The difference of clinical characteristics and behavioral patterns in mild cognitive impairment subtypes using Korean version of neuropsychiatric inventory

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The difference of clinical characteristics and behavioral patterns in mild cognitive impairment subtypes using Korean version of neuropsychiatric inventory

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ABSTRACT

The difference of clinical characteristics and behavioral patterns in mild cognitive impairment subtypes using Korean version of neuropsychiatric inventory

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Background: Mild cognitive impairment (MCI) has been subtyped according to its cognitive features and its likely etiology. We aimed to investigate the neuropsychiatric features of the MCI using the Neuropsychiatric Inventory (NPI) and compare them according to subtypes.

Methods: MCI patients were classified according to cognitive features (e.g., amnestic MCI vs non-amnestic MCI), likely etiology (e.g., vascular MCI, non-vascular MCI) and functional status (e.g., MCI-I vs MCI-II). The percentage of subjects exhibiting each of the 12 behaviors in the NPI was compared among the groups using a chi-square test.

Results: There were 382 subjects in the MCI group. In terms of each neuropsychiatric symptom, there were no differences in frequency between MCI groups subtyped according to cognitive features or likely etiology. However, a significantly higher frequency of delusion, aggression, irritability, and eating behavior has been observed in the MCI-II group in comparison to the MCI-I group.

Conclusion: Differences in neuropsychiatric symptoms were distinctive between MCI groups subtyped according to functional status.

Key words: mild cognitive impairment, subtypes, neuropsychiatric inventory, neuropsychiatric symptoms

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I. INTRODUCTION

Mild cognitive impairment (MCI) is a syndrome defined as a cognitive decline greater than expected for an individual's age and education level, but which does not interfere notably with activities of daily living (ADL).[1] MCI has been subtyped according to its cognitive features, clinical presentation, likely etiology, neuroimaging findings, genetic features, or according to its progression rate.[2] The majority of data present in the literature refer to amnestic MCI and very few concern other subtypes of the condition. In terms of MCI subtyping by its cognitive features, which Peterson proposes, it is conceivable that amnestic MCI subjects have a high likelihood of progression to Alzheimer's disease (AD), while non-amnestic MCI are assumed to convert more frequently to non-AD dementia.[3] In MCI subtyping by its likely etiology and in accordance with the clinical categorization of dementia, non-vascular MCI subjects are considered to have a high likelihood of progression to AD,[4] while those with vascular MCI are assumed to convert more frequently to vascular dementia.[5]

Vascular MCI resulting from cerebrovascular disease has been relatively understudied compared with the more pre-Alzheimer concept of MCI. However, community studies have shown a higher prevalence of presumed vascular MCI (2.6%) than vascular dementia (1.5%).[5] The role of cerebrovascular disease in MCI is probably under-represented, particularly in population studies.[6] Both cerebrovascular disease and neurodegenerative features were shown to contribute to MCI. MCI subtyping by its functional status has not been suggested until now, but incorporating difficulties in performing ADL has been found to ameliorate the original diagnostic algorithm for MCI and better detect subjects at risk of conversion to dementia.[7]

Although cognitive domains have been the core features of MCI up to now, there is an increasing awareness of neuropsychiatric symptoms (NPS), which include anxiety, depression, and irritability.[8] NPS are commonly observed and clinically relevant in MCI. Depending on the population type studied and the methods used, prevalence can range from 35 to 75%.[8-11] Several studies report rates of NPS according to MCI subtypes, but that subtyping has been limited to cognitive features criteria. In the case of predominately amnestic MCI, the percentage of individuals exhibiting NPS has ranged from 35%[8] to 59%.[10] Amnestic MCI is associated with significant NPS, especially mood disturbances and apathy.[11] The prevalence of hallucinations, sleep disorders, or extrapyramidal signs was higher in non-amnestic MCI than in amnestic MCI.[12] Behavioral symptoms were more severe in subcortical vascular MCI than amnestic MCI, although the differences were not statistically significant.[13]

Despite efforts to classify MCI according to several features, the preclinical stages of dementias other than AD are not well delineated.[2] The distinction of which NPS occur in several MCI subtypes may be valuable and offer prognostic information. To our knowledge, there has been no one, comprehensive population-based estimate of the frequency of NPS in MCI patients, made according to cognitive features (e.g., amnestic vs non-amnestic), its likely

etiology (e.g., non-vascular vs vascular) or functional status (e.g., subtle instrumental ADL impairment or not). In the current study, we investigate the neuropsychiatric features of MCI using the Neuropsychiatric Inventory (NPI) and compare them by subtype.

II. MATERIALS AND METHODS

In all, 382 MCI subjects presenting with memory complaints were consecutively recruited from October 2005 to February 2007 from the community mental health center in Gwangju-si, Gyeonggi-do, Republic of Korea. The study was approved by institutional review boards and written informed consent was obtained after providing a complete description of the study to the subjects and their relatives. Diagnostic evaluation included gathering complete medical history, undertaking physical and neurologic examinations, and performing neuropsychological testing and dementia-related blood tests. The final diagnosis was reached by consensus of the neurologists and psychiatrists, using all available information.

1. MCI diagnostic criteria

To be eligible for the study, all participants had to meet the adapted operational criteria for MCI, including: (1) Complaints of subjective memory or other cognitive impairment by patients or informants, and (2) Evidence of objective memory or other cognitive function impairment in neuropsychological tests. Subjects with verbal and visuospatial memory impairment were defined as having scores below the cutoff values in the Seoul Verbal Learning Test (SVLT)[14] for delayed recall and Simple Rey Figure Test (SRFT)[15] for delayed recall, respectively. In addition, language and visuospatial function impairment was determined by the Korean version of the Boston Naming Test (K-BNT)[16] and the copy score of the Simple Rey Figure Test, respectively. Frontal lobe function impairment was defined as the condition where more than two domains showed impairment in motor, fluency, and stroop domain. Motor function was assessed by contrasting program, go-no go, fist-edge-palm, and Luria loop. Motor impairment was defined as the condition where two or more of the tests showed abnormal results. Fluency was assessed by semantic and phonemic

Controlled Oral Word Association Test (COWAT). Abnormal stroop was defined as being below the cutoff values in stroop color reading. The last two adapted operational criteria for MCI, which all participants had to meet, include (3) ADL was largely maintained, and instrumental activity of daily living (IADL) was minimally impaired, and (4) the individual was not demented.

A. MCI subtypes according to cognitive features

MCI patients were classified as aMCI if they had prominent memory impairment, either alone or with other cognitive impairments, or as naMCI if a single nonmemory domain was impaired alone or in combination with other nonmemory deficits.

B. MCI subtypes according to likely etiology

Vascular MCI was defined as having conditions that satisfy the aforementioned MCI operational criteria. Additionally, there should be a Hachinski ischemia scale score > 7 and a neurologic examination abnormality. A neurologic examination abnormality is defined as one or more focal symptoms or signs, such as dysarthria, swallowing difficulty, pathologic laughing, external ocular movement disturbance, facial palsy, hemiparesis, sensory deficit, increased deep tendon reflex (DTR), Babinski sign, Chaddock sign, rigidity, bradykinesia, gait disturbance (e.g., stooped posture, decreased arm swing, short step gait, shuffling, multiple step turning, festination).

C. MCI subtypes according to functional status

MCI-II is different from MCI-I, in that complex instrumental function is impaired but not definite in dementia, as demonstrated by history or a Seoul Instrumental Activity of Daily Living (S-IADL)[17] score greater than 7. There were many subjects who were neither normal nor demented, and whose complex instrumental functions were impaired according to Petersen's criteria. If the operational definition of amnestic MCI proposed by Petersen is closer to

normal than dementia, our working criteria of MCI-II are closer to those for dementia than normal.

2. Neuropsychiatric Inventory

The NPI has scripted screening questions for each of 12 behaviors that had potentially been present in the preceding four weeks. The NPI was administered by a nurse who had completed NPI training and had been periodically retrained to prevent rater drift. She was blind to study hypotheses. The NPI has been shown to be valid and reliable.

3. Statistical analysis

The percentage of subjects exhibiting each of the 12 behaviors was compared with the two groups using a chi-square test with adjustment for type I errors of multiple comparisons, i.e., $p < 0.005$ (= 0.05/10). Descriptive statistics are presented as percentages, according to the nature of the variable. The two-sample t test was used to compare continuous variables and the chi-square test for dichotomous ones. All tests were two-tailed at a probability level of 0.05. All analyses were performed using SPSS software version 12.0.

III. RESULTS

1. General characteristics of the subjects

There were 382 subjects in the MCI group. The mean (SD) age was 72.26 (6.47) and the mean of years of education was 4.98 (4.58). There were 132 males (34.6%) and 250 females (65.4%). Illiteracy was 70 (18.4%). NPI score was 2.14 (4.07), and Geriatric depression scale (GDS) score was 6.02 (3.97).

Table 1. General characteristics of mild cognitive impairment according to subtypes

	Total MCI n=382		Total MCI n=382		Total MCI n=382	
	Amnestic MCI n=217	Non-amnestic MCI n=165	Non-vascular MCI n=335	Vascular MCI n=47	MCI-I N=324	MCI-II N=58
Age (yrs)	72.8±6.9	71.5±5.8	72.6±6.6	69.8±5.3**	71.5±6.1	76.3±7.1**
Education (yrs)	4.9±4.7	5.1±4.4	4.6±4.4	7.4±5.0**	5.3±4.5	3.2±4.4**
Height (cm)	155.2±9.3	155.3±8.4	154.8±8.9	158.4±8.4*	155.6±8.8	153.0±9.3
Weight (kg)	57.9±9.2	58.5±8.7	57.7±8.9	61.7±9.1**	58.7±8.9	54.8±8.9**
K-MMSE	20.8±4.5	22.1±3.8**	21.3±4.3	22.1±3.9	22.0±3.9	18.9±3.7**
CDR	0.5±0.3	0.4±0.2**	0.4±0.3	0.5±0.2	0.4±0.2	0.6±0.3**
S-IADL	4.4±4.9	2.8±2.9**	3.6±4.0	4.3±5.3	2.6±2.6**	10.5±5.3**
K-GDS	6.1±3.7	5.9±4.3	6.1±4.0	5.4±3.6	5.9±4.1	6.9±3.1
Gender(M/F) (M%)	82/135 (37.8%)	50/115 (30.3%)	110/225 (32.8%)	22/25 (46.8%)	117/207 (36.1%)	15/43 (25.9%)
Literacy (illiteracy%)	46/171 (21.2%)	24/140 (14.6%)	63/271 (18.9%)	7/40 (14.9%)	49/275 (15.2%)	21/37 (36.2%)**
ApoE4	105/25 (80.8%)	94/26 (78.3%)	179/46 (79.6%)	20/5 (80.0%)	177/44 (80.1%)	22/7 (75.9%)

* p <.05 , ** p <.01

K-MMSE; Korean version of mini-mental state examination, CDR; clinical dementia rating scale, S-IADL; Seoul instrumental activity of daily living, K-GDS; Korean version of geriatric depression scale.

According to cognitive features, 217 patients were classified in the aMCI group, and 165 subjects in the naMCI group. According to likely etiology, 337 patients were classified in the non-vascular MCI group, and 47 patients in the vascular MCI group. Table 1 shows general characteristics of MCI according to subtype. The prevalence of at least one NPS was found to be 160 (41.2%). The most prevalent symptom was found to be depression (19.80%), followed by sleep disturbances (18.3%), irritability (12.8%), and anxiety (10.7%).

2. NPS in MCI subtypes according to cognitive features.

Table 2 lists the percentages of patients with symptoms in the 12 behavioral domains of the four groups. Among subjects with aMCI, the most prevalent symptom was depression (20.3%), followed by sleep disorders (18.0%) and irritability (16.6%). In the naMCI group, the most frequent symptoms were depression (18.8%) and sleep disorders (18.8%), followed by irritability (7.9%). Using the chi-square test to compare the four groups, no significant difference in the prevalence of NPS was found.

Table 2. Prevalence of each domain of neuropsychiatric inventory, according to MCI subtypes by cognitive feature

	Total MCI n=382				*p*
	Amnestic MCI n=217		Non-amnestic MCI n=165		
	Single n=52	Multiple n=123	Single n=154	Multiple n=53	
Delusions	0 (0%)	0 (0%)	3 (1.9%)	1 (1.9%)	0.331
Hallucinations	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Agitation/Aggression	0 (0%)	2 (1.6%)	4 (2.6%)	4 (7.5%)	0.074
Depression/Dysphoria	7 (13.5%)	22 (17.9%)	38 (24.7%)	8 (15.1%)	0.198
Anxiety	3 (5.8%)	15 (12.2%)	17 (11.0%)	6 (11.3%)	0.649
Elation/euphoria	0 (0%)	2 (1.6%)	1 (0.6%)	0 (0%)	0.576
Apathy/Indifference	3 (5.8%)	2 (1.6%)	4 (2.6%)	0 (0%)	0.237
Disinhibition	1 (1.9%)	3 (2.4%)	5 (3.2%)	1 (1.9%)	0.927
Irritability/lability	8 (15.4%)	13 (10.6%)	21 (13.6%)	7 (13.2%)	0.810
Aberrant motor behavior	1 (1.9%)	1 (0.8%)	1 (0.6%)	0 (0%)	0.724
Sleep/night-time behavior	7 (13.5%)	23 (18.7%)	30 (19.5%)	10 (18.9%)	0.806
Appetitie/eating disorders	1 (1.9%)	5 (4.1%)	11 (7.1%)	2 (3.8%)	0.402
No of NPI domain	0.596±1.209	0.715±1.120	0.877±1.265	0.736±1.211	0.462
No of subjects with NPI >=1	16 (30.8%)	50 (40.7%)	73 (47.4%)	21 (39.6%)	0.191

3. NPS in MCI subtypes according to likely etiology

Table 3 lists the percentages of patients with symptoms in the 12 behavioral domains of the two groups. Among subjects with non-vascular MCI, the most prevalent symptom was depression (19.7%), followed by sleep disorders (17.3%) and irritability (11.3%).

Table 3. Prevalence of each domain of neuropsychiatric inventory. according to MCI subtypes by likely etiology

	Total MCI n=382		*P*
	Non-vascular MCI n=335	Vascular MCI n=47	
Delusions	4 (1.2%)	0 (0%)	1.0*
Hallucinations	0 (0%)	0 (0%)	
Agitation/aggression	7 (2.1%)	3 (6.4%)	0.113
Depression/dysphoria	66 (19.7%)	9 (19.1%)	0.929
Anxiety	34 (10.1%)	7 (14.9%)	0.325
Elation/euphoria	1 (0.3%)	2 (4.3%)	0.041
Apathy/indifference	7 (2.1%)	2 (4.3%)	0.306
Disinhibition	8 (2.4%)	2 (4.3%)	0.354
Irritability/lability	38 (11.3%)	11 (23.4%)	0.021
Aberrant motor behavior	3 (0.9%)	0 (0%)	1.0
Sleep/night-time behavior	58 (17.3%)	12 (25.5%)	0.173
Appetitie/eating disorders	17 (5.1%)	2 (4.3%)	1.0
No of NPI domain	0.73±1.15	1.06±1.52	0.071
No of subjects with NPI >=1	135 (40.3%)	25 (53.2%)	0.093

In the vascular MCI group, the most frequent symptoms were sleep disorders (25.5%) and irritability (23.4%), followed by depression (19.1%). Using the chi-square test to compare the two groups, a significantly higher prevalence of elation and irritability was observed in the vascular MCI group, without multiple comparisons.

4. NPS in MCI subtypes according to functional status.

Table 4. Prevalence of each domain of neuropsychiatric inventory, according to MCI subtypes by functional status

	Total MCI n=382		
	MCI-I n=324	MCI-II n=58	*P*
Delusions	1 (0.3%)	3 (5.2%)	0.001
Hallucinations	0 (0%)	0 (0%)	
Agitation/aggression	4 (1.2%)	6 (10.3%)	0.0001
Depression/dysphoria	58 (17.9%)	17 (29.3%)	0.044
Anxiety	31 (9.6%)	10 (17.2%)	0.082
Elation/euphoria	2 (0.6%)	1 (1.7%)	0.379
Apathy/indifference	5 (1.5%)	4 (6.9%)	0.013
Disinhibition	7 (2.2%)	3 (5.2%)	0.186
Irritability/lability	34 (10.5%)	15 (25.9%)	0.001
Aberrant motor behavior	2 (0.6%)	1 (1.7%)	0.379
Sleep/night-time behavior	57 (17.6%)	13 (22.4%)	0.382
Appetitie/eating disorders	10 (3.1%)	9 (15.5%)	0.0001
No of NPI domain	0.651±1.064	1.412±1.665	0.0001
No of subjects with NPI >=1	128 (39.5%)	32 (55.2%)	0.026

Table 4 lists the percentages of patients with symptoms in the 12 behavioral domains of the groups. Using the chi-square test to compare the two groups, a significantly higher prevalence of delusion, aggression, depression, apathy, irritability, and eating disorders was observed in the MCI-II group. The number of NPS was 0.65±1.06 and 1.41±1.66 in MCI-I and MCI-II, respectively. The number of subjects with NPI scores greater than 1 was higher in the MCI-II group (55.2%) than in the MCI-I group (38.5%).

IV. DISCUSSION

The major objective of the present study was to examine the prevalence of NPS in a group of MCI patients, subtyped according to cognitive features, likely etiology, and functional status. There were two main findings: (1) There were no differences among neuropsychiatric symptoms in MCI subtyped according to cognitive features and likely etiology, and (2) differences in neuropsychiatric symptoms were distinctive between MCI groups subtyped according to functional status.

In our study, the prevalence of NPS was found to be 41.2%. The most prevalent symptom was found to be depression (19.8%), followed by sleep disturbances (18.3%), irritability (12.8%), and anxiety (10.7%). This pattern of symptoms is very consistent with the results reported in previous population-based studies that reported the prevalence of NPS as 43% and the prevalence of depression, irritability, and anxiety as 20%, 15%, and 10%, respectively.[18] Another population study of 320 subjects with MCI confirmed that the most frequent clinically significant symptoms in MCI were sleep disturbances and irritability.[8] Apathy commonly starts during the MCI stage and progressively increases as AD progresses[19] ; in our study, the reported prevalence of apathy was relatively low in comparison to previous studies (36%). Apathy seems to be less commonly reported in Asian patients with dementia.[20]

The difference in NPS among MCI subjects subtyped according to cognitive features was not significant in our study. A previous study suggests that the prevalence of hallucinations, sleep disorders, and extrapyramidal signs is higher in non-amnestic MCI than in amnestic MCI.[12] The observed differences are partly accounted for by the different sampling methods. Depression, anxiety, and agitation were less prevalent, while aberrant motor

behavior and irritability were more common in population-based versus tertiary care center studies.[21] When community-dwelling subjects were studied, the frequencies of NPS based on the NPI were, in general, substantially lower than those of the clinically referred subjects.[21] Other possible explanations are that previous studies analyzed only subjects whose NPI total score was greater than 0, and that multiple comparisons were not used.

NPS in vascular dementia and vascular cognitive impairment are very common,[18] and the total prevalence of NPS was similar in the AD and vascular dementia groups. Our results were consistent with previous findings,[13] that although NPS were more severe in subjects with vascular MCI than those with non-vascular MCI, the differences were not statistically significant.[22] This finding also supports the assertion that there are no significant differences between patients with AD and those with vascular dementia.[8]

Our results show that a significantly higher prevalence of delusion, aggression, depression, apathy, irritability, and eating disorders was observed in the MCI-II group, whose complex instrumental function was impaired but not definite in dementia. NPS in MCI are associated with declining cognitive and functional ability.[10,23-26] Depression, apathy, and agitation have been shown to increase the likelihood of later conversion to AD.[10,27,28] Also, the degree of cognitive and functional impairment is greater in MCI with NPS, and the presence of NPS is associated with a more severe somatic comorbidity and functional disability, in terms of both ADL and IADL.[29]

The several limitations of this study should be acknowledged. First, this is a cross-sectional study, so it does not reflect symptom fluctuations during the longitudinal course. Second, we did not have MRI data, which would have been useful for MCI subtyping according to likely etiology. To compensate for this weak point, we used stringent working criteria comprising medical history, neurologic exam, and scoring according to the Hachinski ischemia scale.

The current study has a strength, in that it at once estimates the frequency

of NPS in MCI patients dwelling within the community, according to cognitive features, likely etiology, and functional status. This study could therefore provide insight into the frequency and type of NPS observed in community-dwelling MCI patients, as categorized into a variety of subtypes.

V. CONCLUSION

There were no differences among neuropsychiatric symptoms in mild cognitive impairment subtyped according to cognitive features and likely etiology. Differences in neuropsychiatric symptoms were distinctive between mild cognitive impairment groups subtyped according to functional status.

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ABSTRACT (IN KOREAN)

한국판 neuropsychiatric inventory로 본 경도인지장애의 아형에 따른 임상적 특징 및 행동양식의 차이

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서론: 경도인지장애(mild cognitive impairment, MCI)는 정상인지기능과 치매의 중간단계로 알려져 있으며 현재까지 인지기능상의 특징 혹은 원인에 따라 여러 가지 아형으로 분류되어 왔다. 본 연구에서는 한국판 neuropsychiatric inventory를 이용하여 경도인지장애에서의 신경정신행동증상의 특징을 살펴보고 또한 경도인지장애의 각 아형별 신경정신행동증상의 차이를 규명해보고자 한다.

재료 및 방법: 신경심리검사, 신경학적 검사, 정신상태 검사, 보호자 문진등의 정보를 종합한 후에 신경과 및 정신과 전문의 2인 이상의 동의에 의하여 경도인지장애로 진단하였다. 1차적으로 경도인지장애를 진단한 후에 인지기능상의 특징에 따라 (amnestic vs non-amnestic), 원인에 따라 (non-vascular vs vascular), 기능수준에 따라 (MCI-I vs MCI-II) 2차적으로 아형별로 분류하였다. 신경정신행동증상은 한국판 neuropsychiatric inventory를 사용하여 숙련된 간호사가 환자 및 보호자와의 인터뷰를 통해 측정하였다.

결과: 382명의 경도인지장애로 진단된 환자가 연구에 참여하였다. 인지기능상의 특징 혹은 원인에 따라 경도인지장애를 분류하였을

경우 한국판 neuropsychiatric inventory에 나타난 12개 영역의 행동증상의 빈도에서 차이가 관찰되지 않았다. 그러나 기능수준에 따라 경도인지장애를 분류하였을 경우 기능수준의 저하가 있는 군에서 그렇지 않은 군에 비해 망상, 공격성, 이자극성, 식이행동의 문제 등이 더 빈번하게 나타나는 통계적 차이가 관찰되었다.

결론: 경도인지장애를 기능수준에 따라 분류하였을 경우 신경정신행동 증상의 빈도가 가장 두드러진 차이를 나타내었다.

핵심되는 말: 경도인지장애, 아형, 한국판 neuropsychiatric inventory, 신경정신행동 증상