American Journal of Alzheimer's Disease & Other Dementias®
25(5) 455-460

DOI: 10.1177/1533317510370956
http://ajadd.sagepub.com
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Executive Functions Deficit in Parkinson's Disease With Amnestic Mild Cognitive Impairment

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Abstract

Recent studies suggest that onset of dementia in Parkinson's disease (PD) is preceded by a phase known as mild cognitive impairment (MCI). Different clinical subtypes of MCI in PD were found. The objective of this study was to investigate whether patients with PD diagnosed with amnestic MCI (aPD-MCI) have also subtle deficits in other cognitive domains and especially in attention/executive functions and, therefore to clarify whether all subcomponents of executive control are equally affected in aPD-MCI. We investigated 23 patients with aPD-MCI (modified Petersen's criteria) and 25 normal controls. Relative to controls, the aPD-MCI group showed significant deficits with reference to tasks that encompass various aspects of attention/executive functions, including Trail Making Test, Stroop test, Modified Card Sorting Test, and digit span backward, as well as phonemic and semantic verbal fluency. This suggests that executive dysfunction is consistently presented in PD with MCI, even in "amnestic" PD-MCI due to cortical–subcortical dysfunction.

Keywords

Parkinson's disease, mild cognitive impairment, cognition, executive functions

Introduction

Parkinson's disease (PD) is often associated with cognitive impairment and dementia. The average prevalence of mild cognitive impairment (MCI) in nondemented PD was reported to range from 21% to 55%.[1,2] Similar to Alzheimer's disease (AD), the presence of MCI in PD (PD-MCI) was found to be associated with increased risk of subsequent dementia.[3] Furthermore, the mild cognitive changes in patients with nondemented PD were also determined to affect quality of life.[4] The strict application of the initial definition of MCI was soon shown to be heterogeneous and unstable in terms of progression. This heterogeneity includes the clinical presentation, profile of progression, and etiological factors.[5] Recent studies suggest that the different MCI subtypes (amnestic, single-domain nonmemory and multiple domains slightly impaired MCI) progress to different dementia disorders.[6] Patients with amnestic MCI usually progress to AD at a high rate,[7] whereas patients with single domain nonmemory MCI are more likely to progress to a non-AD dementia.[6,8]

Therefore, we could expect that the PD-MCI, as a precursor of PD with dementia (PDD), will include exclusively single domain nonmemory and multiple domains slightly impaired MCI subtypes but not amnestic MCI subtype. However, in recent years, the literature has reported that although the first 2 of the previous MCI subtypes are the most frequent in PD-MCI, there are also some patients with PD who cover the criteria of amnestic MCI subtype.[2,3] It could be suggested that the different underlying pathological factors in addition to Lewy body pathology in these patients bring to the different cognitive profiles in them similar to the data from PDD studies.[9]

However, the specific cognitive profile of the amnestic PD-MCI subtype is not quite clear. Patients with aPD-MCI could demonstrate deficits only on verbal episodic memory. The performance of the same group on measures assessing other cognitive domains could be equivalent to that of healthy older controls. This profile of cognitive deficits is typically observed in amnestic MCI[7] precursor of AD and it suggests the similarity of underlying pathological process in both the amnestic MCI groups (with and without PD). Another suggestion may be that the amnestic PD-MCI group will also have subtle widespread deficits in executive functions and the other frontal lobe tests due to disruption of the frontal–subcortical circuit.[10] In this case, it will be also interesting to investigate whether all different subcomponents of executive functions are present in amnestic

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PD-MCI. Therefore, knowledge of the exact pattern of cognitive impairment in amnestic PD-MCI could provide information about the underlying neuropathological factors. However, it should be pointed out that the choice of control group (PD or non-PD), tasks used to examine aspects of cognitive function, and the PD-MCI definition could influence the determination of the affected cognitive domains in amnestic PD-MCI and preclude the comparison with other cognitive studies. Consequently, we selected executive tasks and clinical criteria that were "universally" accepted. The objective was to avoid further clouding the issues by introducing additional measures. In addition, several recent studies noticed that even patients with "cognitive intact" PD, who do not cover the MCI criteria, show some neuropsychological and neuroimaging features similar to PD-MCI groups.[11-13] Therefore, in this study, we only chose a cohort of elderly cognitive intact participants without PD as a control group to detect subtle cognitive deficits in our amnestic PD-MCI group. The aims of our study were to investigate whether patients with PD diagnosed with amnestic MCI have also impairment in other cognitive domains and especially in attention/executive functions. Furthermore, we wanted to clarify whether all subcomponents of executive control are equally affected in amnestic PD-MCI.

Methods

Participants

Patients were recruited from participants who sought consultation at the University Hospital "Alexandrovska" in Sofia, because of Parkinsonian's signs and for the treatment of their parkinsonism as well. The research was approved by the ethics committee of the Medical University-Sofia, and all participants provided their own written informed consent prior to study participation.

The evaluation procedure consisted of detailed medical history, physical and neurological examinations, cognitive evaluations, appropriate laboratory tests, and neuroimaging. All patients underwent brain computed tomography (CT) or magnetic resonance imaging (MRI). History of medical, neurological, and psychiatric problems was obtained from the patient and family members (usually the patient's spouse or children). The psychiatric evaluation included a semistructured interview and the Geriatric Depression Scale (GDS). Since depression may influence cognition and especially executive functions in patients with PD,[14-16] a measure of depression, 15-item GDS[17] was included, which has been validated in patients with PD and recommended for use in this population.[18] Participants with a score more than 4, indicating clinically significant depression,[18,19] were excluded.

Cognitive status was evaluated by the Mini-Mental State Examination (MMSE)[20] and Mattis Dementia Rating Scale (DRS).[21] The DRS is commonly used screening instrument and comprises items that were specifically designed for executive function assessment.[22] The scale is divided into 5 subscales, measuring attention, initiation and perseveration, conceptualization, construction, and memory. For patients with PD, DRS has been shown to be a valid scale of cognitive functioning in nondemented and demented patients,[23,24] and the subscales show strong convergent and discriminant validity.[24] The Clinical Dementia Rating (CDR) scale[25] was also completed.

All available information was evaluated by an experienced neurologist (who is also trained in brain imaging) and by a neuropsychologist. Among the 353 patients fulfilling the UK Parkinson's disease Society (UKPDS) Brain Bank criteria for PD,[26] 199 patients were excluded because of the following: (1) patients with coexisting dementia and/or major depression (according to Diagnostic and Statistical Manual of Mental Disorders [fourth edition; DSM–IV] criteria) and/or score of GDS higher than 4 ($n = 93$); (2) patients who presented any of the following: history of minor stroke events, clinical course with abrupt deterioration of cognitive function, stepwise decline or fluctuation, and evidence of relevant cerebrovascular disease by brain imaging (CT or MRI findings of single or multiple small subcortical infarcts and extensive white matter changes; $n = 98$); and (3) patients with uncorrected visual deficit ($n = 8$). From the remaining 154 patients with nondemented and nondepressive PD, 72 were cognitively intact and 82 were with PD-MCI. In PD-MCI group, 23 patients were diagnosed with amnestic PD-MCI, according to the criteria defined below.

Mild Cognitive Impairment Group

The absence of a consensus on the definition of MCI in PD led us to adopt MCI criteria used to classify participants at risk for AD to categorize our patients with PD as cognitively intact or MCI. The diagnosis of MCI was made according to a modified criteria proposed by Petersen and colleagues.[27] The patients with PD in MCI group had (1) memory or other cognitive complaint by the patient or a reliable informant; (2) normal global cognitive function (MMSE >26); (3) objective cognitive impairment of at least 1.5 SDs below age- and education-matched norms, as previously developed, on one or more of the subscales of DRS; and (4) generally preserved functional capacity and activities of daily living both by history and by functional scale (CDR = 0 or 0.5) assessment.

According to these criteria, the 82 patients with PD-MCI were classified in 3 subtypes: (1) amnestic MCI ($n = 23$), that is, individuals with impaired performance on the memory subscale but who are performing reasonably well on other subscales of the DRS; (2) multiple domains slightly impaired MCI ($n = 29$), that is, impairment on 2 or more cognitive measures; (3) single nonmemory domain MCI ($n = 30$), that is, impairment in a single cognitive domain other than memory.

Severity of Parkinsonism in patients with PD was evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) part III[28] and the Hoehn and Yahr staging[29] in the patient's best on state.

Normal Control Group

To compare the neuropsychologic performances of amnestic PD-MCI group, we composed a control group of 25 elderly

participants without history or symptoms of psychiatric or neurologic disease and with integrity of their cognitive functions. They were matched to patient groups according to age, sex, and educational level.

Neuropsychological Assessment

Cognitive functions were evaluated in all participants by a comprehensive neuropsychologic battery consisting of subtests and modified short forms of commonly used neuropsychologic measures. The neuropsychological assessment was blinded to the clinical diagnosis. Episodic memory was assessed with the Buschke Free and Cued Selective Reminding Test (FCSRT),[30] assessing free recall (number of items retrieved over 3 learning trials), total recall (number of words recalled with free and cued procedures over 3 learning trials), recognition, and the delayed-free and total recall. Attention and executive functions were tested by the Trail Making Test part A (TMT-A) and part B (TMT-B;[31] assessing the time to correctly relay all items in each of the trials), the Modified Card Sorting Test (MCST;[32] assessing the number of categories achieved and perseverative errors), Digit Span forward and backward of the Wechsler Adult Intelligence Scale (WAIS),[33] and the Stroop Test[34] (assessing, in 3 parts, the number of items correctly named in 45 seconds). Language abilities were assessed by the 15-item subset of the Boston Naming Test (BNT),[35] the semantic verbal fluency (categories animals, assessing number of animals produced in 60 seconds), and the phonemic verbal fluency (letters M, assessing the number of words produced in 60 seconds).[36] Visuospatial abilities and constructional praxis were evaluated by the copy 5 complex Designs[37] and Clock drawing test.[38]

Statistical Analysis

An analysis of variance (ANOVA) on each test variable was performed separately. Categorical data were analyzed by using the χ^2 test. Pearson correlation between UPDRS motor subscale and cognitive variables was evaluated in patients with PD. Differences were interpreted as significant by at least $P < .05$. All analyses were computed using Statistical Package for the Social Sciences (SPSS) version 14.0 statistical software.

Results

Demographic characteristics of the patients with PD with amnestic MCI (aPD-MCI) and controls were presented in Table 1. The ANOVA was used to examine group differences in age, education, and MMSE scores.

Patients with aPD-MCI had lower DRS scores than controls, but there were no significant differences regarding age, education, MMSE scores, and gender ($\chi^2 = 0.083$; $P = .773$). The average degree of motor disorder for the PD group fell within the mild-to-moderate range as evaluated by the Hoehn and Yahr 2.3 (0.6) and the UPDRS motor section 21.2 (6.7). The average disease's duration of our PD group from the first motor symptom was 6.3 years. The neuropsychological performances of the 2 groups included in this study are shown in Table 2.

With regard to the pattern of performance on FCSRT, statistical analysis indicated that patients with aPD-MCI performed significantly less well than controls on immediate and delayed free recall, as well as on immediate and delayed total recall, but not on recognition. In terms of tasks that encompass various aspects of attention and executive functions, statistical analysis indicated that patient group was significantly impaired relative to controls on all tests, except digit span forward.

With regard to language tasks, intergroup comparisons indicated that patients performed within normal limits on the BNT but not on the category and phonemic verbal fluency test. Similarly, no significant difference was found between patients and controls on Clock Drawing Test and copy of complex designs.

Discussion

Our findings show that in addition to the impairment of the verbal episodic memory, our patients with aPD-MCI demonstrated significant deficits in almost all measures of attention/executive functions. However, the performance on measures assessing language, visuospatial abilities, and constructional praxis in PD group was comparable with that of normal controls (NCs). Although this was not the main goal of our study, we would like to stress on the type of memory impairment in our patients with aPD-MCI. Several recent studies found that impairment in recognition memory was nearly as common as free recall in patients with PD supposing the appearance of deficits in both encoding and retrieval.[39] In contrast to them, it was noted in our study that patients with aPD-MCI recalled significantly fewer words on immediate recall but demonstrated improved cued recall and normal recognition, finding typically observed in patients with frontostriatal dysfunction who considerably benefit from prompts.[40]

In addition to the severely abnormal episodic memory performance, we also found significant impairment in some neuropsychological measures largely accepted as measures of executive functions. The PD group showed significantly lower number of correct responses on the third part of the Stroop test and the Modified WCST (number of categories and perseverations). Both tests are well-known and validated executive tasks measuring the ability to inhibit irrelevant responses, the set shifting and cognitive flexibility, or the supervisory attentional system. These findings are in agreement with the results of Kensinger and colleagues[41] who reported disproportionately affected ability to inhibit automatic or prepotent responses in early PD as compared with mild AD.

Compared to controls, our patients with aPD-MCI were also significantly slower on the 2 parts of TMT. The impairment in TMT was frequently found even in nondemented patients with newly diagnosed PD.[42] This test evaluates the ability to follow a complex plan and require cognitive flexibility in the execution of that plan. The deficit in these abilities in our PD group is clearly demonstrated in subtraction of TMTA-TMTB, when the motor component of the response can be controlled.

Table 1. Demographic Characteristics of Patients With PD-MCI and NC[a]

	NC (n = 25)	PD-MCI (n = 23)	*F*	*P*
Mean age (year)	67.4 (6.9)	67.9 (8.9)	0.05	.824
Education	14.5 (2.4)	13.5 (3.3)	1.44	.237
MMSE	28.6 (0.8)	28.2 (1.0)	1.79	.187
DRS	139.6 (2.3)	133.7 (3.5)	26.12	.000

Abbreviations: DRS, Mattis Dementia Rating Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NCs, normal controls; PD, Parkinson's disease.
[a] The values are mean (SD).

Table 2. Neuropsychological Performance of Both Groups[a]

	NC	PD-MCI	F	*P*
Memory				
FCSRT (free recall)	27.1 (3.1)	20.2 (5.9)	26.12	.000
FCSRT (total recall)	45.4 (1.2)	41.2 (4.1)	23.4	.000
FCSRT (recognition)	15.8 (0.4)	15.6 (0.6)	2.72	.106
FCSRT (free delayed recall)	10.7 (1.6)	8.5 (2.4)	14.37	.000
FCSRT (total delayed recall)	15.7 (0.5)	14.5 (1.6)	12.72	.001
Attention/executive function				
Digit span (forward)	6.2 (0.6)	5.9 (0.7)	2.33	.134
Digit span (backward)	4.7 (0.8)	3.7 (0.7)	21.84	.000
TMT A (time)	50.2 (13.5)	76.4 (27.1)	18.37	.000
TMT B (time)	119.1 (33.1)	183.4 (85.6)	12.13	.001
TMT B-A (time)	68.9 (33.5)	107.0 (81.4)	4.63	.037
MCST (categories)	5.9 (0.3)	4.8 (1.8)	10.22	.003
MCST perseverations	1.2 (1.2)	6.4 (8.1)	9.89	.003
SCIT part 3	33.9 (5.8)	29.0 (7.7)	6.1	.017
Language				
BNT	15.0 (0.2)	14.9 (0.5)	0.81	.373
Semantic fluency (animals)	20.7 (3.9)	18.4 (3.3)	4.96	.031
Phonemic fluency (letter M)	12.8 (3.1)	8.8 (3.0)	19.75	.000
Visuospatial/abilities				
Copy designs	10.1 (0.6)	9.8 (1.0)	1.54	.222
Clock drawing test	9.5 (0.5)	9.2 (1.2)	1.40	.244

Abbreviations: BNT, Boston Naming Test; FCSRT, Free and Cued Selective Reminding Test; MCI, mild cognitive impairment; MCST, Modified Card Sorting Test; NCs, normal controls; PD, Parkinson's disease; SCIT, Stroop Color Interference test; TMT A, Trail Making Test part A; TMT B, Trail Making Test part B.
[a] The values are mean (SD).

In our study, aPD-MCI group demonstrated deficit in digit span backward but not in digit span forward. Similar results were reported by Altgassen and colleagues,[43] in a recent study investigating the role of all 4 components of the revised working memory model using the digit span forward as a measure for phonological loop. In contrast to the reduced central executive and episodic buffer efficiency, their PD group did not demonstrate impairment in verbal and visuospatial buffer functioning.

In the domain of language, we found that naming, cognitive function with relatively low executive load was within the normal range in patients with aPD-MCI.[32] However, the language functions with highly involved executive component as semantic and phonemic fluency[44] showed marked deficiency. These data are in-line with the results of Song and colleagues.[45]

Concerning the visuospatial and constructive abilities, our PD group performed similarly to NC, on the CDT and figure copying test. These data partly correlated with the results of Muslimovic and colleagues,[42,46] who also did not find significant difference in CDT between PD group and controls. Song and colleagues also noticed the preservation of visuospatial and constructive abilities in patients with PD-MCI in contrast to patients with PDD who showed significant impairment in this cognitive domain. [45] Because aPD-MCI cases in our study were defined by single domain dysfunction of memory ability, one might expect the statistical difference we found only on corresponding tests. However, there were also significant differences between aPD-MCI and controls for attention/executive functions but not for constructive and language abilities. We believe that this reflects the presence of a dysfunction of fronto–subcortical pathways in these patients with PD-MCI. Our results support the data of several other authors,[13,45] namely that MCI in PD is more related to fronto–subcortical dysfunction than to cortical alterations.

There are some limitations to the current study. First, an important consideration in studies of patients with PD concerns the accuracy of the clinical diagnosis. Although we cannot exclude that some patients in our sample might have been misdiagnosed, we minimized this possibility by using the UKPDS Brain Bank criteria, estimated in a clinicpathological study to have a diagnostic accuracy of 90%.[47] Second, slowness in motor performance may have affected patient's scores on cognitive testing. However, the neuropsychological examination was performed in the on state and Pearson's correlation did not demonstrate significant relationship between scores of UPDRS-motor subscale and cognitive variables in patients with PD. Thus, it is less likely that motor functioning significantly contributed to performance of patients with PD during cognitive testing. Third, in our attempt to exclude possible confounding factors, both groups in our study are very small. This could influence tests with lower sensitivity and a low ceiling effect, for example, the CDT, because of the low power of the study to detect small differences between cases and controls. Finally, coming from a clinic-based study our observations are of limited generalizability.

In conclusion, our results show that executive functions are impaired even in patients with ''amnestic'' PD-MCI. The results of our study highlight the need of more complex cognitive examination focusing on executive and memory patterns for early detection of cortico–subcortical dysfunction and better differentiation of the subtypes of PD-MCI. Several previous studies addressing the different MCI subtypes as predictors of PDD have yielded inconsistent results.[3,11] More prospective studies are needed to understand the longitudinal course of MCI in PD to determine which of the MCI subtypes represent a precursor to a more widespread dementia. In our future prospective work, we are planning to include more PD-MCI to increase the power of the study to detect small differences between cases and controls. We are also planning to evaluate more profoundly the possible relationship between these early executive changes and motor deficit, as well as behavior changes in these patients with PD-MCI.

Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research and/or authorship of this article: a grant no 51/2007 from the Medical University-Sofia, Bulgaria.

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