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Mild Cognitive Impairment in Parkinson's Disease

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Background: To determine the frequency of mild cognitive impairment (MCI) of Parkinson's disease (PD, PDMCI) and its subtypes among non-demented PD patients, and to identify the influence of the age and presenting symptom on the development of PDMCI. **Methods:** A total 141 non-demented PD patients underwent a comprehensive neuropsychological assessment including attention, language, visuospatial, memory and frontal functions. PDMCI was defined by neuropsychological testing and was classified into five subtypes. Patients were divided into two groups (tremor vs. akinetic-rigid type) for presenting symptom and three groups according to the age. Neuropsychological performance of patients was compared with normative data. **Results:** Almost half (49.6%) of non-demented PD patients had impairment in at least one domain and can be considered as having PDMCI. Executive type of PDMCI was the most frequent and amnestic, visuospatial, linguistic and attention types followed in the order of frequency. The population of PDMCI was increasing as the age of disease onset was higher. Whereas the frequency of executive and amnestic types of PDMCI was comparable in younger group, executive type was the most frequent in older group. The patients with tremor dominant type performed worse on tests, particularly on attention test. **Conclusions:** MCI was common even in the early stage of PD and the subtype was diverse. Unlike MCI developing Alzheimer's disease later, executive type of PDMCI was the most common. Age was an important risk factor for development of MCI in PD. The concept of MCI should be introduced in PD. ***Journal of Movement Disorders 1(1):19-25, 2008***

Key Words: Parkinson's disease, Mild cognitive impairment, Parkinson's disease dementia

INTRODUCTION

Mild cognitive impairment (MCI), a transitional state between the cognitive changes of normal aging and early dementia, can be found not only in patients who will develop Alzheimer's disease (AD) or other neurodegenerative disorders later but also in patients with Parkinson's disease (PD). Initial diagnostic criteria for amnestic form of MCI, proposed by Petersen and colleagues, which required the presence of memory complaints and was corroborated by neuropsychological testing (>1.5 standard deviations (SDs) below age-related normative memory scores), in the absence of dementia, were designed mainly for AD.[1] There are several reasons that we can not adopt these criteria for the diagnosis of MCI in PD. Unlike AD, there can exist various subtypes of MCI in PD, but there have been no established classification and criteria for them. Patients with subtypes of MCI other than amnestic type do not complain subjective symptom corresponding to memory impairment in amnestic MCI. Additionally, the subjective symptom, for example, memory impairment in amnestic MCI may not be important for the diagnosis of MCI because the complaint of memory impairment is very prevalent among individuals whose cognition ranges from normal to severely decreased and patients who are severely demented sometimes do not complain memory disturbance. Therefore, in this study, we defined MCI as impaired performance (i.e., 1.5 SDs or more below the mean of the control group) on

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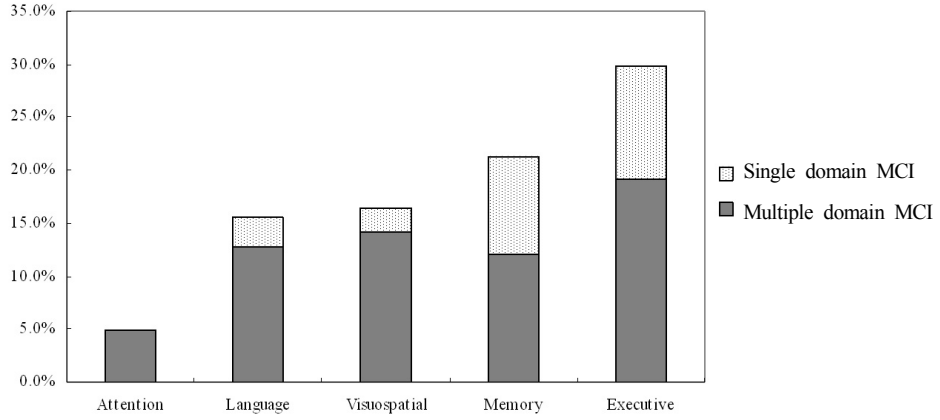

Fig. Distribution and frequency of cognitive dysfucntions.

at least one among five neuropsychological test with or without subjective complaints in the absence of dementia, and called the disorder MCI of PD ('PDMCI').

Several clinical subtypes of MCI exist; amnestic, multiple domain, and single nonmemory domain MCI. This is the case in PD and that is areason we need to introduce the concept of subtypes of PDMCI. We classified PDMCI into 5 types according to the results of neuropsychological tests; amnestic, executive, linguistic, visuospatial and attention type. Different cognitive profiles may exist within PD. In a study of recently diagnosed patients with PD, 11% had a specific frontostriatal type deficit, 8% had a specific temporal lobe type deficit, whereas 18% had cognitive deficits in both domains.[2] In a community-based study of PD patients with longstanding disease, over 50% of the nondemented patients with PD had some form of cognitive impairment: 20% exhibited predominantly memory deficits, 30% a dominant executive impairment, whereas 50% had a global cognitive impairment.[3]

The aim of this study was to explore the population of PDMCI and its subtypes among non-demented PD patients and to examine the influence of the age at disease onset and clinical presentation on the development of PDMCI.

MATERIALS AND METHODS

1. Subjects

The study population comprised 141 consecutive patients with PD recruited between 2003 and 2006 from neurology department in Dong-A University Medical Center. The clinical diagnosis of PD was based on United Kingdom Parkinson's Disease Society Brain Bank and a diagnosis of Parkinson's disease dementia (PDD) the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-4, code 294.1). Exclusion criteria included patients with 1) education periods of less than 3 years 2) clinically overt dementia 3) major depression 4) K-MMSE scores less than 20 5) the use of a cholinesterase inhibitors or anticholinergic drugs on a regular basis. Neurological examination and a comprehensive neuropsychological assessment were conducted in all patients. At the time of neuropsychological test, most patients were taking levodopa in combination with a dopamine agonist or amantadine. Seven patients were taking anticholinergics on irregular basis. To calculate levodopa dose, we pooled different drugs in a levodopa equivalent dose. Written informed consent was obtained from all subjects. The study was approved by the ethics committees of Dong-A University Medical Center.

2. Neurological examination

A detailed neurological examination was performed in all patients to check the onset of disease, initial dominant symptoms, medication, and response to medication. The

severity of symptoms triad was rated using the motor part of the Unified Parkinson's Disease Rating Scales (UPDRS); item 20 (tremor at rest), 22 (rigidity), 23 (finger taps) and 26 (leg agility). The stage of disease was determined with the Hoehn and Yahr (HY) rating scale. Dominant symptoms were divided into temor and akinetic-rigid (including gait disturbance and axial symptoms) dominant groups, according to main complaints and symptoms of patients at disease onset.

3. Neuropsychological assessment

All patients underwent a comprehensive neuropsychological test using Seoul Neuropsychological Screening Battery (SNSB).[4] Five domains were selected and evaluated as following; attention was assessed with forward digit span. Language function was examined with the Korean version of the Boston Naming Test. Visuospatial abilities were assessed with Rey Complex Figure Test. Memory was assessed with delayed recall of Seoul verbal learning test. Executive functions were examined with Stroop Color Word Test.

4. Neuropsychological definition of PDMCI

PDMCI was defined by neuropsychological testing as impaired performance (i.e., 1.5 standard deviation less below the mean of the control group) on at least one among five neuropsychological tests with or without subjective complaints in the absence of ADL impairment. PDMCI was classified into 5 types according to the results of neuropsychological tests amnestic, executive, linguistic, visuospatial and attention type. Each subtype has single domain MCI (sMCI) or multiple domain MCI (mMCI). For example, mMCI of executive type designates impairment of more than one domain including executive function.

5. Demographic and clinical correlates

To examine whether the age and presenting symptom were related to the development of PDMCI, we divided the patients into 3 groups based on the age at examination; younger than 55 years old, between 55-65 and older than 65. We also divided the patients into 2 groups based on clinical presentation; tremor and akinetic- rigid type. The impaired cognition (PDMCI) and normal cognition groups were compared with respect to demographic and clinical characteristics to identify the variables associated with cognitive function in PD. We analyzed the differences between the groups with respect to age, education periods, K-MMSE scores, symptom duration, treatment duration, levodopa dosage, the UPDRS motor scores of symptoms triad, HY staging and depression scores.

6. Data analysis

We used *t*-test to compare the demographic and clinical characteristics between impaired cognition and intact

Table 1. Demographic and clinical characteristics of cognitively intact and abnormal (MCI) patients

	Normal (*n*=71)	MCI (*n*=70)	*p*-value
Age	56.3±9.3	63.4±7.3	<.001
Sex (male:female)	29 : 42	37 : 33	.178
Duration of symptom (months)	44.6±63.2	45.9±48.1	.891
Duration of treatment (months)	12.4±29.8	18.5±31.9	.243
Hoehn and Yahr stage	2.2±0.6	2.3±0.5	.225
Levodopa dose (mg/day)	340.7±291.1	353.9±347.9	.807
Score of motor symptoms	8.8±4.0	10.0±4.1	.091
Geriatric depression scale	17.2±8.0	18.2±7.1	.434
Tremor : Akinetic-rigid	32 : 39	42 : 38	.092
Education (years)	10.0±3.8	9.6±4.0	.550
K-MMSE score	28.5±1.6	26.7±2.2	<.001

MCI; mild cognitive impairment, K-MMSE; Korean version of Mini-Mental Status Examination.

cognition groups using SPSS 12.0 (SPSS Inc., Chicago, IL, USA). Fisher's exact test and Likelihood ratio test for trend were used to compare the frequency of abnormal cognitive function tests according to grouping variables, such as age, education periods, K-MMSE scores, symptom duration, treatment duration, tremor versus akinetic-rigid, levodopa dosage, the UPDRS motor scores of symptoms triad, HY staging and depression scores. *p*-values of less than 0.05 were accepted as statistically significant results.

RESULTS

1. Demographic and clinical characteristics

PDMCI patients were older and had lower K-MMSE scores than PD patients with normal cognitive function (Table 1). There were no differences between the two groups with respect to sex distribution, education periods, treatment duration, levodopa dosage and geriatric depression scale. Neither disease duration nor disease severity as evaluated by the HY rating scale and the UPDRS motor scores influence the development of PDMCI. The average degree of motor disorder for the patients fell within the mild-to-moderate range.

2. Frequency and subtypes of PDMCI

Almost half of non-demented PD patients (49.6%) in this study had impairment in at least one domain and can be considered as having PDMCI defined by neuropsychological testing. Among all non-demented PD patients, the highest frequency (29.8%) of impairment was seen on Stroop Color Word test, sensitive to frontal lobe function. This means that 29.8% of non-demented PD patients have either sMCI or mMCI of frontal type. Verbal memory was impaired in 21.3% of patients, visuospatial function in 16.3%, language in 15.6% and attention in 5.0% in the order of frequency. 10.6% had SMCI of frontal type. This means that 10.6% of non-demented PD patients had only impairment of frontal domain. Among 70 patients with PDMCI, sMCI and mMCI are equally distributed, and sMCI of frontal type (15 of 35) was most frequent and followed by sMCI of amnestic type (13 of 35). Among 70 patients with PDMCI, 15 patients (21.4%) had a single frontal type, 13 (18.6%) a single amnestic type, 4 (5.7%) linguistic type, 3 (4.3%) visuospatial type and no patient had attention type only, and 35 patients (50%) mMCI type (Fig.).

The severity of PDMCI was diverse. The involvement ranges from single domain to all domains; 35 patients with PDMCI (50%) had impairment in only one domain, 21 (30%) in 2, 10 (14.3%) in 3, 3 (4.3%) in 4 and 1 (1.4%) in all domains.

3. Influence of age at disease onset

The population of PDMCI was increasing as the age of disease onset was higher; 27.5% in younger group, 51.8% in middle aged group and 66.7% in older group. The pattern of involvement was somewhat different depending on the age at disease onset (Table 2). In the older group, frontal executive dysfunction (40.0%) was the most common ($p<0.01$). Verbal memory (28.9%) and visuospatial dysfunction (24.4%) were also common. On the other hand,

Table 2. Distribution of MCI patients according to clinical characteristics

	Age at disease onset (years)				Dominant symptom			Symptom duration(months)		
	≤55	56-65	>65	*p*-value	tremor	akinetic	*p*-value	≤26	>26	*p*-value
Attention	2.5	1.8	11.1	.062	9.5	0	.014	2.8	7.2	.268
Language	5.0	21.4	17.8	.052	18.9	11.9	.353	12.5	18.8	.357
Visuospatial	7.5	16.1	24.4	.096	20.3	11.9	.254	12.5	20.3	.257
Memory	12.5	21.4	28.9	.172	27.0	14.9	.100	16.7	26.1	.218
Executive	12.5	33.9	40.0	.009	33.8	25.4	.273	2.6	36.2	.100

MCI; mild cognitive impairment.

frontal and verbal memory dysfunctions (12.5%, each) were comparable in frequency among the younger group (Table 2). Compared to the younger group, more frequent impairment on all domains was found in the older group, but frontal and visuospatial functions were two domains in which the difference between the two groups reached statistical significance (p<0.01 and p<0.05, respectively). Additionally, multiple domain PDMCI was more frequent in older group (35.6% vs 7.5%, p<0.01). Conversely, the frequency of impairment was lower and mainly restricted to single domain (8 out of 11) in the younger group.

4. Influence of presenting symptom

The patients with tremor dominant type performed worse on all domains than those with akinetic-rigid type, but attention was the only domain in which the difference between the two groups reached statistical significance (p<0.05)(Table 2).

DISCUSSION

The present study examined the frequency and clinical spectrum of PDMCI defined by neuropsychological test. PDMCI, 49.6% among non-demented patients, was fairly common. This high proportion can be attributed to the definition of PDMCI, which includes patients with impairment of at least one domain of neuropsychological tests, regardless of subjective complaints. Another characteristic finding in our study was that the subtypes of PDMCI were diverse; whereas MCI converting to AD is mainly amnestic type,[1] PDMCI has diverse subtypes. Although executive and amnestic types were most common, visuospatial and linguistic types were not uncommon. This finding indicates that neural substrate responsible for cognitive dysfunction in PD is more diverse and the lesion sites are more widespread and multifocal, contributing to the presence of deficits in multiple neuropsychological domains. Non-demented patients included in this study may not reflect the whole population because we excluded the patients with the education periods less than 3 years who showed a wide spectrum of cognitive state ranging from highly intelligent to illiterate.

Unlike the MCI developing AD later where amnestic type is far most prevalent,[1] frontal type was the most frequent in PDMCI. This finding is consistent with models describing PD-related changes in dorsolateral prefrontal regions participating in "cognitive" basal ganglia-thalamocortical circuits.[5] In this study, the population of PDMCI increased as the age at disease onset was higher, confirming that the age at disease onset was the most important determinant for cognitive impairment even in non-demented PD, that is, a risk factor for PDMCI. This result was in agreement with previous studies which focused on cognitive decline in non-demented PD as well as PD dementia.[6,7]

Age influenced not only the population of PDMCI but also the pattern of PDMCI. Whereas PDMCI was mainly restricted to single domain in the younger group, the involvement of multiple domain of PDMCI was more common in older group, demonstrating that patients beginning PD at later age had more widespread brain damage. Moreover, in younger group, MCI of amnestic type was as common as MCI of frontal executive type, but in older group, MCI of frontal executive type was much more common than amnestic type of MCI, indicating that frontal dysfunction is more vulnerable in elderly patients with PD. The reason for that is an older individual is more vulnerable to the loss of dopamine (DA) than a young one in PD because a reserve of DA capacity is small in an older individual.[8,9] And it is generally assumed that, among the 5 domains, frontal executive dysfunction is most closely related to DA loss, explaining it is most frequently involved in PD, particularly in elderly patients.

Our results indicate that the duration of illness had no association with development of PDMCI. This could be attributed to relatively short periods of disease duration, an average of 4.7 years from the disease onset. Longer periods of follow up study will be needed.

Our study showed that the severity as evaluated by the HY rating scale and the UPDRS motor scores did not influence the development of PDMCI. This finding suggests

that neural substrate responsible for the cardinal motor symptoms in PD are not associated with cognitive function, which is supported by the observation that cognitive impairments dose not improve with dopaminergic medication. Certainly, it should be interpreted cautiously for the patients with early stage of the illness because the opposite results for the advanced patients were also present.[10] Intriguingly, however, our study indicated that the presenting motor symptoms had an association with some parts of cognition in PDMCI. Contrary to the previous studies,[11] where patients with tremor dominant type generally showed better performance on tests, patients with tremor dominant type, in our results, performed worse on all domains, but attention was the only domain in which the difference between the two groups reached statistical significance. Several explanations are possible. First, it is conceivable that tremor, most sensitive to emotional stress, could influence performance of test, particularly on attention among the tested domains. Second, it could be also conceivable that the change of neural substrate responsible for tremor, the symptom least responding to dopaminergic agents among the cardinal motor symptoms, might have an association with cognitive dysfunction. This assumption can be supported by the fact that patients who had greater severity of speech disturbance and axial symptoms such as gait disturbance and posture, which are believed to be predominantly mediated by non-dopaminergic systems, exhibited more cognitive impairment.[12]

Our results showed that depression was not associated with cognitive impairment in the early stages of PD. The finding that geriatric depression scale was not different between patients with normal cognitive function and patients with PDMCI indicate that development of PDMCI can not explained by the presence of depression. This result was not in agreement with the previous study[13] reporting that depression could exacerbate cognitive impairments in the early stages of PD. The discrepancy could be explained by different methods of assessment of cognition.

To date, there have been no separate criteria for MCI in PD. The introduction of the concept of MCI in PD is now needed for several reasons. First, the criteria of DSM-4 were adopted to diagnose PDD because there are no separate criteria for that. The diagnosis of PDD is often confounded by contamination of medication and disabling motor symptom which often precede the cognitive impairment in advanced stage of PD, leading to effort to revise the criteria of PDD. Therefore, we think the evaluation of the cognitive status before patient become severely ill is more important for the assessment of clinical course. Second, to know the influence of different subtypes on the rate of conversion from PDMCI to PDD, we have to examine the existence of different subtypes of PDMCI. There is some evidence suggesting that the different MCI subtypes progress to different dementia disorders. Patients with amnestic MCI usually progress to AD at a high rate, whereas patients with single nonmemory MCI (i.e., executive or visuospatial impairment) are more likely to progress to a non-AD dementia such as dementia with Lewy body, frontotemporal dementia, Huntington's disease as well as PDD. It is intriguing that PDMCI of amnestic type is not likely to have a higher association with later development of PDD. In the previous study,[14] single domain nonmemory MCI and multiple domains slightly impaired MCI, but not amnestic MCI, were associated with later development of dementia in PD. Certainly, it should be interpreted with caution because a small number of subjects were included in that study. Third, while the efficacy of rivastigmine was proven in the treatment of PDD,[15] the efficacy of acetylcholinesterase inhibitor on PDMCI needs to be investigated. If the efficacy of acetylcholinesterase inhibitor on PDMCI is proven, it can be justified that patient with PDMCI be encouraged to be treated as early as possible.

REFERENCES

1. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985-1992.
2. Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's disease in the UK. The CamPaIGN study. Brain 2004;127:550-560.
3. Janvin C, Aarsland D, Larsen JP, Hugdahl K. Neuropsychological profile of patients with Parkinson's disease without dementia. Dement Geriatr Cogn Disord 2003;15:126-131.

4. Kang Y, Na DL. Seoul Neuropsychological Screening Battery. Incheon: Human Brain Research & Consulting Co.; 2003.
5. Alexander G, Delong M, Strick P. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357-381.
6. Katzen HL, Levin BE, Llabre ML. Age of disease onset influences cognition in Parkinson's disease. J Int Neuropsychol Soc 1998;4:285-290.
7. Locascio JL, Corkin S, Growdon JH. Relation between clinical characteristics of Parkinson's disease and cognitive decline. J Clin Exp Neuropsychol 2003;25:94-109.
8. Dubois B, Pillon B, Sternic N, Lhermitte F, Agid Y. Age-induced cognitive disturbances in Parkinson's disease. Neurology 1990;40:38-41.
9. Hietanen M, Teräväinen H. The effect of age of disease onset on neuropsychological performance in Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:244-249.
10. Green J, McDonald WM, Vitek JL, Evatt M, Freeman A, Haber M, et al. Cognitive impairments in advanced Parkinson's disease without dementia. Neurology 2002;59: 1320-1324.
11. Caparros-Lefebvre D, Pécheux N, Petit V, Duhamel A, Petit H. Which factors predict cognitive decline in Parkinson's disease. J Neurol Neurosurg Psychiatry 1995;58:51-55.
12. Pillon B, Dubois B, Cusimano G, Bonnet AM, Lhermitte F, Agid Y. Does cognitive impairment in Parkinson's disease result from non-dopaminergic lesions? J Neurol Neurosurg Psychiatry 1989;52:201-206.
13. Elderkin-Thompson V, Kumar A, Bilker WB, Dunkin JJ, Mintz J, Moberg PJ, et al. Neuropsychological deficits among patients with late-onset minor and major depression. Arch Clin Neuropsychol 2003;18:529-549.
14. Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. Mov Disord 2006;21:1343-1349.
15. Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, et al. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med 2004;351:2509-2518.