) tended to be associated with AD converters than low grade WMLs (Table 2). WMLs may affect cognitive performance by disconnecting the cortex from subcortical nuclei or distant cortical territories. VRFs
may be risk factors of incident AD, and treatment of VRFs reduced both the risk of dementia\textsuperscript{10, 27} and the cognitive decline of AD\textsuperscript{28}. However, the present study showed no difference among the three subgroups with regards to VRFs (Table 2), suggesting that it does not reflect a true effect of VRFs in conversion or reversion in a short study period such as one year. Previous studies of VRFs and AD followed up more than a period of 2 years time between the onset and diagnosis of AD\textsuperscript{10, 29}. In addition, a systematic review and meta-analysis reported that VRFs in midlife increased the risk of AD in later life, but in our study was late life\textsuperscript{30}. Cognitive decline is particularly related to medial temporal lobe atrophy\textsuperscript{31-34}. In the present study, there was a significant increasing trend of the VSRAD value among the three subgroups (Fig. 3), suggesting the impact of PGA conversion to AD. A recent meta-analysis found that MCI subjects consistently showed a small hippocampus and amygdala than healthy controls\textsuperscript{35}, but did not show a relation with hippocampal size between MCI subjects and AD.

In summary, the present study showed that educational attainment, baseline MMSE score, WMLs, and the baseline Z-score of VSRAD in MCI subjects were significantly associated with AD conversion or reversion, suggesting that they could be suitable clinical and demographic predictors of MCI conversion to subsequent AD or reversion to normal cognition.

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Footnotes

The authors have declared no conflicts of interest.

References


Table 1. Clinical and demographic characteristics of MCI subgroups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Reverters (n=6)</th>
<th>Sustained MCI (n=39)</th>
<th>Converters (n=29)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n, (%)</td>
<td>6 (8.1)</td>
<td>39 (52.7)</td>
<td>29 (39.2)</td>
<td></td>
</tr>
<tr>
<td>Gender, M / F</td>
<td>2 / 4</td>
<td>18 / 21</td>
<td>9 / 20</td>
<td>0.42 b</td>
</tr>
<tr>
<td>Age, y</td>
<td>74.3 ± 8.8 (78.5)</td>
<td>75.8 ± 8.3 (79.0)</td>
<td>77.2 ± 7.0 (79.0)</td>
<td>0.64 a</td>
</tr>
<tr>
<td>Educational attainment, y</td>
<td>14.0 ± 2.2 (14.0)</td>
<td>12.1 ± 2.3 (12.0)</td>
<td>11.3 ± 1.1 (12.0)</td>
<td>0.03 a</td>
</tr>
<tr>
<td>Test interval, d</td>
<td>372.8 ± 84.5 (358.0)</td>
<td>364.4 ± 72.1 (371.0)</td>
<td>364.2 ± 87.4 (392.0)</td>
<td>0.96 a</td>
</tr>
<tr>
<td>PVH grade 0 / 1 / 2 / 3</td>
<td>1 / 4 / 1 / 0</td>
<td>4 / 20 / 13 / 2</td>
<td>1 / 8 / 15 / 4</td>
<td>0.20 b</td>
</tr>
<tr>
<td>DWMH grade 0 / 1 / 2 / 3</td>
<td>1 / 4 / 1 / 0</td>
<td>4 / 17 / 13 / 5</td>
<td>1 / 8 / 13 / 7</td>
<td>0.26 b</td>
</tr>
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<td>VSRAD</td>
<td>1.3 ± 0.9 (1.3)</td>
<td>2.2 ± 1.1 (2.0)</td>
<td>2.7 ± 1.2 (2.8)</td>
<td>0.13 a</td>
</tr>
<tr>
<td>Baseline MMSE</td>
<td>28.3 ± 1.0 (28.0)</td>
<td>26.7 ± 2.1 (27.0)</td>
<td>25.8 ± 1.6 (26.0)</td>
<td>&lt;0.001 a</td>
</tr>
<tr>
<td>Follow-up MMSE</td>
<td>28.5 ± 1.8 (29.0)</td>
<td>26.7 ± 1.9 (27.0)</td>
<td>22.7 ± 1.9 (23.0)</td>
<td>&lt;0.001 a</td>
</tr>
<tr>
<td>Baseline CDR</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Follow-up CDR</td>
<td>0 ± 0</td>
<td>0.5 ± 0</td>
<td>0.7 ± 0.3</td>
<td></td>
</tr>
</tbody>
</table>

y, year; d, day.

a Kruskal–Wallis test. b Fisher’s exact test

Data are presented as mean ± SD (median).

PVH, periventricular hyperintensity; DWMH, deep white matter hyperintensity

VSRAD, voxel-based specific regional analysis system for Alzheimer’s disease

MMSE, mini-mental state examination; CDR, clinical dementia rating
Table 2. Number of subjects with vascular risk factors and white matter lesions within MCI subgroups.

<table>
<thead>
<tr>
<th>Vascular risk factors</th>
<th>Reverters (n=6)</th>
<th>Sustained MCI (n=39)</th>
<th>Converters (n=29)</th>
<th>p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-)</td>
<td>4</td>
<td>16</td>
<td>13</td>
<td>0.52</td>
<td>0.63</td>
</tr>
<tr>
<td>(+)</td>
<td>2</td>
<td>23</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipemia</td>
<td>(-)</td>
<td>3</td>
<td>23</td>
<td>18</td>
<td>0.88</td>
</tr>
<tr>
<td>(+)</td>
<td>3</td>
<td>16</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>(-)</td>
<td>6</td>
<td>31</td>
<td>21</td>
<td>0.42</td>
</tr>
<tr>
<td>(+)</td>
<td>0</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>(-)</td>
<td>3</td>
<td>30</td>
<td>23</td>
<td>0.32</td>
</tr>
<tr>
<td>history</td>
<td>(+)</td>
<td>3</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>White matter lesion</td>
<td>PVH grade</td>
<td>0 and 1</td>
<td>5</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>2 and 3</td>
<td>1</td>
<td>15</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>White matter lesion (Fazekas scale)</td>
<td>DWMH grade</td>
<td>0 and 1</td>
<td>5</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>2 and 3</td>
<td>1</td>
<td>18</td>
<td>20</td>
<td></td>
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</table>

Data are presented as numbers.
Fig. 1. Educational attainment (years) in MCI subgroups. Reverters (white box), sustained MCI (gray box), and converters (black box).
Fig. 2. Baseline and follow-up MMSE in MCI subgroups. Reverters (white box), sustained MCI (gray box), and converters (black box).
Fig. 3. VSRAD Z scores in MCI subgroups. Reverters (white box), sustained MCI (gray box), and converters (black box).