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Extrapyramidal Signs and Risk of Progression from Mild Cognitive Impairment to Dementia: A Clinical Research Center for Dementia of South Korea Study

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Objective Extrapyramidal signs (EPS) are common in patients with mild cognitive impairment (MCI). However, few studies have assessed the effect of EPS on the clinical course of MCI. We aimed to evaluate whether patients with EPS show more frequent progression from MCI to Alzheimer's disease (AD) and to other types of dementia.

Methods Participants (n=882) with MCI were recruited, and were followed for up to 5 years. The EPS positive group was defined by the presence of at least one EPS based on a focused neurologic examination at baseline.

Results A total of 234 converted to dementia during the follow-up period. The risk of progression to AD was lower in the patients with EPS after adjusting for potential confounders [hazard ratio (HR)=0.70, 95% confidence interval (CI)=0.53–0.93, p=0.01]. In contrast, the patients with EPS had a six-fold elevated risk of progression to dementia other than AD (HR=6.33, 95%CI=2.30–17.39, p<0.001).

Conclusion EPS in patients with MCI is a strong risk factor for progression of MCI to non-Alzheimer dementia. The careful neurologic examination for EPS in patients with MCI can yield important clinical information for prognosis.

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Key Words Alzheimer disease, Mild cognitive disorder, Extrapyramidal signs, Progression.

INTRODUCTION

Mild cognitive impairment (MCI) is a clinical entity defined as abnormal cognitive function relative to age and education, with preserved activities of daily living.[1] Based on several longitudinal studies,[2-5] MCI has attracted much attention as a prodromal phase to dementia. The prevalence of MCI is estimated at between 10−20% in elderly populations[6-8] and the annual progression rates to Alzheimer's disease (AD) is estimated at approximately 5−10% in a meta-analysis.[9] Female gender, older age, low educational level, diabetes mellitus (DM), subclinical depression, white matter hyperintensities (WMH), and presence of the APOE ε4 allele are reported as risk factors for progression from MCI to incident demen-

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tia.[2-4,10-12] However, little has been known about focal neurological signs as a risk factor for the progression from MCI to incident dementia.

Extrapyramidal signs (EPS) are common in elderly people without any diagnosed neurological disease and also in individuals with MCI.[13] These neurological signs include rigidity, resting tremor, impaired gait and balance, and they are readily observed in the clinical setting without expensive laboratory equipment. For two decades, multiple studies have revealed that EPS in AD is related to functional impairment,[14,15] faster cognitive decline,[16] greater risk of institutionalization[17] and higher mortality.[18] Recent population based prospective studies have demonstrated that EPS in nondemented elderly subjects are associated with incident dementia.[19,20] However, few studies have assessed the clinical impact of EPS in MCI, especially in terms of progression to dementia. Moreover, as far as we know there is no study that examined the effect of EPS on the progression to dementia other than AD. In this study, we investigated the role of EPS as a risk factor for the progression from MCI to AD and to other types of dementia in a large cohort collected through a coordinated national clinical network.

METHODS

Subjects

This study was conducted as a part of the Clinical Research Center for Dementia of South Korea (CREDOS) study, an ongoing, prospective, nationwide, hospital-based multi-center study with fifty-six participating hospitals.[21]

All patients were diagnosed with MCI and they had at least one longitudinal clinical review after baseline. The criteria for MCI in the CREDOS study[22] are as follows: 1) presence of concern about a change in cognition; 2) intact function in Activities of Daily Living except performing complex functional tasks; 3) objective cognitive impairment (at least -1.0 standard deviation below age-and education-adjusted norms) in more than one cognitive domain on standardized neuropsychological testing[23]; 4) Clinical Dementia Rating (CDR) of 0.5,[24] and 5) not demented according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR criteria.[25] All subjects had to have a reliable informant familiar with the patient's daily activities. None of the subjects presented any of the following exclusion criteria: 1) history of significant hearing or visual impairment rendering participation in the interview difficult; 2) neurological disorders (e.g., territorial infarction, intracranial hemorrhage, brain tumor, hydrocephalus, multiple scle-

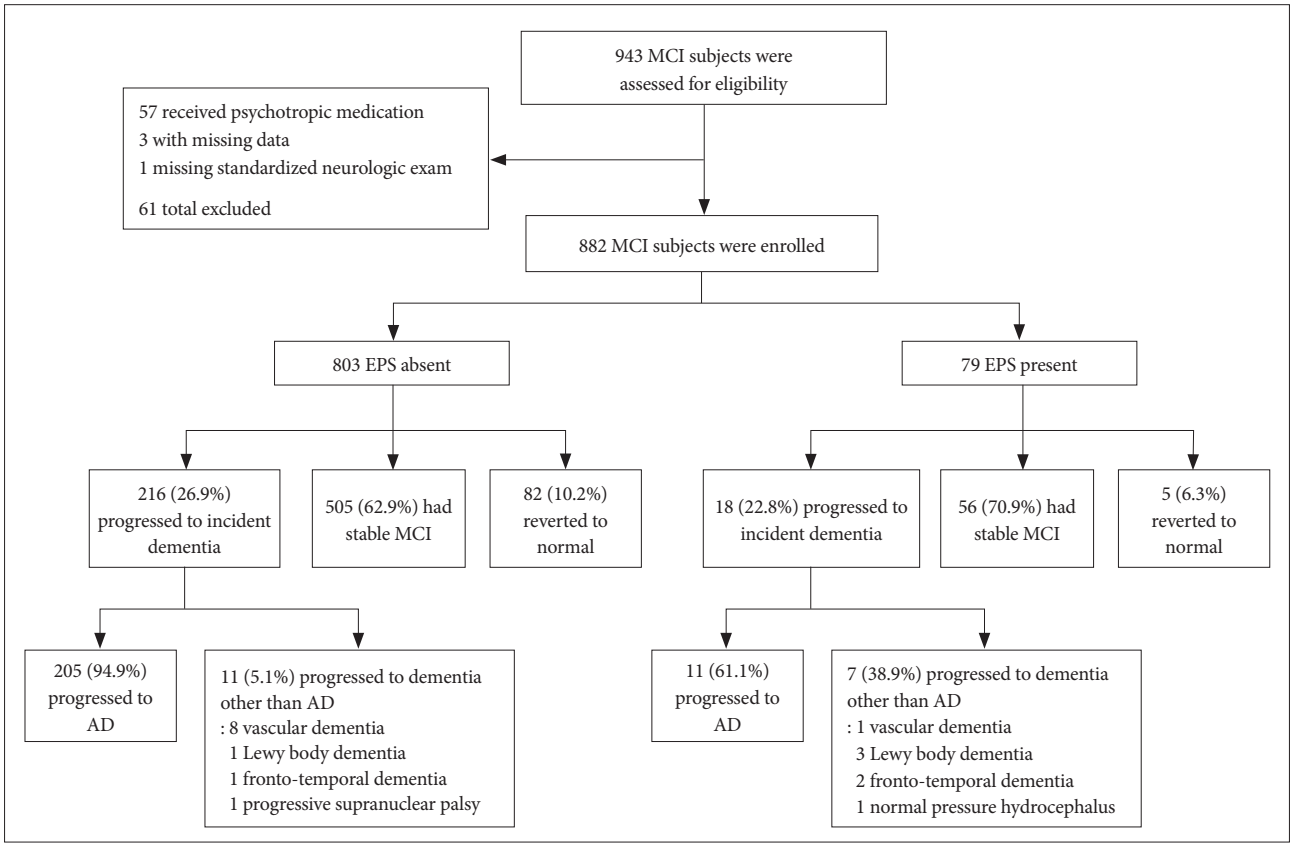

Figure 1. Flow of participants in the study. MCI: mild cognitive impairment, EPS: extrapyramidal symptom, AD: Alzheimer's disease.

rosis, Parkinson disease, Huntington's disease, tardive dyskinesia); 3) major psychiatric disorders (e.g., schizophrenia, mental retardation, mania); and 4) physical illnesses that could interfere with the clinical study (e.g., severe cardiac, respiratory diseases, uncontrolled diabetes, malignancy). In addition, absence of current psychotropic drug use was required in order to exclude drug-induced EPS.

There were 943 MCI subjects drawn from the CREDOS cohort (November 2005 to May 2012) and screened for eligibility. Of these, 57 patients with current psychotropic drug use, three patients with missing data, and 1 patient who did not receive a standardized neurological examination were excluded (Figure 1). The remaining 882 MCI subjects were followed for up to 5 years [1.44 (1.02, 2.24)]. The study protocol was approved by the Institutional Review Boards of participating centers. Informed consent was provided by all subjects and family informants.

Clinical evaluation

We evaluated all participants with a complete medical interview, physical and neurological examinations, and neuropsychological tests. We assessed routine laboratory tests at baseline, including complete blood counts, blood chemistry profiles, vitamin B_{12}/folate levels, syphilis serology, and thyroid function tests. Brain magnetic resonance imaging (MRI) scans were obtained in all cases at baseline, with transaxial T_2, T_1-weighted scans, and fluid-attenuated inversion recovery slices. Scans were rated for white matter hyperintensity (WMH) on a rating scale developed for CREDOS.[26,27] Patients were classified into two groups (mild vs. moderate or severe) based on their WMH around the lateral ventricles or in deep white matter. We classified amnestic MCI (aMCI) based on memory function, which was considered abnormal when the performance in the delayed recall item of either the Seoul Verbal Learning Test (SVLT) or the Rey Complex Figure Test (RCFT) was lower than -1.0 standard deviation compared to age and education matched norms.[28]

In addition, we used the Korean version of the Mini-Mental State Examination (K-MMSE) to assess baseline global cognitive function.[29] Depressive symptoms were assessed using the 15-item Geriatric Depression Scale (GDS-15).[30] Neurological examination was conducted by physicians who followed a standardized protocol for identifying EPS. Patients were classified into the EPS group if they had at least one of the following 11 signs: resting tremor, rigidity (upper, lower, or axial), bradykinesia, decreased arm swing, stooped posture, short step gait, festination, shuffling, or impaired pivot turning.[15] All psychometric tests were scheduled at 6-month intervals for as long as each case remained in follow-up.

Diagnosis of dementia

Dementia diagnoses and specific cause assignments were made in accordance with DSM-IV-TR criteria[25] and required objective deficits on neuropsychological testing as well as impairment in activities of daily living. Additionally, specific diagnostic criteria were used for dementia classification. A diagnosis of probable AD was adapted from the criteria from the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA).[31] Subcortical vascular dementia was diagnosed in accordance with National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria[32] and imaging criteria proposed by Erkinjuntti.[33] Onset of dementia was defined as the date on which the clinical symptoms and neuropsychological tests first allowed the diagnosis of dementia to be made. Only one diagnosis of dementia was allowed for each subject. Patients with mixed dementia were classified as one diagnosis according to the judgment of the clinicians.

Statistical analysis

Continuous variables and categorical variables are presented as median (interquartile range) and frequency (proportion), respectively. The chi-square test and Fisher's exact test were used to compare categorical variables and the Wilcoxon rank-sum test was used to compare continuous variables between the EPS and non-EPS groups. We used Cox regression for competing risk to analyze the effect of EPS on AD, treating dementia other than AD as a competing risk, and then on dementia other than AD, treating AD as a competing risk. The time variable was defined as the interval from MCI diagnosis to probable AD onset, or to onset of dementia other than AD. Durations at risk were estimated from baseline to the last follow-up or to a diagnosis of dementia. The assumptions of proportional hazards were confirmed by the residuals-based test.[34] In addition, we conducted Cox regression without consideration of competing risk as a sensitivity analysis. Results were considered statistically significant at the two-tailed threshold of $p< 0.05$. R 3.1.0 public statistics software (http://www.r-project.org) was used for all statistical analyses.

RESULTS

Subject characteristics

The clinical and demographic characteristics of the patients at baseline are shown in Table 1. The proportion of patients with EPS was 9.0% (79/882). We recruited 298 male patients and 584 female patients, the male to female ratio was 0.51 similar results in recent population study in Korean elderly.[35] The

Table 1. Clinical and demographic characteristics at baseline*

Variables	Total (N=882)	Non-EPS group (N=803)	EPS group (N=79)	p
Gender, male (%)†	298 (33.8)	271 (33.8)	27 (34.2)	0.94
Age (year)‡	71 (66, 76)	71 (66, 76)	73 (70, 77)	0.01
Education (year)‡	6.5 (5, 12)	7 (5, 12)	6 (3, 11)	0.05
Diabetes (%)†	190 (21.5)	173 (21.5)	17 (21.5)	1.00
Hypertension (%)†	449 (50.9)	408 (50.8)	41 (51.9)	0.85
K-MMSE score‡	25 (23, 27)	25 (23, 27)	25 (22, 27)	0.09
GDS-15 score‡	5 (3, 10)	5 (3, 10)	7 (4, 10)	0.03
White matter hyperintensity (moderate or severe) (%)†	226 (25.6)	196 (24.4)	30 (38.0)	<0.01
Amnestic MCI (%)†	727 (82.4)	666 (82.9)	61 (77.2)	0.20
APOE ε4 carrier (%)†§	196 (38.4)	189 (39.4)	7 (23.3)	0.08

*continuous variables and categorical variables are presented as median (interquartile range) and frequency (proportion), respectively, †chi-square test was used, ‡wilcoxon rank-sum test was used, §for logistic reasons, only 510 patients (57.8%) were genotyped for APOE gene. MCI: mild cognitive impairment, EPS: extrapyramidal signs, K-MMSE score: Korean Mini Mental State Examination score, GDS-15: 15-item Geriatric Depression Scale

Table 2. Univariate analysis: Cox regression for competing risk for EPS in individuals with MCI who progressed to dementia

Variables	AD (N=216)			Dementia other than AD (N=18)		
	HR	95%CI	p	HR	95%CI	p
EPS	0.48	0.26−0.90	0.02	6.48	2.52−16.7	<0.0001
Gender, male	0.09	0.65−1.14	0.31	1.30	0.51−3.34	0.58
Age	1.05	1.02−1.07	<0.0001	1.04	0.98−1.11	0.18
Education	1.01	0.98−1.03	0.68	1.01	0.92−1.11	0.79
Diabetes mellitus	0.98	0.71−1.37	0.92	0.75	0.28−2.58	0.65
Hypertension	0.80	0.62−1.04	0.10	0.94	0.37−2.35	0.89
K-MMSE score	0.88	0.85−0.91	<0.0001	0.96	0.87−1.06	0.41
GDS-15	0.98	0.95−1.02	0.32	1.03	0.92−1.15	0.66
White matter hyperintensity (moderate or severe)	1.35	1.01−1.82	0.05	1.95	0.75−5.07	0.17
Amnestic MCI	2.65	1.60−4.38	<0.001	3.39	0.45−25.70	0.24

MCI: mild cognitive impairment, AD: Alzheimer's disease, HR: hazard ratio, CI: confidence interval, EPS: extrapyramidal signs, K-MMSE score: Korean Mini Mental State Examination score, GDS-15: 15-item Geriatric Depression Scale

median age was 71 (66, 76). Patients with EPS were older and had higher GDS-15 scores than the patients without EPS ($p< 0.05$). No significant differences were found in education, MMSE score, or the proportions with diabetes or hypertension. The prevalence of WMH was significantly higher in the EPS group (38.0% vs. 24.4%, $p<0.01$). For logistic reasons, only 510 patients (57.8%) were genotyped for APOE gene. The APOE ε4 carrier status was not associated with EPS. In the EPS group, the median number of EPS was 2 (1, 3), and the most frequent symptom was rigidity of upper arms (45.6%, 36/79).

Longitudinal progression of subjects

Among the 882 patients with MCI (Figure 1), 803 patients exhibited no EPS. Of these, 216 (26.9%) converted to dementia, 505 (62.9%) had stable MCI, and 82 (10.2%) reverted to a normal state. Among the 216 patients without EPS who progressed to incident dementia, 205 subjects (94.9%) were classified as AD, and 11 subjects (5.1%) were diagnosed with other dementia than AD (8 vascular dementia, 1 Lewy body dementia, 1 Fronto-temporal dementia, and 1 progressive supranuclear palsy). Among the 79 patients with EPS, 18 (22.8%) converted to dementia, 56 (70.9%) remained in the range of MCI, and 5 (6.3%) reverted to a normal state. Among the 18 patients in the EPS positive group who progressed to dementia, 11 subjects (61.1%) were diagnosed with AD, and 7 (38.9%) progressed to dementia other than AD (1 vascular dementia, 3 Lewy body dementia, 2 Fronto-temporal dementia, and 1 normal pressure hydrocephalus).

There was no significant difference in follow-up interval between two groups ($p=0.34$). The observed conversion rate to AD

was significantly associated with the presence of EPS [EPS negative group: 205/803 (25.5%); EPS positive group: 11/79 (13.9%), p=0.03]. In addition, the association between EPS and the observed conversion rate to dementia other than AD also was significant [EPS negative group: 11/803 (1.4%); EPS positive group: 7/79 (8.9%), p<0.001].

Risk factors for progression from MCI to dementia

Table 2 presents the results of univariate analyses of competing risks regression for AD and for dementia other than AD. Patients with EPS, younger age, higher K-MMSE score, mild WMH or non-amnestic MCI were less likely to progress from MCI to AD in univariate analyses (p<0.05). In addition, patients with EPS were more likely to progress from MCI to dementia other than AD (p<0.0001).

From multivariable analysis (Table 3), patients with EPS had a significantly lower HR for AD progression [HR=0.70, 95% confidence interval (CI)=0.53−0.93, p=0.01] after controlling gender, age, education, DM, HTN, K-MMSE score, GDS-15, WMH and amnestic MCI. Figure 2A showed greater hazard for AD among individuals with MCI without EPS. In contrast, a significantly elevated HR was observed in those with EPS for progression to dementia other than AD (HR=6.33, 95%CI=2.30−17.39, p<0.001) (Table 3, Figure 2B). The effects of EPS on AD and dementia other than AD progression was preserved in sensitivity analyses without consideration of competing risks (HR=0.52, 95%CI=0.28−0.96, p=0.04 for AD progression; HR=6.00, 95%CI=2.28−15.78, p<0.0001 for progression to dementia other than AD). Additionally, the number of EPS symptom, as a continuous variable, was significantly associated with progression to dementia. As the number of EPS symptom increased, the risk of progression to AD decreased (HR=0.70, 95%CI=0.53−0.93, p=0.01 for AD progression), while the risk of progression to dementia other than AD in-

Table 3. Multivariable analysis: Cox regression for competing risk for EPS in individuals with MCI who progressed to dementia

Variables	AD (N=216)			Dementia other than AD (N=18)		
	HR	95%CI	p	HR	95%CI	p
EPS	0.70	0.53−0.93	0.01	6.33	2.30−17.39	<0.001
Gender, male	0.76	0.55−1.05	0.09	1.16	0.45−3.02	0.76
Age	1.03	1.01−1.06	<0.01	1.03	0.96−1.11	0.44
Education	1.08	1.04−1.11	<0.0001	1.02	0.93−1.13	0.65
Diabetes	1.12	0.82−1.54	0.48	0.75	0.22−2.62	0.65
Hypertension	0.72	0.55−0.94	0.02	0.88	0.33−2.35	0.80
K-MMSE score	0.84	0.8−0.88	<0.0001	0.97	0.86−1.09	0.57
GDS-15	1.00	0.97−1.03	0.78	1.02	0.89−1.17	0.75
White matter hyperintensity (moderate or severe)	1.17	0.86−1.6	0.33	1.55	0.55−4.41	0.41
Amnestic MCI	2.09	1.26−3.45	<0.01	3.67	0.49−27.75	0.21

MCI: mild cognitive impairment, AD: Alzheimer's disease, HR: hazard ratio, CI: confidence interval, EPS: extrapyramidal signs, K-MMSE score: Korean Mini Mental State Examination score, GDS-15: 15-item Geriatric Depression Scale

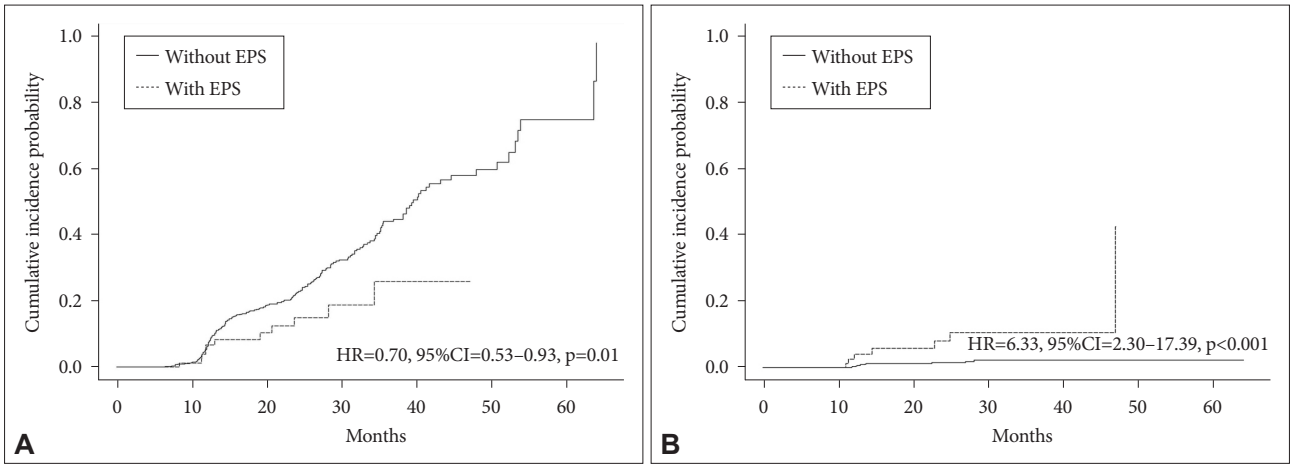

Figure 2. Cumulative incidence probability curves for dementia according to EPS, estimated by competing risks regression model. A: Progressed to Alzheimer disease from MCI. B: Progressed to dementia other than AD from MCI. EPS: extrapyramidal symptom, HR: hazard ratio, CI: confidence interval.

creased (HR=1.58, 95%CI=1.21−2.06, p<0.001 for progression to dementia other than AD).

In addition, for progression to AD significantly higher HRs were observed for increasing age and education, absence of hypertension, and lower K-MMSE score (Table 3). Amnestic MCI also was associated with progression to AD. However, these variables conferred no significant risk for progression to dementia other than AD.

DISCUSSION

In this study, we investigated the effects of EPS on progression to dementia in a prospective cohort of individuals with MCI examined for up to 5 years. We found that risk of progression to AD was decreased in the patients with EPS, whereas these patients had a six-fold elevated risk of progression to dementia other than AD.

Previous studies have shown different results. Wilson et al.[20] reported that baseline EPS were associated with incident AD in the non-demented elderly. Louis et al.[19] also reported a similar finding that EPS are a risk factor for developing dementia in elderly subjects without current cognitive impairment or Parkinson disease. We can suggest several reasons for such discrepancies. The first is different subject characteristics between previous studies and the present study. Although some patients with MCI may have been included, these two previous studies mainly included normal elderly subjects. Another previous study that investigated the association of EPS with progression to dementia in individuals with MCI reported inconsistent results. Israeli-Korn et al.[36] reported that EPS were not associated with progression to dementia in individuals with MCI. Unlike our results, this study also found no reduction of risk for progression to AD associated with EPS. However their sample size was too small to detect a significant effect of EPS (n=111).

Another plausible reason for the lack of agreement between our results and previous reports is the different analytic method for dealing with dementia other than AD. Previous studies did not consider the competing risk of dementia other than AD; they simply excluded other forms of dementia in their analysis. Assistance by brain imaging for the differential diagnosis in our study could be another reason for the discrepancy. In previous studies, brain imaging was not routinely performed. Wilson et al.[20] reported that, among all cases progressing to dementia, only five persons developed dementia other than AD whereas 114 persons developed AD. This proportion (5/119, 4.2%) is considerably lower than in the present study (18/234, 7.7%). There is a possibility that some patients with other forms of dementia were misdiagnosed as AD in their study.

The differences in recruitment settings between previous studies and the present study should be noted. It is known that the progression rate is higher in studies that recruit subjects from memory clinics than from community-based samples. The progression ratio was 26.5% (234/882) in this study from the CREDOS memory clinics, which is higher than those in two previous community cohorts with comparable follow-up duration (13.8% for 4.6 years of mean follow-up period[20] and 21.8% for 5.6 years of mean follow-up period[19]). In addition, majority of cases progressed to AD (216/234, 93%) with small proportion of dementia other than AD. This contrasts with the proportion of dementia other than AD in previous studies.[9,37] We excluded individuals with MCI who had vascular risk factor (e.g., territorial infarction) in CREDOS study. While this does not invalidate our results, it may account for the differences between our results and other studies.[38]

In contrast with the result of progression to AD, individuals with MCI with EPS had a 6-fold higher risk for progression to dementia other than AD. There are several reasons to suggest that EPS may share similar pathologies with dementia other than AD. EPS are associated with vascular risk factors and white matter changes[37] which are more frequent in vascular dementia than in AD. Neural loss and alpha-synuclein pathology in the substantia nigra have been found in patients with both EPS[39] and dementia with Lewy bodies.[40] Moreover, parkinsonian features are commonly observed in progressive supranuclear palsy and normal pressure hydrocephalus.[41] Therefore, EPS in MCI could be potential indicators of dementia other than AD. Larger studies will be helpful to confirm our results and to reveal underlying mechanisms in specific forms of non-AD dementia.

In the normal population, it is widely known that low educational level is a risk factor for AD, and high education level has a protective effect in cognition. However, in our sample, a higher education level was positively associated with progression to AD. This paradoxical finding could be explained by the concept of cognitive reserve.[42] Those with higher cognitive reserve (high education level) can tolerate more pathology so the time point at which cognitive functions begin to be impaired will be delayed in comparison to those with lower cognitive reserve (low education level). However, they showed more rapid cognitive decline when the pathology is more advanced.[43] In addition, Ye et al.[44] reported that the protective effects of education against cognitive decline disappear in late-stage MCI. This finding gives a possible reason for the paradoxical association of higher education with progression to AD in our results.

Our study has several strengths. First, we included a relatively large sample of more than 900 patients with MCI in multicenter clinics. Second, we considered various confound-

ing factors identified from previous research. Because brain MRI images of all subjects were assessed at the baseline, we could control on WMH as a covariate.[45] We also controlled for severity of depressive symptoms assessed by the GDS-15. Third, we employed Cox regression for analysis of competing risk. This statistical analysis was developed for situations in which observation of one outcome may obscure observation of the other. In our study, the effect of EPS on AD could be obscured by the incidence of dementia other than AD and vice versa. Ignorance of such competing events results in an overestimate of the cumulative incidences.[46] Competing risks regression has been used infrequently in dementia progression studies. Our study may direct attention to this statistical approach in this field.

There are several limitations that should be mentioned. First, we did not evaluate EPS by using a scale of severity. Thus, we could not analyze the association between severity of EPS and dementia progression in individuals with MCI. Alternatively, we found the relationship between number of EPS symptom and progression to dementia. Second, it is difficult to draw a line between AD versus vascular dementia in clinical setting. Although, we assessed brain MRI images in all subjects, there is possibility of misclassification. Third, we could not obtain APOE ε4 allele status from all of the participants (Table 1), as was the case in other previous studies. However, the APOE ε4 carrier status was not associated with EPS in our data, in line with previous reports.[47] Lastly, we could not consider potential variables such as musculoskeletal diseases or physical pain that could influence on the movement symptoms.

In conclusion, our study demonstrated that baseline EPS in individuals with MCI are associated with a decreased risk of progression to AD, but with a six folds increased risk of progression to dementia other than AD. Thus, our results suggest that careful assessment of EPS in patients with incident MCI can yield important clinical information for prognosis.

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