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

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ABSTRACT

Objective: To identify clinical and demographic predictors for mild cognitive impairment (MCI) conversion to Alzheimer's disease (AD) or reversion to normal cognition, and sustained MCI.
Methods: In total, 74 baseline MCI subjects were retrospectively investigated and categorized into three subgroups: conversion to AD, sustained MCI, or reversion to normal cognition during one year. The clinical and demographic characteristics assessed were age, gender, educational attainment, vascular risk factors, white matter lesions (WMLs), and parahippocampal gyrus atrophy (PGA), analyzed by magnetic resonance imaging (MRI) using the voxel-based specific regional analysis system for AD (VSRAD).
Results: Of the 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 and deep white matter hyperintensity 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 low VSRAD *Z*-scores without WMLs were associated with reversion to normal cognitive function.
Conclusions: Risk factors for MCI conversion to AD were low educational attainment, low baseline MMSE scores, high grade WMLs, and high VSRAD *Z*-scores. High educational attainment, low VSRAD *Z*-scores, and no WMLs characterized reversion to normal cognition.

1. Introduction

Mild cognitive impairment (MCI) is defined as the transition state between healthy aging and dementia, such as Alzheimer's disease (AD) [1]. The annual conversion rate from MCI to AD is 8.3% to 33.6% [2,3], with a high rate of MCI subjects exhibiting sustained MCI (64%) [4] and reversion to normal cognition varying from 2% to 53% [5–7]. Detecting predictors for MCI converting to AD or reverting to normal cognition is important to prevent or delay further cognitive decline and promote reversion.

Previous studies have implicated a number of clinical and demographic predictive factors for AD or reversion to normal cognition, including age, gender, educational attainment, apolipoprotein E (*APOE*) ε4 allele, cognitive status, vascular risk factors (VRFs), white matter lesions (WMLs), medial temporal lobe atrophy, and AD neuropathology biomarkers [7–11]. Risk factors for converting to AD are inversely associated with reversion to normal cognition [4]. However, these previous reports have only studied a single direction, either MCI conversion to AD or reversion to normal cognition.

Here, we investigated MCI subjects using clinical and demographic predictors in both directions, MCI conversion to AD or reversion to normal cognition, as well as sustained MCI.

2. Methods

2.1. Patients

The computerized database of the Okayama University Hospital, Japan was used to perform this observational study. In total, 74 patients (age range 58–89 years) were retrospectively investigated. The patients

Abbreviations: 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.

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had MCI based on the Alzheimer's disease neuroimaging initiative (ADNI) criteria, which consists of mini-mental state examination (MMSE) scores between 24–30 (inclusive), memory complaint, clinical dementia rating (CDR) of 0.5, essentially preserved activities of daily living, and absence of dementia [12]. At follow-up approximately 1 year later, cognitive status was reassessed and categorized into three types: converters to mild AD, sustained MCI, or reverters to normal cognition.There were three inclusion criteria for patients with mild AD: (1) MMSE score of 20–26 (inclusive); (2) CDR of 0.5 or 1.0; and (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 score of 24–30 (inclusive); (2) CDR of 0; and (3) no MCI or 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 determined using the voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) [14], with T1 weighted images of the entire brain taken using a 1.5 Tesla MRI device.

Location and severity of WMLs were estimated using Fazekas scale from T2 and fluid attenuated inversion recovery (FLAIR) scans by a trained neurologist [15]. 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 split our patient 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 defined as ≥ 2, and high grade DWMH as ≥ 2.

2.2. 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 medical or psychological conditions that prevented completion of assessment tasks.

2.3. Statistical analysis

Comparisons were performed using the Kruskal–Wallis test (with Steel–Dwass post-hoc test) or Fisher's exact test, as appropriate, and trends were analyzed using the Cochran–Armitage and Jonckheere–Terpstra tests. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Japan), a graphical user interface for R (The R Foundation for Statistical Computing) [16]. Specifically, it is a modified version of R commander with incorporation of 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.

3. Results

The data was not normally distributed, therefore statistical significance was assessed using nonparametric tests and data presented as median values. Seventy-four subjects with a median age of 79.0 years were enrolled. Of the 74 subjects, 29 were male and 45 female, with 12.0 years median years of education, 371.0 days median of test intervals, and 26.0 points median MMSE score of all MCI subjects.

As shown in Table 1, 29 subjects (39.2%) were classified in the subgroup “converters”, 39 (52.7%) as sustained MCI, and 6 (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 the 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, in descending order, 19/29 (65.5%) (converters), 15/39 (38.5%) (sustained MCI), and 1/6 (16.7%) (reverters). Similarly, the proportion of high grade DWMH was, in descending order, 20/29 (69.0%) (converters), 18/39 (46.2%) (sustained MCI), and 1/6 (16.7%) (reverters). There were significant differences between high grade PVH and DWMH proportions among the subgroups ($^{*}p = 0.02$ and $^{*}p = 0.03$, respectively). The proportion of subjects with high grade PVH and DWMH gradually increased linearly ($^{\#\#\#}p < 0.001$ in both cases).

There were significant differences in educational attainment among the three subgroups (Table 1; $^{*}p = 0.03$). Compared with reverters, the median period of education was significantly shorter in converters (Fig. 1; 12.0 vs 14.0 years, $^{*}p = 0.02$), while not significantly different in sustained MCI. Furthermore, there was no significant difference between converters and sustained MCI (Fig. 1; 12.0 vs 12.0 years). Trend analysis showed a statistically

Table 1
Clinical and demographic characteristics of MCI subgroups.

Characteristics	Reverters (n = 6)	Sustained MCI (n = 39)	Converters (n = 29)	p-value
n, (%)	6 (8.1)	39 (52.7)	29 (39.2)	
Gender, M / F	2 / 4	18 / 21	9 / 20	0.42 [b]
Age, y	74.3 ± 88.8 (78.5)	75.8 ± 88.3(79.0)	77.2 ± 87.0 (79.0)	0.64 [a]
Educational attainment, y	14.0 ± 82.2 (14.0)	12.1 ± 82.3 (12.0)	11.3 ± 81.1 (12.0)	0.03 [a]
Test interval, d	372.8 ± 84.5 (358.0)	364.4 ± 72.1 (371.0)	364.2 ± 87.4 (392.0)	0.96 [a]
PVH grade 0 / 1 / 2 / 3	1 / 4 / 1 / 0	4 / 20 / 13 / 2	1 / 9 / 15 / 4	0.20 [b]
DWMH grade 0 / 1 / 2 / 3	1 / 4 / 1 / 0	4 / 17 / 13 / 5	1 / 8 / 13 / 7	0.26 [b]
VSRAD	1.3 ± 80.9 (1.3)	2.2 ± 81.1 (2.0)	2.7 ± 81.2 (2.8)	0.13 [a]
Baseline MMSE	28.3 ± 81.0 (28.0)	26.7 ± 82.1 (27.0)	25.8 ± 81.6 (26.0)	<0.001 [a]
Follow-up MMSE	28.5 ± 81.8 (29.0)	26.7 ± 81.9 (27.0)	22.7 ± 81.9 (23.0)	<0.001 [a]
Baseline CDR	0.5	0.5	0.5	
Follow-up CDR	0.2 ± 80	0.5 ± 00	0.7 ± 80.3	

y, year; d, day.
PVH, periventricular hyperintensity; DWMH, deep white matter hyperintensity [a] Kruskal–Wallis test. [b] Fisher's exact test
VSRAD, voxel-based specific regional analysis system for Alzheimer's disease Data are presented as mean ± SD (median)
MMSE, mini-mental state examination; CDR, clinical dementia rating

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