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ORIGINAL ARTICLE

Clinical Predictors for Mild Cognitive Impairment Progression in a Korean Cohort

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Background and Purpose Patients with mild cognitive impairment (MCI) and their caregivers are concerned with the likelihood and time course of progression to dementia. This study was performed to identify the clinical predictors of the MCI progression in a Korean registry, and investigated the effects of medications without evidence, frequently prescribed in clinical practice.

Methods Using a Korean cohort that included older adults with MCI who completed at least one follow-up visit, clinical characteristics and total medical expenses including prescribed medications were compared between two groups: progressed to dementia or not. Cox proportional hazards regression analysis was conducted.

Results During the mean 1.42±0.72 years, 215 (27.63%) of 778 participants progressed to dementia. The best predictors were age [hazard ratio (HR), 1.036; 95% confidence interval (CI), 1.006–1.067; p=0.018], apolipoprotein ε4 allele (HR, 2.247; 95% CI, 1.512–3.337; p<0.001), Clinical Dementia Rating scale-sum of boxes scores (HR, 1.367; 95% CI, 1.143–1.636; p=0.001), Instrumental Activities of Daily Living scores (HR, 1.035; 95% CI, 1.003–1.067; p=0.029), and lower Mini-Mental State Examination scores (HR, 0.892; 95% CI, 0.839–0.949; p<0.001). Total medical expenses were not different.

Conclusions Our data are in accordance with previous reports about clinical predictors for the progression from MCI to dementia. Total medical expenses were not different between groups with and without progression.

Key Words cholinesterase inhibitors, dementia, mild cognitive impairment, predictors.

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INTRODUCTION

Mild cognitive impairment (MCI) represents an intermediate state between normal aging and dementia.[1] Several longitudinal studies have shown that most persons with MCI are at increased risk for the development of dementia.[2,3] Especially, when memory loss is the predominant symptom, it is termed "amnestic MCI" and is frequently seen as a prodromal stage of Alzheimer's disease (AD).[4] Therefore, MCI has been receiving considerable attention in clinical practice and research settings.

A question commonly raised by patients with MCI and their family members concerns the likelihood and time course of progression to dementia. Although the general rate of progression among those with a diagnosis of MCI is estimated at 10–15% per year,[1] certain factors predict a more rapid progression. The degree of memory impairment at presentation is a clinical predictor of progression,[5] probably because these patients are closer to the threshold for the diagnosis of dementia. Longitudinal data have shown that the progression to dementia is more rapid among carriers of the apolipoprotein (APOE) ε4 allele than among noncarriers.[6] Other considerations such as old age and low education were also reported.[7]

As MCI may represent a prodromal state to clinical AD, treatments proposed for AD, such as cholinesterase inhibitors (ChEIs), may be considered for MCI, too. However, until now, there is no proven treatment for MCI.[8] Several potential treatments are still under investigation.[9] Although the risk-benefit ratio is questionable, some interventions in patients with MCI are being used in clinical practice without evidence.

We planned this study to investigate the effects of medications without evidence, frequently prescribed in clinical practice, such as ChEIs and neural pills including nootropics and Ginkgo Biloba, on progression to dementia, in addition to determine the potential clinical predictors of progression from MCI in a Korean cohort.

METHODS

Participants

This study was conducted as part of the Clinical Research Center for Dementia of South Korea (CREDOS) study, which is a multicenter hospital-based prospective cohort study. From May 2007 to September 2011, 778 patients who completed at least one follow-up visit were included in the study. The Institutional Review Boards at all participating centers approved this study. Written, informed consent was obtained from patients and caregivers.

All patients with MCI met the following guidelines based on the criteria proposed by Petersen:[10] 1) subjective memory complaint, 2) normal general cognitive function as defined by scores on the Korean version of the Mini-Mental State Examination (K-MMSE)[11] ≥-1.0 standard deviation of the norms for age- and education-matched normal subjects, 3) normal activities of daily living (ADL), as judged both clinically and on the ADL scale described below, 4) objective cognitive impairment on at least one of the four domains of comprehensive neuropsychological tests with scores below the 16th percentile, and 5) not demented. Patients with MCI were divided into amnestic or nonamnestic.

Patients with neurological or psychiatric illnesses such as schizophrenia, epilepsy, and encephalitis were excluded. Patients with physical illnesses that could interfere with the clinical study, such as hearing or vision loss, aphasia, malignancy, and hepatic or renal disorders were excluded. Blood tests for excluding medical diseases included a complete blood count, blood chemistry tests, vitamin B12/folate, syphilis serology, and thyroid function tests. Conventional brain magnetic resonance imaging (MRI) scans confirmed the absence of structural lesions such as tumors, traumatic brain injuries, hydrocephalus, or severe white matter hyperintensities (WMHs).

Clinical assessments

We used the Dementia Evaluation Package developed by CREDOS, which is composed of the Clinical Evaluation Form and Caregiver Questionnaire Form.[12] The Clinical Evaluation Form included: 1) the history of cognitive decline from the caregiver, 2) K-MMSE,[11] 3) Clinical Dementia Rating (CDR) and CDR Sum of Boxes (CDR-SOB),[13] 4) Hachinski ischemia scale,[14] 5) body mass index (BMI), 6) neurological examinations, and 7) Geriatric depression scale (GDS).[15] The Caregiver Questionnaire Form included: 1) basic demographic data, 2) medical history, including vascular risk factors, and 3) the Seoul Instrumental ADL (S-IADL).[16] All participants underwent a standardized neuropsychological battery known as the Seoul Neuropsychological Screening Battery.[17]

MRI was performed on all participants, based on the protocol of MRI acquisition for CREDOS registration.[12] WMHs were represented by a final ischemia score of minimal, moderate, or severe.[18] Additionally, APOE genotype was determined by polymerase chain reaction.

At the follow-up visit, all cognitive and neuropsychological assessments except laboratory tests and MRI were performed annually. The diagnosis of dementia was based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Some other participants remained with MCI or reversed into normal cognition. Specific diagnostic criteria were used for designation of dementia classification. Using the criteria from the National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association,[19] National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences,[20] criteria modified from McKeith et al.[21] for Dementia with Lewy Body (DLB), and research criteria for frontotemporal dementia (FTD) proposed by Knopman et al.,[22] all dementia participants were assigned to one of the following specific dementia diagnosis classifications: 1) AD; 2) vascular dementia (VaD); 3) DLB; or 4) FTD.

Linkage to the National health insurance claims database

With help of the National Strategic Coordinating Center for Clinical Research, the national health insurance claims database from 2007 to 2011 was analyzed to investigate medications prescribed and total medical costs. The claims data were provided through an IRB approval of the Health Insurance Review and Assessment Service that builds a national claims database for the total population. Using these data files, total medical expenses including medication costs (medicine cost dispensed by prescription) and number of used medical care institutions were analyzed. Total costs only by public health insurance were analyzed. Total medical expenses for 1 year were calculated. Medication domain was classified as ChEIs including donepezil, galantamine, and rivastigmine, and neural pills including acetyl-L-carnitine, choline alphoscerate, nicergoline, oxiracetam, and Ginkgo Biloba extract. All the costs were calculated in Korean Won.

Statistical analyses

SAS (version 9.3; SAS Institute Inc., Cary, NC, USA) and SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL, USA) were used for data analyses. We analyzed the frequencies and the mean values of the variables to determine group differences in total medical expenses as well as demographic and clinical characteristics between the progressed to dementia and not progressed groups. Age and K-MMSE scores were included as covariates for analyses of covariance.

Factors were analyzed as predictors of time to dementia diagnosis using a Cox proportional hazard regression model. Covariates included age and baseline K-MMSE scores. To further analyze the best predictors of dementia progression, we re-performed the analyses with factors that showed significance at the first Cox proportional hazard regression model, such as education, APOE ε4 allele, CDR-SOB, S-IADL, BMI, and changes of GDS, as covariates in addition to age and K-MMSE scores. Time to the event was defined as the time from study entry to the follow-up visit during which a first-time diagnosis of dementia was made. Participants that did not progress into AD were treated as censored observations from the time of their final follow-up evaluation.

RESULTS

Of the 778 participants with MCI who completed at least one follow-up visit, 215 (27.63%) progressed to dementia (200 AD, 8 VaD, 4 DLB, and 3 FTD) and 74 (9.51%) reversed to normal cognition. The demographic and clinical characteristics of the participants who progressed into dementia, remained in MCI, and revised into normal cognition, are summarized in Table 1. Mean follow-up duration was 1.42±0.72 years, and not different between groups. Participants who progressed to dementia were older and had lower K-MMSE scores at the baseline evaluation, compared with those who did not progress. Even after adjusting for age and K-MMSE scores, CDR-SOB score, BMI value, and frequency of presence of APOE ε4 allele were different. GDS scores were different at follow-up (p=0.0006), although these were not different at

Table 1. Characteristics of the study population at baseline

	Total (n=778)	Remained MCI (n=489)	To normal (n=74)	To dementia (n=215)		p value
					AD (n=200)	
Age (years)	70.62±7.40	70.55±7.45	66.82±7.33	72.07±6.85	72.11±6.98	<0.001†
Sx. duration (months)	25.00±24.62	24.66±23.58	28.59±29.81	24.61±25.12	24.58±25.39	0.7616
Gender (M:F)	264:514	175:314	22:52	67:148	60:140	0.366
Education (years)	8.04±5.09	7.84±5.08	8.09±4.82	8.46±5.21	8.32±5.19	0.327
K-MMSE	24.70±3.50	24.96±3.30	26.47±2.92	23.52±3.77	23.48±3.83	<0.001†‡
CDR-SOB	1.61±0.90	1.56±0.87	1.07±0.68	1.90±0.91	1.91±0.92	<0.001†‡
BMI (kg/m^2)	23.79±3.13	23.95±3.08	24.56±2.97	23.16±3.21	23.14±3.24	0.0042
HIS	1.89±1.76	1.95±1.85	1.70±1.83	1.81±1.51	1.79±1.49	0.352
GDS	6.22±4.29	6.30±4.33	6.70±4.29	5.87±4.19	5.78±4.23	0.285
Severity of WMHs*	571:192:15	350:129:10	62:12:00	159:51:05	151:46:03	0.239
APOE ε4	169/437 (38.67%)	82/266 (30.83%)	6/31 (19.35%)	81/140 (57.86%)	79/128 (61.72%)	<0.001†‡

Data are mean±SD or n (%) values.
*Severity of WMHs was represented as minimal: moderate: severe. The analyses were performed by analysis of covariance (ANCOVA), adjusted for age and K-MMSE score, †Difference between those who remained with MCI and reversed to normal, at the post hoc analysis by using the Scheffe's method, ‡Difference between those who remained with MCI and progressed to dementia, at the post hoc analysis by using the Scheffe's method.
AD: Alzheimer's disease, APOE: apolipoprotein, BMI: body mass index, CDR-SOB: Clinical Dementia Severity–Sum of Boxes, F: female, GDS: Geriatric Depression Scale, HIS: Hachinski Ischemic Scale, K-MMSE: Korean version of Mini-Mental State Examination, M: male, MCI: mild cognitive impairment, SD: standard deviation, Sx.: symptom, WMHs: white matter hyperintensities.

baseline. The change of GDS scores during follow-up was 1.79±5.11 in participants who progressed to dementia, which was higher compared to -0.28±4.17 in those remained, and -1.24±3.16 in those reversed (p=0.0001). Distribution of other characteristics including family history of dementia and history of concomitant medical diseases was not different.

Table 2 shows the differences of total medical expenses including medication costs and number of used medical institutions, and the prescription frequency of ChEIs and neural pills during follow-up. During the follow-up period, neural pills were prescribed to 539 (69.28%) MCI participants and ChEIs were used by 395 (50.77%). ChEIs were prescribed to 172 (80.00%) participants with progression to dementia, 208 (42.54%) remained, and 15 (20.27%) reversed (p<0.001). Other differences were not observed.

Initial Cox proportional hazard models, adjusted for age and K-MMSE score, revealed that some factors were associated with a higher risk of MCI progression: lower education years, lower BMI values, amnesia, higher CDR-SOB and S-IADL scores at baseline, increased GDS scores during follow-up, and presence of APOE ε4 allele, in addition to older age and lower K-MMSE score at baseline (Table 3). To further analyze the best predictors of dementia progression, we performed Cox proportional hazard analyses entering all the above factors showing significance at the initial analysis. Older age [hazard ratio (HR), 1.036; 95% confidence interval (CI), 1.006–1.067; p=0.018], APOE ε4 allele (HR, 2.247; 95% CI, 1.512–3.337; p<0.001), higher CDR-SOB score (HR, 1.367; 95% CI, 1.143–1.636; p=0.001), higher S-IADL score (HR, 1.035; 95% CI, 1.003–1.067; p=0.029), and lower K-MMSE score (HR, 0.892; 95% CI, 0.839–0.949; p<0.001) predicted greater hazard (Table 3).

DISCUSSION

This study shows the risk of progression from MCI to dementia and its underlying predictors, in a clinical Korean cohort for dementia research. Older age, worse baseline cognitive and global function, and presence of the APOE ε4 allele are the best predictors. Additionally, lower education years, lower BMI values, presence of amnesia at baseline, and increased GDS scores during follow-up had some influence on the progression to dementia. The present findings are in agreement with those from previous studies.[5-7,23,24] Furthermore, with linkage to the national health insurance claims database, we show that total medical expenses are not different between MCI participants who progressed to dementia and those who did not. Although it was based on a clinical cohort, we believe that the present evidence will add to the existing knowledge

Table 2. Total medical expenses including medication costs and number of used medical care institutions during the follow-up period

	Total (n=778)	Remained MCI (n=489)	To norma (n=74)	To dementia (n=215)		p value
					AD (n=200)	
During the follow-up period	1.42±0.72	1.39±0.70	1.47±0.64	1.46±0.78	1.47±0.78	0.409
Participants taking Neural pills	539	329 (67.28%)	59 (79.73%)	151 (70.23%)	138	0.0873
Participants taking ChEIs	395	208 (42.54%)	15 (20.27%)	172 (80.00%)	161	<0.001
Medication costs (won)	2837487.23±2438626.53	2763990.07±2531720.49	2708054.24±1930424.91	3022804.33±2381547.43	3072940.85±2414079.37	0.138
Visited medical institutions per person	7.68±5.07	7.72±5.12	8.22±4.97	7.40±5.02	7.29±5.02	0.476

Data are mean±SD or n (%) values. The analyses were performed by analysis of covariance (ANCOVA), adjusted for age and K-MMSE score.
AD: Alzheimer's disease, ChEIs: cholinesterase inhibitors, MCI: mild cognitive impairment, SD: standard deviation.

Table 3. Cox proportional hazards models

	HR	95% CI		*p* value
Age (years)	1.362	1.277	1.451	<0.001*
Education (years)	0.921	0.893	0.95	<0.001
Sx. duration (months)	1.938	1.575	2.381	<0.001
Amnesia	2.101	1.277	3.46	0.004
APOE ε4	2.883	2.013	4.127	<0.001*
K-MMSE	0.871	0.839	0.904	<0.001*
CDR-SOB	1.329	1.134	1.557	<0.001*
S-IADL	1.038	1.015	1.063	0.002*
BMI (kg/m²)	0.91	0.87	0.952	<0.001
GDS	0.969	0.936	1.003	0.078
Change of GDS	1.066	1.036	1.092	<0.001
ChEIs prescribed during the follow-up	3.546	2.481	5.076	<0.001

*After the initial Cox proportional hazard regression analysis, adjusted for age and K-MMSE score, the second Cox proportional hazard analysis entering all the above factors showing significance at the initial analysis was performed to further analyze the best predictors for dementia progression. Older age (HR, 1.036; 95% CI, 1.006–1.067; p=0.018), APOE ε4 allele (HR, 2.247; 95% CI, 1.512–3.337; p<0.001), higher CDR-SOB score (HR, 1.367; 95% CI, 1.143–1.636; p=0.001), higher S-IADL score (HR, 1.035; 95% CI, 1.003–1.067; p=0.029), and lower K-MMSE score (HR, 0.892; 95% CI, 0.839–0.949; p<0.001) predicted greater hazard.
APOE: apolipoprotein, BMI: body mass index, CDR-SOB: Clincial Dementia Severity-Sum of Boxes, ChEIs: cholinesterase inhibitors, CI: confidence interval, GDS: Geriatric Depression Scale, HR: hazard ratio, K-MMSE: Korean version of Mini-Mental State Examination, S-IADL: Seoul-Instrumental Activities of Daily Living, Sx.: symptom.

on the risk of dementia, especially AD, in Korea, which has been accumulated mostly from epidemiological studies in this country.[24]

At present, there has been no medication approved for the treatment of MCI. In several placebo-controlled clinical trials, there was no significant reduction in the rates of progression to dementia among MCI patients who were treated with ChEIs.[6,25-27] In one trial, donepezil significantly reduced the risk of progression to AD for the first 12 months of the study (and for up to 24 months in subgroups who were carriers of APOE ε4) but had no significant effect on the risk of AD at 36 months, which was the primary study outcome.[6] The present study showed that, at the initial Cox proportional hazard models, HR for ChEIs during follow-up was 3.546 (95% CI, 2.48–5.08, p<0.001). However, the result was not significant after multivariate analysis. We do not suggest that ChEIs might make patients with MCI progress rapidly. During the follow-up of mean 1.42 years, 396 (50.77%) participants with MCI were prescribed with ChEIs. Eighty percent of MCI participants who progressed into dementia were prescribed with ChEIs, which was higher than in those who did not progress. During follow-up, changes in K-MMSE, CDR-SOB, and S-IADL scores were more severe in participants who progressed to dementia. We do not have information on whether the participants were already taking ChEIs before being enrolled into the claims database. However, mean age at the initial visit was older, and initial and follow-up scores of K-MMSE were lower in participants prescribed with ChEIs during follow-up. Our findings might indicate that substantial MCI patients in Korea, who were considered as severe as dementia by clinicians, could be prescribed with ChEIs, but this medication could not prevent the progression to dementia. In our cohort data, the annualized rate of progression to AD in our study (17.49%) was slightly higher than the original estimate (10 to 15% per year) by Petersen et al.[1] Another study performed in Korea showed the annual conversion rate of 15.48%.[28]

This study has some limitations. The first is regarding the rates of progression to dementia or reversion to normal cognition observed in our study. Within the mean 1.5 years of follow-up, 27.63% of participants progressed to dementia, which represents an annual conversion rate slightly higher than those found by most studies, generally ranging from 10 to 15% (1–3). This might be due to a selection bias. We investigated only those participants with follow-up evaluations. Several individuals who had MCI at baseline were excluded from our analyses for missing a follow-up evaluation. These individuals differed significantly from those remaining in the study. Patients without cognitive decline would not visit the clinic for a follow-up evaluation. Moreover, 9.51% participants showed reversion to normal cognition, which could be by seeking help for their cognitive difficulties through higher cognitive, physical, and social activities. Consequently, we may be reporting an overestimated prevalence of reversion. An association between age and reversion was not found in this study, but there are reports that individuals younger than 70 years may show different predictors of reversion.[29] Moreover, the relatively short duration of follow-up in this study provides only a narrow window of investigation. A longer follow-up period is needed to determine the extent to which unstable MCI represents a very early MCI stage of serious cognitive decline. A final limitation is our lack of consideration of transitory cognitive impairment associated with factors like stress, acute illness, or poor motivation, with MCI diagnosed under such conditions at greater than normal chances of reversion to normal cognition.[29,30] Additionally, we could not exclude the possibility that MCI patients who progressed to dementia already took ChEIs or neural pills at other clinics (not in the database) before the baseline enrollment in the database. K-MMSE score at initial visit was lower in participants prescribed with ChEIs during the follow-up. Although adjustment for K-MMSE score was performed, matching the baseline cognitive status between those who were prescribed with and without ChEIs could further evaluate the effect of ChEIs on the rate of cognitive decline.

However, this Korean multi-hospital based cohort database showed that 215 (27.63%) of 778 participants with MCI progressed to dementia including 200 AD, during mean 1.42±0.72 years of follow-up duration, and the best predictors for progression were older age, lower K-MMSE scores, higher CDR-SOB, and S-IADL scores, and APOE ε4 allele. Lower education years, lower BMI values, and increased GDS scores during follow-up can have some effect on the prognosis.

Conflicts of Interest

The authors have no financial conflicts of interest.

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