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Cognitive Profiles and Subtypes of Patients with Mild Cognitive Impairment: Data from a Clinical Follow-Up Study*

Kyung Won Park[1#], Eun-Joo Kim[2], Hwan Joo[3], Sung-Man Jeon[4], Seong-Ho Choi[5], Jay C. Kwon[6], Byoung Gwon Kim[7], Jae Woo Kim[1]

[1]Department of Neurology, Dong-A University College of Medicine, Dong-A University Medical Center, Busan, South Korea; [2]Department of Neurology, Pusan National University Hospital, Pusan National University School of Medicine and Medical Research Institute, Busan, South Korea; [3]Department of Neurology, Busan Medical Center, Busan, South Korea; [4]Department of Neurology, Bong Seng Memorial Hospital, Busan, South Korea; [5]Department of Neurology, Wallace Memorial Baptist Hospital, Busan, South Korea; [6]Department of Neurology, Changwon Fatima Hospital, Changwon, South Korea; [7]Department of Preventive Medicine, Dong-A University College of Medicine, Busan, South Korea.
Email: #neuropark@dau.ac.kr

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ABSTRACT

Background: Mild cognitive impairment (MCI) is a heterogeneous condition with a variety of clinical outcomes, the presence of which correlates with risk of Alzheimer's disease as well as pre-clinical stages of other dementia subtypes. The aims of this study were to assess the specific patterns of cognitive profiles and to identify changes from baseline to 24 weeks in patients with MCI using detailed neuropsychological testing. **Methods:** We consecutively recruited 120 MCI patients at baseline according to the Petersen's clinical diagnostic criteria, who were admitted to the Dementia and Memory Clinics. We analyzed patients who fulfilled both inclusion and exclusion criteria for MCI and classified them into four subtypes according to deficits in major cognitive domains; amnestic MCI single domain (aMCI-s), amnestic multiple domain MCI (aMCI-m), non-amnestic single domain MCI (naMCI-s) and non-amnestic multiple domain MCI (naMCI-m). Four groups of MCI were evaluated by a detailed neuropsychological battery test. **Results:** 83 patients with MCI at the 24-week follow-up were classified into four subtypes. The most frequent subtype was amnestic multi-domain MCI, with the frequency of MCI subtypes as follows: aMCI-s (n = 21, 25.3%), aMCI-m (n = 53, 63.9%), naMCI-s (n = 5, 6.0%) and naMCI-m (n = 4, 4.8%). In the major cognitive items of the SNSB-D, there were significant changes between the initial and follow-up tests in the domains of language, memory and the frontal/executive function ($p < 0.05$), except for attention, in all MCI patient subtypes. At 24-weeks follow-up, the conversion rate to Alzheimer's disease was 2.4% (n = 2) from a subtype of amnestic multi-domain MCI. **Conclusions:** Our study revealed the most frequent subtype of MCI to be multiple domain amnestic MCI, with this subtype having a higher tendency of conversion to Alzheimer's disease.

Keywords: Mild Cognitive Impairment; Alzheimer's Dementia; Neuropsychology; Conversion

1. Introduction

The recent increase of an elderly population in developed countries like South Korea has led to a renewed focus on degenerative disorders such as dementia. MCI refers to a mild regression of cognitive functions, in particular memory impairment in patients compared to that of normal people, although the condition is not severe enough to be classified as dementia due to retainment of activeties of daily living, or ADL [1]. According to some epidemiological studies, people with MCI are in a high risk group that may progress to Alzheimer's disease [2-4]. Whereas 1 to 2 percent of normal control groups develop dementia annually, 10 to 15 percent of MCI patients develop dementia, in particular, Alzheimer's disease [5]. This condition is clinically important because it is the earliest stage that Alzheimer's disease can be detected and the effects of treatment could therefore be maximized. MCI is a syndrome involving heterogeneous clinical manifestations and diverse causative diseases. The discovery that MCI patients were likely to develop dementia led to the recognition that early diagnosis of MCI patients was crucial.

Furthermore, the classification of MCI patients ac-

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#Corresponding author.

cording to manifestations of cognitive dysfunction resulted in a renewed focus to verify which groups experience a high incidence of Alzheimer's disease among different types of MCI patients [6-8]. Structural or functional brain imaging techniques, such as Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT), were heavily employed for this research, with efforts to verify differences in progression patterns in accordance with the prognoses or types of MCI [6].

A classification of MCI patient subtypes along with detailed neuropsychological tests, in addition to brain imaging techniques, while observing changes in cognitive patterns and prognoses can provide important clues in determining whether to apply pharmacotherapy in a practical clinic setting and make long-term follow-up observations. In a report presenting the international standards for, and classification of MCI [6] suggested that memory disorder was not the only symptom of MCI patients, and that diverse cognitive disabilities may be present, such as visuospatial and language impairment, as well as frontal lobe dysfunction even from an early state of the disease. Therefore, they noted that MCI may be classified into the subtypes of amnestic MCI and non-amnestic MCI, according to whether patients have memory impairment or not. They may also be classified into single and multiple domain disorders, according to the presence of a failing single cognitive domain or of multiple domains. In order to classify patients according to the definitions of the four subtypes of MCI, a working criterion in consideration of age and educational background were used, with neuropsychological test tools representing each cognitive area. Based on the neuropsychological performances, MCI divided into the subtypes: amnestic single domain MCI (aMCI-s), when the patient lacked on the memory function; amnestic multiple domain MCI (aMCI-m), when there were impairments on several cognitive areas, including memory; non-amnestic single domain MCI (naMCI-s), presence of an impairment in another cognitive area, with normal memory; and non-amnestic multiple domain MCI (naMCI-m), with impairments in more than one cognitive domain, with normal memory.

The frequency and pattern of progression of each subtype of MCI were inconsistent due to the presence of diverse diagnostic criteria, as well as different sampling and assessment methods. The authors performed this study with the following objectives: First, to classify new patients, who visited hospitals from September 2008 to April 2009 that were participating in the study and who were diagnosed with MCI into subtypes (amnestic single domain, amnestic multiple domain, non-amnestic single domain, and non-amnestic multiple domain), and investigate each subtype's frequency and patterns. Second, after six months elapsed, we observed whether the MCI subtypes had changed and whether they had progressed into dementia.

2. Subjects and Methods

This was a multi-center, observational study conducted for 24 weeks across 13 hospitals located in Busan Metropolitan City, Gyeongnam Province from September 2008 to February 2010. We performed this study with full approval from the respective Institutional Review Boards of each hospital, after inspection of the clinical trial plan, written explanation for subjects, and after obtaining each subjects' informed consent.

2.1. Subjects

We enrolled patients according to working criteria based on the clinical diagnostic criteria for MCI [5,6]: 1) the presence of subjective memory complaint as reported by participants or informants; 2) intact ability to perform activities of normal daily living; 3) normal general cognitive function defined as cognitive performance above the range of 1.0 standard deviation (SD) of normative data in an extensive neuropsychological test; 4) abnormal cognitive function including memory domain for age and education documented by performance of at least 1.0 SD below mean normative data in cognitive tasks; 5) non-demented according to DSM-IV criteria and excluded by fulfilling criteria (2) and (3). The participants included in the present study were 55 to 85 years of age, had not taken acetylcholinesterase inhibitors, memantine or ginkgo bilboa for at least 4 weeks prior to the study initiation, were ambulatory or ambulatory-aided (*i.e.*, walker or cane), had brain MRI or CT scans revealing no clinical evidence of other diseases capable of producing a dementia syndrome, and had a reliable caregiver who met the patient at least once a week and provide the investigator with accurate information. The following exclusion criteria were adopted: 1) major depressive disorder, bipolar disorder, schizophrenia, substance use disorder, or mental retardation according to criteria of the DSM-IV; 2) cerebrovascular disorders, hydrocephalus or intracranial mass, documented by CT or MRI within the past 12 months; 3) abnormalities in serum folate and vitamin B12, syphilis serology, or thyroid hormone levels; 4) history of traumatic brain injury or other neurologic disease; and 5) significant medical problems (e.g. poorly controlled diabetes or hypertension; cancer within the past 5 years; clinically significant hepatic, renal, cardiac or pulmonary disorders).

2.2. Neuropsychological Tests

The patients' general cognitive functions were measured

with the Korean version of the mini-mental state exam (K-MMSE) [9]. The severity of dementia was evaluated with a clinical dementia rating (CDR) [10] and the scores in the six areas of CDR were combined to calculate the sum of boxes (SOB) in each item. Overall severity was expressed with global CDR. All patients underwent neuropsychological tests using a standardized neuropsychological battery called the Seoul Neuropsychological Screening Battery—Dementia Version (SNSB-D) [11,12]. This screening battery contains tests for attention, language, praxis, parietal function, visuoconstructive function, verbal and visual memory, and frontal executive function. The neuropsychological tests were: digit span (forward and backward), the Korean version of the Boston Naming Test (K-BNT) [13], ideomotor praxis, Rey-Osterrieth Complex Figure Test (RCFT; copying, immediate and 20-min delayed recall and recognition), the Seoul Verbal Learning Test (SVLT; three learning-free recall trials of 12 words, 20-min delayed recall trial for these 12 items and a recognition test), phonemic and semantic Controlled Oral Word Association Test (COWAT) and the Stroop test (word and color reading of 112 items during a 2-min period). Age-, gender- and education-specific norms for each test based on 447 normal subjects are available. The scores of these cognitive tests were classified as abnormal when they were below the 16th percentile of the norms for respective age-, gender- and education-matched normal subjects.

2.3. Classification of MCI Patients According to Subtypes

In order to classify patients according to the definitions of the four subtypes of MCI, a working criteria in consideration of age and educational background were used, with neuropsychological test tools representing each cognitive area that was specified by the standard established through data research. An experienced neuropsychologist performed the neuropsychological tests on all patients, and based on the results, divided them into the subtypes: 1) amnestic single domain MCI (aMCI-s), when the patient lacked disability in other cognitive areas, except for degraded memory; 2) amnestic multiple domain MCI (aMCI-m), when there were disabilities in other cognitive areas, including memory; 3) non-amnestic single domain MCI (naMCI-s), presence of a disability in another cognitive area, with normal memory; and 4) non-amnestic multiple domain MCI (naMCI-m), with disabilities in more than one cognitive domain, with normal memory.

2.4. Statistical Analysis

STATA/SE 11.2 (Stata Corp. 2009, College Station, TX, USA) was used for all statistical analyses, and a two-tailed test was performed with the level of significance set at 0.05.

A frequency analysis was done of the subtypes, and all data collected through the neuropsychological tests were analyzed using descriptive statistics. Mean values of continuous variables of the data were compared with a paired t-test and non-continuous variables were compared with a chi-square test. When the P value was less than 0.05, a difference was considered to be statistically significant. Based on the findings from the neuropsychological tests performed again six months later and the clinicians' own judgments, we calculated the frequency of patients whose MCI progressed to dementia and calculated the rate of conversion of MCI to dementia in each subtype. We ascertained the frequency of each subtype of MCI and the number of MCI patients in each subtype who had changed since the initial diagnosis. In order to verify which cognitive domain underwent the most and least changes, the scores of each of the four cognitive domains (memory, visuospatial ability, linguistic ability and frontal lobe function) were measured, and the scores in the beginning and in the 24th week were compared.

3. Results

3.1. Frequency of Subtypes of MCI at Baseline

Among the 120 subjects of this study, the follow-up tests of a total of 83 patients were completed. In total, 23 patients dropped out (follow-up loss), 9 patients withdrew their consent to participate in the study, 2 patients were relocated to other hospitals, 1 patient died, 1 patient was excluded due to use of a banned medication and 1 patient was excluded due to the onset of cerebral infarction, all during the follow-up test period. The most common subtype among MCI patients was found to be amnestic multiple domain MCI (aMCI-m). Each subtype's frequency was as follows: aMCI-s is 25.3% (n = 21), aMCI-m is 63.9% (n = 53), naMCI-s is 6.0% (n = 5), and naMCI-m is 4.8% (n = 4) (**Table 1**).

The rate of male to female patients among the subjects, their average age, and their number of years of education were 34.2% to 65.8%, 68.5 ± 7.5 years, and 7.0 ± 4.3 years, respectively (**Table 1**).

3.2. Changes of Neuropsychological Test Results in Each Subtype at 24 Weeks Follow-Up

The total score and follow-up score changes of the Seoul Neuropsychological Screening Battery-Dementia Version (SNSB-D) in each subtype are shown in detail in **Tables 2-5**. After the 24 weeks follow-up period, all MCI patients showed significant improvements in cognitive function on the total score of SNSB-D compared with the baseline assessment ($P < 0.05$). Furthermore,

Table 1. Demographic paramters and frequency in patients with MCI according to subtypes.

	Total MCI patients (n = 120)	Amnestic single MCI patients (n = 29)	Amnestic multiple MCI patients (n = 74)	Non-amnestic single MCI patients (n = 11)	Non-amnestic multiple MCI patients (n = 6)	P value
Female, n (%)	79 (65.8)	22 (75.9)	45 (60.8)	7 (63.6)	5 (83.3)	0.397
Age, years	68.5 ± 7.5	65.4 ± 7.8	69.0 ± 7.2	69.2 ± 6.9	75.0 ± 5.9	0.015
Education, years	7.0 ± 4.3	6.9 ± 3.8	7.0 ± 4.7	7.5 ± 3.3	6.5 ± 4.0	0.909
BMI	24.1 ± 3.0	24.1 ± 2.7	24.1 ± 3.3	24.3 ± 2.5	23.7 ± 2.9	0.973
Hypertension, n (%)	42 (35.0)	10 (23.8)	22 (52.4)	6 (14.3)	4 (9.5)	0.145
Diabetes mellitus, n (%)	23 (19.1)	5 (21.7)	14 (60.9)	2 (8.7)	2 (8.7)	0.842
Hyperlipidemia, n (%)	13 (10.0)	4 (30.7)	7 (53.9)	0 (0.0)	2 (15.4)	0.180
Heart disease, n (%)	19 (15.8)	7 (36.8)	9 (47.4)	1 (5.3)	2 (10.5)	0.261
Alcohol drinking, n (%)	3(2.5)	0 (0.0)	3 (4.1)	0 (0.0)	0 (0.0)	0.431
Smoking, n (%)	29 (24.4)	4 (13.8)	22 (31.1)	2 (18.1)	1 (16.7)	0.557
Depression, n (%)	4 (3.3)	2 (6.0)	2 (2.0)	0 (0.0)	0 (0.0)	0.611
Family history of dementia, n (%)	23 (19.3)	3 (10.3)	14 (19.2)	4 (36.4)	2 (33.3)	0.230
ApoE4 genotype (n = 22), positive, n	8	3	3	1	1	NS

Values are presented as number (%) and mean ± SD. MCI, mild cognitive impairment; BMI, body mass index.

Table 2. Mean changes in cognitive function on neuropsychological tests in patients with all subtypes of MCI.

Outcome measure	Baseline mean (SD) (n = 83)	24-week F/U mean (SD) (n = 83)	P value
MMSE	26.3 (2.3)	26.4 (2.4)	0.4238
Attention	9.1 (1.9)	9.4 (2.1)	0.1796
Forward	5.8 (1.5)	6.0 (1.4)	0.0494
Backward	3.4 (0.9)	3.3 (1.1)	0.7313
Language & related function	20.0 (3.8)	20.8 (3.8)	0.0012
Naming (K-BNT)	10.4 (2.9)	10.9 (2.7)	0.0279
Calculation	9.6 (2.4)	9.9 (2.4)	0.0221
Visuospatial function	27.6 (8.0)	29.1 (6.9)	0.0394
Rey figure copy	27.6 (8.0)	29.1 (8.0)	0.0394
Memory	53.8 (17.4)	61.9 (21.5)	<0.001
Orientation	5.6 (0.6)	5.6 (0.7)	0.7650
Verbal immediate recall	15.8 (5.7)	16.9 (6.1)	0.0319
Verbal delayed recall	3.5 (2.4)	5.1 (2.8)	0.0000
Verbal recognition index	7.4 (2.1)	7.6 (2.6)	0.5153
Visual immediate/delayed recall	15.2 (11.7)	20.2 (13.8)	<0.001
Visual recognition	6.2 (2.4)	6.5 (2.5)	0.2782
Frontal/executive	44.4 (10.2)	46.3 (9.8)	0.0039
Impersistence	3.0 (0.0)	3.0 (0.0)	N/A
Contrasting program	2.6 (0.7)	2.7 (0.5)	0.1316
Go-no-go test	2.0 (1.0)	2.3 (0.8)	0.0011
Fist-edge-palm	2.7 (0.5)	2.7 (0.5)	0.8587
Luria loop	2.6 (0.9)	2.8 (0.7)	0.0356
Word fluency-animal	13.1 (3.9)	12.8 (3.6)	0.3324
Word fluency-phonemic	5.6 (3.9)	5.9 (3.4)	0.4209
Stroop test-color	12.8 (4.5)	14.0 (4.7)	0.0010
SNSB-D	154.9 (32.6)	167.4 (35.9)	<0.001
CDR sum of box	1.3 (0.8)	1.2 (0.8)	0.0357
IADL	3.5 (3.6)	2.7 (3.8)	0.0362
NPI	4.0 (8.3)	3.8 (8.0)	0.7711
Geriatric depression scale	16.9 (6.8)	15.6 (7.0)	0.0555

MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SNSB-D, Seoul Neuropsychological Screening Battery-Dementia Version; K-BNT, Korean Boston Naming Test; CDR, Clinical Dementia Rating; IADL, Instrumental Activities of Daily Living; NPI, Neuropsychiatric inventory.

Table 3. Mean changes in cognitive function on neuropsychological tests in patients with aMCI-s.

Outcome measure	aMCI-s (n = 21)		
	Baseline mean (SD)	24-week F/U mean (SD)	P value
MMSE	26.9 (1.7)	27.2 (1.7)	0.4127
Attention	9.8 (2.4)	10.2 (2.2)	0.4123
Forward	6.1 (1.7)	6.4 (1.4)	0.4361
Backward	3.7 (0.9)	3.8 (1.3)	0.7152
Language & related function	21.0 (3.4)	21.7 (3.5)	0.0784
Naming (K-BNT)	11.1 (2.1)	11.5 (2.5)	0.3081
Calculation	9.8 (2.5)	10.1 (2.2)	0.0571
Visuospatial function	31.8 (4.8)	31.4 (4.5)	0.8171
Rey figure copy	31.8 (4.8)	31.5 (4.5)	0.8171
emory	57.8 (22.2)	67.9 (22.0)	0.0063
Orientation	5.7 (0.6)	5.6 (0.7)	0.5402
Verbal immediate recall	14.9 (5.7)	16.8 (6.80.)	0.1290
Verbal delayed recall	3.2 (2.5)	5.3 (2.8)	0.0022
Verbal recognition index	7.1 (1.9	7.9 (2.3)	0.0725
Visual immediate/delayed recall	20.2 (15.9)	25.1 (13.7)	0.0539
Visual recognition rey	6.6 (2.2)	7.2 (2.4)	0.3000
Frontal/executive	50.7 (9.9)	51.4 (9.3)	0.5190
Impersistence	3.0 (0.0)	3.0 (0.0)	-
Contrasting program	2.8 (0.5)	2.9 (0.4)	0.7477
Go-no-go test	2.0 (0.9)	2.5 (0.7)	0.0466
Fist-edge-palm	2.8 (0.5)	2.8 (0.5)	1.0000
Luria loop	2.7 (0.7)	3.0 (0.0)	0.0829
Word fluency-animal	14.2 (4.5)	14.0 (3.8)	0.6799
Word fluency-phonemic	6.4 (3.8)	6.7 (3.8)	0.6708
Stroop test-color	16.7 (3.4)	16.7 (4.0)	0.9157
SNSB-D	171.0 (33.8)	152.7 (32.6)	0.0127
CDR sum of box	1.1 (0.6)	1.0 (0.6)	0.0829
IADL	2.8 (3.9)	1.6 (2.7)	0.0146
NPI	4.0 (10.9)	4.0 (12.1)	0.9114
Geriatric depression scale	19.0 (5.9)	16.4 (8.6)	0.0494

aMCI-s, single domain amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination; SNSB-D, Seoul Neuropsychological Screening Battery-Dementia Version; K-BNT, Korean Boston Naming Test; CDR, Clinical Dementia Rating; IADL, Instrumental Activities of Daily Living; NPI, Neuropsychiatric inventory.

patients with each subtype of MCI showed significant improvement on the total score of SNSB-D compared with the baseline assessment ($P < 0.05$). The mean differences of total scores of SNSB-D in patients with MCI were as follows; entire MCI (12.5 ± 18.7), aMCI-s (11.7 ± 19.6), aMCI-m (12.6 ± 19.9), naMCI-s (13.0 ± 9.7), naMCI-m (15.3 ± 5.3). The other changes in the cognitive outcome measures are shown in detail in **Tables 2-5**.

3.3. Progression of Subjects with MCI

In the follow-up test after 24 weeks, two MCI patients (2.4%) progressed to Alzheimer's disease; while their subtype during the initial test was aMCI-m. No patient progressed to a type of dementia other than Alzheimer's disease. The number of MCI patients who underwent conversion to a normal condition was five (6%) and their MCI subtypes were aMCI-s (1 person), aMCI-m (3 persons) and naMCI-s (1 person). After 24 weeks, the frequencies of each subtype were as follows: aMCi-s was 25.5%, aMCI-m was 42.1%, naMCI-s was 16.9%, and naMCI-m was 7.2%.

4. Discussion

Previous research on MCI has revealed that it not only consists of the amnestic type, but rather a range of dif-

Table 4. Mean changes in cognitive function on neuropsychological tests in patients with aMCI-m.

Outcome measure	aMCI-m (n = 53)		
	Baseline mean (SD)	24-week F/U mean (SD)	P value
MMSE	25.9 (2.4)	26.0 (2.7)	0.6770
Attention	9.0 (1.8)	9.1 (2.0)	0.3503
Forward	5.7 (1.4)	6.0 (1.4)	0.0795
Backward	3.2 (0.9)	3.1 (1.1)	0.5603
Language & related function	19.3 (3.9)	20.1 (3.9)	0.0159
Naming (K-BNT)	9.9 (3.2)	10.4 (2.7)	0.0751
Calculation	9.4 (2.6)	9.6 (2.5)	0.1593
Visuospatial function	25.9 (8.9)	28.0 (7.9)	0.0287
Rey figure copy	25.9 (8.9)	28.0 (7.8)	0.0287
Memory	50.5 (15.1)	57.7 (21.2)	0.0004
Orientation	5.5 (0.6)	5.6 (0.8)	0.3742
Verbal immediate recall	16.0 (5.6)	16.5 (5.6)	0.3862
Verbal delayed recall	3.4 (2.4)	4.9 (2.8)	0.0000
Verbal recognition index	7.3 (2.3)	7.2 (2.7)	0.6062
Visual immediate/delayed recall	12.2 (9.3)	17.4 (13.6)	0.0009
Visual recognition rey	6.0 (2.6)	6.2 (2.5)	0.6641
Frontal/executive	41.9 (9.6)	44.1 (9.6)	0.0126
Impersistence	3.0 (0.0)	3.0 (0.0)	-
Contrasting program	2.5 (0.8)	2.7 (0.5)	0.1066
Go-no-go test	1.9 (1.0)	2.2 (0.9)	0.0177
Fist-edge-palm	2.7 (0.5)	2.8 (0.5)	0.6590
Luria loop	2.4 (1.0)	2.7 (0.9)	0.0963
Word fluency-animal	12.4 (3.6)	12.3 (3.6)	0.7112
Word fluency-phonemic	5.4 (3.8)	5.5 (3.1)	0.7719
Stroop test-color	11.5 (4.2)	13.0 (4.9)	0.0053
SNSB-D	146.5 (31.0)	159.0 (36.9)	0.0000
CDR sum of box	1.5 (0.9)	1.3 (0.8)	0.1212
IADL	3.8 (3.7)	3.3 (4.3)	0.3476
NPI	4.5 (7.8)	4.0 (6.4)	0.5156
Geriatric depression scale	16.1 (7.1)	1537 (6.4)	0.6306

aMCI-m, multiple domain amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination; SNSB-D, Seoul Neuropsychological Screening Battery-Dementia Version; K-BNT, Korean Boston Naming Test; CDR, Clinical Dementia Rating; IADL, Instrumental Activities of Daily Living; NPI, Neuropsychiatric inventory.

ferent subtypes. As proposed by Winbald *et al.* [6], MCI can be classified into four different types, according to disabilities in domains identified by neuropsychological tests. We consider that each subtype has different causes and prognoses. Recently published research has reported a classification of MCI patients into subtypes according to neuropsychological tests with the observation of each subtype's clinical manifestations and prognoses. This resulted in the finding that MCI was not a pre-stage of Alzheimer's disease, but rather consisted of a group of heterogeneous diseases with various kinds of prognoses [1,14]. According to further research, aMCI-m is likely to progress to Alzheimer's disease, while naMCI-s or naMCI-m are likely to progress to vascular dementia, frontotemporal dementia or dementia with Lewy bodies [1,15].

To our knowledge, this is the first regional study of its kind performing neuropsychological assessments on 120 MCI patients, calculating the frequency of each subtype of MCI, observing changes in each subtype's frequency after a 24-week follow-up test and analysis of the changes in the cognitive functions of each type of patient. We found that the most common subtype of MCI was aMCI-m (63.9%), followed by aMCI-s (25.3%), naMCI-s (6.0%), and naMCI-m (4.8%). Our results differ from that of a prior study (Fischer *et al.*, 2007), where the

Table 5. Mean changes in cognitive function on neuropsychological tests in patients with naMCI.

Outcome measure	naMCI (n = 9)		
	Baseline mean (SD)	24-week F/U mean (SD)	P value
MMSE	26.8 (2.5)	26.9 (1.8)	0.8695
Attention			
Forward	5.1 (1.3)	5.4 (1.7)	0.4714
Backward	3.5 (0.5)	3.4 (0.5)	0.3466
Language & related function			
Naming (K-BNT)	11.3 (2.4)	11.7 (2.6)	0.3466
Calculation	10.7 (1.3)	11.1 (1.2)	0.1950
Visuospatial function			
Rey figure copy	28.0 (4.4)	29.8 (3.4)	0.3321
Memory			
Orientation	5.7 (0.5)	5.6 (0.5)	0.5943
Verbal immediate recall	16.8 (6.1)	19.3 (7.4)	0.0171
Verbal delayed recall	5.0 (1.7)	6.1 (2.8)	0.0619
Verbal recognition index	8.6 (1.1)	9.3 (1.3)	0.1411
Visual immediate/delayed recall	21.6 (6.6)	25.6 (10.3)	0.1577
Visual recognition rey	6.4 (2.1)	6.8 (1.8)	0.6454
Frontal/executive			
Contrasting program	2.6 (1.0)	2.7 (0.7)	0.7995
Go-no-go test	2.3 (1.0)	2.6 (0.7)	0.3466
Fist-edge-palm	2.7 (0.7)	2.6 (0.7)	0.3466
Luria loop	3.0 (0.0)	2.9 (0.3)	0.3466
Word fluency-animal	14.8 (3.5)	13.2 (3.3)	0.2021
Word fluency-phonemic	4.9 (4.4)	6.0 (4.2)	0.1786
Stroop test-color	11.1 (3.4)	14.0 (2.8)	0.0064
SNSB-D	167.2 (22.1)	181.2 (21.2)	0.0006
CDR sum of box	0.8 (0.3)	0.8 (0.4)	0.5943
IADL	3.2 (2.0)	1.9 (1.8)	0.2572
NPI	0.3 (1.0)	2.2 (3.5)	0.1276
Geriatric depression scale	17.0 (7.0)	13.4 (7.0)	0.1354

naMCI, non-amnestic mild cognitive impairment; F/U, follow-up; MMSE, Mini-Mental State Examination; SNSB-D, Seoul Neuropsychological Screening Battery-Dementia Version; K-BNT, Korean Boston Naming Test; CDR, Clinical Dementia Rating; IADL, Instrumental Activities of Daily Living; NPI, Neuropsychiatric inventory.

frequency of subtypes of MCI patients were 48 out of 141 (34%) patients with aMCI and 93 out of 141 (66%) patients with naMCI. The frequency of MCI subtypes in further studies showed that the prevalence of each subtype of MCI in research, where the subjects were from the general population, was different to that of the current study [16,17]. They reported that the nonamnestic MCI type was as frequent as the amnestic MCI type, while the single domain amnestic MCI was more prevalent than multiple domain amnestic MCI. Another study reported that the prevalence of aMCI and naMCI was around 9% and 15%, respectively. The overall rate of naMCI was even higher than that of aMCI in the community-based study [18].

One of the main reasons for the different rates in the frequency of MCIs may be due to the difference between hospital-based studies and community-based epidemiological studies. The other reason for differing rates of frequency in MCI subtypes is a dissimilar adaptation of operational criteria for defining MCI. Our study defined memory impairment in the Seoul Verbal Learning Test (SVLT) as 1 standard deviation (SD) below age- and education-matched control subjects, unlike other studies [5,8], therefore a larger number of patients were classified into the aMCI subtype. It is also possible that cultural differences between Korea and other countries affected the scores; for example in the United States, visuospatial impairment displayed during driving, or disabili-

ties in planning or decision making, may have been considered important in addition to memory impairment. Furthermore, this study included cases where patients' guardians or informants reported memory impairment even without subjective memory complaints from the patients, which resulted in a higher rate of MCI cases relative to those of other studies.

During the 24 weeks follow-up period, all patients of MCI with each subtype of MCI showed significant improvements in cognitive function on the total score of the SNSB-D compared with the baseline assessment. In the major cognitive items of the SNSB-D, there was significant change between the initial and the follow-up assessments in the domains of language, memory and the frontal/executive function in all subtypes of MCI. This result is probably due to a relatively large number of patients with high MMSE scores and mild stage of patients being included, and learning effect may have resulted during the relatively short follow-up period. The condition of depression may also have had an influence on the test scores, given that the patients with high depression scores in the initial tests showed improvement in the follow-up tests.

Our study showed that two MCI patients (2.4%) progressed to Alzheimer's disease; their subtype during the initial test was aMCI-m. No patient progressed to other types of dementia other than Alzheimer's disease. A 3-year follow-up research study reported that rates of conversion to Alzheimer's disease for the MCI subtypes were 38% for amnestic MCI, 20% for non-amnestic MCI and 16% for amnestic multiple domain MCI [7]. The other long-term follow-up study revealed a conversion rate to AD at 49% for amnestic MCI and 27% for non-amnestic MCI [8]. Our study did not show in-depth conversion rates due to a shorter follow-up period. However, our results show a tendency for progression to AD from amnestic MCI rather than non-amnestic MCI.

We identified some shortcomings in our study. First, although it was a prospective follow-up study, we did observe changes in the MCI patients' subtypes and their cognitive functions during the short period of 24 weeks, therefore making it difficult to form a precise evaluation of the patients' disease progression or an estimation of the annual rate of conversion from MCI to dementia. Second, the number of patients in each subtype was unevenly distributed, making it difficult to determine true statistical significance. Also, differences in levels of apolipoprotein E4 were not obtained from all patients, nor the analysis of differences in MCI in accordance with the existence or non-existence of cerebrovascular lesions, such as white matter changes or lacunar infarction.

In conclusion, we were able to verify that the SNSB-D is a useful tool to classify MCI subtypes and follow their progression in detail, suggesting that the routine classification of MCI into subtypes and observation of progression may be conducive to predicting a transition of MCI to Alzheimer's disease or other types of dementia. In our study, aMCI-m was the most common subtype among the four subtypes of MCI, and its rate of conversion into Alzheimer's disease was statistically significant. For a more comprehensive investigation, it will be necessary to perform further prospective multi-center research for a period of a few years, with many hundreds of patients as subjects, in region-based cohort studies as well as hospital-based cohort studies.

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