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ORIGINAL ARTICLE

Medication management and treatment adherence in Parkinson's disease patients with mild cognitive impairment

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Abstract

Introduction The key feature that distinguishes mild cognitive impairment (MCI) from dementia is the absence of significant functional decline because of cognitive impairment. In Parkinson's disease patients (PD) with MCI (PD-MCI), the effect of cognitive impairment on complex instrumental daily activities, such as medication management, is not well established.
Method 26 patients with PD-MCI (diagnosed to Level 2 Movement Disorders Society diagnostic criteria) and 32 idiopathic PD patients without cognitive impairment participated in the study. A detailed neuropsychological testing battery (including tests for attention and working memory, executive functions, language, visuospatial functions, episodic memory) and various prospective memory tasks were applied to the patients. Medication taking behaviors were evaluated using two different methods based on the performance (medication management ability assessment) and self-reporting (adherence scale).
Results The PD-MCI group obtained significantly lower scores in medication management assessment and made more mistakes on following prescription instructions (e.g., they took more or less tablets and did not use medications as instructed with regard to meal times). Cognitive areas predicting success in medication management performance were language, event-based prospective memory and visuospatial functions. There was no significant difference between the two groups' self-reporting of adherence.
Conclusion Mild cognitive impairment in patients with PD adversely affects medication management. Diagnosing MCI in PD is important to ensure that the appropriate measures can be taken to provide support and improve the medication management process. Adherence assessments based on self-reporting may not provide reliable and sensitive information in patients with PD-MCI.

Keywords Parkinson's disease · Mild cognitive impairment · Patient adherence · Medication management · Cognition

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with motor and non-motor symptoms. Non-motor symptoms such as cognitive impairment may become more prominent due to disease progression [1]. Cognitive impairment may lead to functional impairment and decrease quality of life [2, 3].

Mild cognitive impairment (MCI) is defined as a decline in cognitive function without having significant impairment manifested in everyday functioning [4]. Diagnostic criteria for Mild Cognitive Impairment in PD (PD-MCI) have been proposed by a Task Force of Movement Disorder Society (MDS) [5]. According to these criteria, the primary feature that distinguishes PD-MCI from dementia is the absence of significant functional decline based on cognitive impairment. However, it was emphasized that impairment in various cognitive domains may lead to a decrease in different aspects of more complex daily functions [5].

One of the more complex instrumental daily activities is medication self-management that requires the ability to

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understand the prescribed medication and instructions about how to take them, to plan out when and what medication you need to take each day amongst daily activities, to remember to take the medication, and to solve problems for the missed doses. Hence, efficient medication self-management requires a range of cognitive processes, such as executive function, sensorimotor ability, prospective memory, verbal memory, attention/working memory, and cognitive flexibility [6, 7].

Medication management is a complex activity of daily living and can provide information about the patient's adherence. It is stated that the competence-performance distinction in cognitive psychology can be adapted to the relationship between medication management and adherence concepts [8]. Understanding the patient's medication-taking behavior is very important to accurately assess the patient's clinical presentation and response [9]. While there is limited research investigating the effect of cognitive impairment on medication management in patients with PD-MCI, there is no study investigating its relationship with adherence. The primary aim of this study is to investigate the effect of cognition on medication management and adherence in patients with PD-MCI. We also investigated which cognitive domains might predict medication management performance.

Methods

Patients and sample size

The effect size (d) was calculated as 0.8 for comparison of the difference between the two independent groups (two tailed) over the pilot study. When alpha error was taken as 0.05 and the power of the study was 0.80, at least 25 people were required to be included in the groups. Participants were selected consecutively among the patients who went to the Outpatient Clinic of Behavioral Neurology and Movement Disorders Unit, Department of Neurology, Istanbul Faculty of Medicine until the required number for our study was reached. Fifty-eight patients with PD took part in this study between April 2018 and May 2019.

Inclusion criteria were a diagnosis of PD according to United Kingdom PD Society Brain Bank criteria and having at least primary school education. PD-MCI was diagnosed according to MDS Level 2 diagnostic criteria [5]. Detailed neuropsychological tests were conducted including 2 tests for each of the five cognitive domains (attention–working memory, executive functions, language, memory, and visuospatial functions). A test performance that was 1.5 SD below the norm for age and education for a test was accepted as impairment. Participants were further divided into cognitive subtypes and classified as single-domain subtypes when the impairment was detected on two tests within only one cognitive domain. Meanwhile, if impairment was detected on at least one test across over one cognitive domain they were classified as multiple domain subtype. All patients and their informants reported their activities of daily living (ADLs) were completely normal and the patient can reliably take the pills without any need for assistance in daily life. Exclusion criteria were dementia (diagnosis based on Movement Disorders Task Force proposed criteria [10]) significant psychiatric or systemic diseases, excessive daytime sleepiness, vision problems, and taking anticholinergic medications that may impair cognition. Patients who received deep brain stimulation, apomorphine infusion, and levodopa/carbidopa intestinal gel treatment were excluded from the study. All participants provided written approval that was obtained from the Ethics Committee of Istanbul Faculty of Medicine, Istanbul University (22.12.2017/21).

Neuropsychological tests and assessment

All neuropsychological tests were performed in the 'on' period in patients with motor fluctuations. Global cognitive function was assessed by the Montreal Cognitive Assessment (MoCA) [11]. Within this scope, neuropsychological assessments including ten tests representing five cognitive domains: for attention and working memory: digit span [12] and trail making test [13]; for executive function: verbal fluency [14] and stroop test [15]; for memory: Wechsler Memory Scale-Logical Memory subtest [16] and 15-word Verbal Memory Test-Oktem Verbal Learning Test version [17]; for visuospatial functions: Benton Judgment of Line Orientation Test [18] and Benton Facial Recognition Test [19]; for language: Boston Naming Test [20] and Responsive Naming Test [21]. This neuropsychological battery was utilized using tests translated into Turkish with norms that have been validated in Turkey (Supplementary).

Raw scores for each cognitive test were transformed to z scores to evaluate results of different tests together and calculate the cognitive domain scores. [z score = (individual's test raw score—average of the test's normative data by education and age)/standard deviation of normative data]. Z scores for timed measures (Stroop and TMT) were inversely coded so that for all domains negative scores indicated deterioration [22]. Composite z scores for each domain were computed by averaging z scores of individual tests.

In addition to full neuropsychological assessment, prospective memory, which was assumed to be relevant for following treatment schedule, was also evaluated. Due to lack of a prospective memory test with Turkish translation and validation, we used various real-world prospective memory tasks similar to the existing tests [23, 24]. Therefore, 2 event-based and 2 time-based prospective memory tasks were used (Supplementary). The time and event-based tasks given to patients were explained. In time-based tasks, the

right answer at the right time was scored as 2 points, the wrong answer at the right time was scored as 1 point. If the patient did not remember the task or answered incorrectly at the wrong time, 0 scores were given. In event-based tasks, 1 score was given if the answer was correct. The 1-min wrong timing was considered correct.

Assessment of medication management and adherence

Medication management was defined as the capacity to follow treatment instructions with no assistance or support. Medication management was assessed by Medication Management Ability Assessment (MMAA) scale which is a role-play task at prescribed simulated medication regimen [25]. Four mock medications were included similar to a patient's typical daily treatment regime. Initially, a detailed instruction of the medication regimen was given to the patient (Supplementary). After about 45–60 min, the patient was asked to plan a day from morning to evening. Patients were given asked when they must take their medications throughout the day. The report of patients (number of medication and times, awakening time, bedtime and mealtime) were recorded. At the end of the test, the scoring was done according to the MMAA scoring sheet. One score was given for each event in which the participant indicates attempting to take the medication, taking the correct number of pills, and adhering to the correct food rules (pills were taken with or without food) and their sum was calculated as the total score. Besides, the total error score (i.e. number of wrong frequency or quantity) and the score of using medication appropriate to mealtimes (i.e. with or without food) were analyzed. The MMAA has shown excellent test–retest reliability (ICC = 0.96) and strong internal consistency (Kuder-Richardson 20 = 0.81) [25].

Adherence is described as the extent to which a patient's behavior corresponds with the prescribed drug regimen in daily life. Adherence was evaluated based on the patient's self-report by 4-question Morisky Adherence Scale developed by Morisky, Green, and Levine [26]. "Yes/no" questions were included; 0 points were given for each 'yes' response and 1 point for 'no' response. As a result, three different adherence levels (high, medium, and low adherence) were determined with respectively 0, 1–2, and 3–4 scores.

Other evaluations

Motor functions and complications were evaluated by Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [27]. The scale consists of four parts; Part I (non-motor symptoms), Part II (motor symptoms), Part III (motor examination) and Part IV (motor complications). Mood and anxiety were evaluated using Hamilton depression scale [28], and Hamilton anxiety scale [29]. The drugs used by the patients were determined and the levodopa equivalent dose (LEDD) was calculated.

Statistical analysis

All analyses were performed using IBM software (SPSS 20.0 for Windows; IBM Corp, Armonk, NY). Continuous variables, if normally distributed, were presented as means ± SDs, and two groups were compared by independent sample t-test. Continuous variables, if not normally distributed, were presented as median (quartile) and compared by Mann–Whitney U-tests. Effect size was calculated with web applications (https://www.socscistatistics.com/effectsize/default3.aspx). Categorical variables were presented as counts (percentages) and compared by Chi-square test. Normality was evaluated by the Shapiro–Wilk test. The linear regression analysis with the stepwise method was used to predict the cognitive domains that affect the MMAA total score. The level of significance was set at ≤ 0.05.

Results

Of the 58 patients enrolled in the study, 26 were diagnosed with PD-MCI according to MDS PD-MCI diagnostic criteria. 32 patients with PD who were found to have normal cognition according to these criteria were included in the PD-normal cognition (PD-NC) group. There was no significant difference in terms of age, education, gender, LEDD, number of medications used for PD and other diseases, depression, anxiety, and motor scores between the two groups. The demographic and clinical characteristics of the PD-MCI and PD-NC groups are shown in Table 1. In the PD-MCI group, 96% (*n*:25) were classified as multi-domain MCI, and 4% (*n*:1) were classified as single-domain MCI. The patients with PD-MCI showed significantly poor performance in all cognitive domains ($p \leq 0.01$) (Table 2).

The average MMAA score in the PD-MCI group was 24.12 points (range 0–33-points) which were significantly lower compared to 28.31 scores of the PD-NC group ($p < 0.01$) (Table 3). Comparison of the errors in medication use according to instructions showed that the PD-MCI group made significantly more total errors (*p*: 0.01). PD-MCI group made more mistakes concerning the timing of medication according to meals ($p < 0.01$). The binomial regression tests with the entering method (PD-NC versus PD-MCI) were conducted to adjust for age and gender. It was significant for the MMAA total and subscore.

Adherence was classified as low, medium, and high according to the Morisky adherence scale. 11.5% (*n*:3) of the PD-MCI patients were found to have low adherence, 57.7% (*n*:15) medium adherence, and 30.8% (*n*:8) high adherence.

Table 1 Demographic and clinical characteristics of PD-MCI and PD-NC groups

	PD-NC (*n*:32)	PD-MCI (*n*:26)	*p*
Gender (male)	21 (66%)	20 (77%)	0.34
Age	62 (56.25–69)	69 (57–72.25)	0.056
Education (years)	5 (5–11)	5 (5–8)	0.23
Duration of PD (years)	6.5 (4–12.37)	6 (3.37–8.62)	0.41
LEDD (mg)	934 (475–934)	755 (499–1194)	0.50
Hamilton depression score	3.5 (1.25–6.75)	6 (2.75–8)	0.12
Hamilton anxiety score	4 (2–5)	6 (3–8.5)	0.41
Hoehn Yahr stage	2 (1–2)	2 (1–2)	0.94
UPDRS total score	41.72 ± 18.11	47.62 ± 18.20	0.18
UPDRS motor score	26.66 ± 12.57	30.58 ± 12.30	0.22
PD medications per day	2.75 ± 0.87	2.53 ± 1.20	0.22
Total medications per day	5.28 ± 2	4.96 ± 1.92	0.58

Normally distributed continuous variables were presented as mean ± SD, non-normally distributed continuous variables were presented as median (Q1–Q3)

PD Parkinson's disease, *PD-NC* Parkinson's disease-normal cognition group, *PD-MCI* Parkinson's disease-mild cognitive impairment group; *LEDD* Levodopa equivalent dose, *MDS-UPDRS* Movement Disorder Society-Unified Parkinson's Disease Rating Scale

In PD-NC group, 3.1% (*n*:1) had low adherence, 53.1% (*n*:17) had medium adherence, and 43.8% (*n*:14) had high adherence. There was no significant difference between the adherence levels of the two groups (χ^2:2.16; *p*:0,339). We also assessed the correlation between medication management and adherence levels. We found no significant relationship between these two parameters in either group ($p > 0.05$).

The correlations between MMAA score and all cognitive domains (attention–working memory, executive functions, language, memory, and visuospatial functions, event and time-based prospective memory) were significant. Linear regression analysis with the stepwise method was conducted to determine which cognitive variables had the greatest effect on MMAA performance. *Z* scores of five cognitive domains (attention–working memory, executive functions, language, memory, and visuospatial functions), event and time-based prospective memory were included in the regression analysis as independent variables. Test of the model showed that event-based prospective memory (OR, 0.388) visuospatial functions (OR, 0.344) and language domain (OR, 0.274) were introduced significantly affected the MMAA score ($p < 0.001$ Adjusted *R* square 0.495) (Table 4).

Discussion

Medication management evaluation may be effective in determining the impact of cognitive changes on daily life, and it can be assessed in routine clinical practice [30, 31]. An MMAA test, which may detect even subtle evidence of functional difficulty [32], was applied in various neurological and psychiatric patient groups [8, 32–35].

We observed significant impairment in medication management in patients with PD-MCI, based on the MMAA scores ($p < 0.01$). Prior to this study, we know that only one study evaluated medication management in patients with PD-MCI and reported significantly lower performance [36]. A recent retrospective study reported PD-MCI patients exhibiting greater difficulty with medication management [37]. As the MDS Task Force pointed out [5], cognitive impairment in patients with PD-MCI can lead to various impairments in complex daily functions, such as medication management. Also patients with PD-MCI had difficulty planning their medication around mealtimes (take tablets with or without food) in this study. This situation should be considered particularly in patients receiving levodopa therapy.

Table 2 Neuropsychological characteristics of PD-MCI and PD-NC groups

Cognitive Domain	PD-NC (*n*:32)	PD-MCI (*n*:26)	*p*	Cohen's d
MoCA	25.30 ± 2.50	20.04 ± 3.24	< 0.001*	1.75
Attention/Working Memory	0.76 ± 1.23	− 1.13 ± 2.91	0.001*	0.88
Memory	0.20 ± 1.87	− 3.20 ± 4.14	< 0.001*	1.12
Executive Functions	− 0.23 ± 0.77	− 1.61 ± 1.03	< 0.001*	1.53
Language	− 0.69 ± 1.05	− 1.63 ± 1.67	< 0.001*	1.16
Visual-Spatial Functions	0.09 ± 0.73	− 0.73 ± 0.96	0.003*	0.97
Time based PM**	2.42 ± 1.54	1.24 ± 1.54	0.009*	0.76
Event-based PM**	1.60 ± 0.56	1.05 ± 0.80	0.011*	0.82

PD Parkinson's disease, *PD-NC* Parkinson's disease-normal cognition group, *PD-MCI* Parkinson's disease-mild cognitive impairment group, *PM* Prospective memory

*$p < 0.05$

**The *z* scores of cognitive domains, excluding subscores of prospective memory, are shown in the table

Table 3 Medication management scores of the PD-MCI and PD-NC groups

MMAA scores	PD-NC (*n*:32)	PD-MCI (*n*:26)	*p*	Cohen's d
Total score	28.31 ± 5.01	24.12 ± 5.79	0.003*	0.78
Total error score	4.63 ± 4.76	8.31 ± 5.75	0.012*	0.70
Number of surplus tablets	0.63 ± 1.04	1.17 ± 2.51	0.5	0.30
Number of missing tablets	2.59 ± 3.33	4.50 ± 3.90	0.25	0.53
Number of surplus attempts	0.47 ± 0.98	0.88 ± 1.67	0.27	0.31
Number of missing attempts	0.88 ± 1.21	1.71 ± 2.01	0.91	0.52
Food rules score	4.31 ± 0.93	3.35 ± 1.19	0.002*	0.91

All data are shown as mean ± standard deviation. *MMAA* Medication Management Ability Assessment, *PD-NC* Parkinson's disease-normal cognition group, *PD-MCI* Parkinson's disease-mild cognitive impairment group

*$p < 0.05$

Table 4 Results from lineer regression analysis about cognitive variables affecting the MMAA score

Variable	*B*	*p*	OR	95% C.I. for EXP(*B*)		VIF
				Lower	Upper	
Language	1.056	0.023*	0.274	0.149	1.963	1.354
Event-based PM	3.249	0.001*	0.388	1.471	5.027	1.102
Visual-spatial memory	2.131	0.004*	0.344	0.734	3.527	1.248

PM prospective memory (Model summary: R^2 0.525, Adjusted R^2 0.495, ANOVA *F* 17.334, $p < 0.001$)

*$p < 0.05$

One previous study reported no relationship between MMAA and cognition [36], while the other reported that poorer MMAA performance was associated with worse delayed memory [37]. Our results indicated that event-based prospective memory, visuospatial functions and language domain had a significant effect on MMAA performance. The MMAA test is a performance evaluation that simulates a patient-physician relationship. In the test, patients are told about the medications and how to use them, and there are labels on the medications (e.g., take two tablets three times a day on an empty stomach). Language domain is important to understand the physician's instructions regarding medication use and, visuospatial functions have a role in using the reminder instructions on the medicine boxes. Important way of identify medicine is code medication by the color and shape in. Various studies have confirmed that the appearance of the tablets affects on adherence [38, 39]. Therefore, visuospatial function can be an important cognitive domain in medication management due to the visual cues of tablets and the instructions on the pharmacy labels.

We reported that event-based prospective memory significantly affect the MMAA score. There is growing evidence of a relationship between prospective memory and medication management in various patient populations [23, 40, 41]. Several studies have reported this association in patients with PD [3], and PD-MCI [42]. Costa et al. indicated that time-based prospective memory defects may be associated with impaired daily living functioning in patients with PD-MCI [42]. The relationship between the subtype of prospective memory and medication management may vary depending on the method used in studies. Prescription instructions given in the MMAA test were mostly event-based prospective memory tasks (e.g., using the medication on an empty stomach at least 1 h before meals).

Several studies have reported that cognitive impairment is one of the predictor of poor adherence among the elderly [43–45]. An association between non-adherence and cognitive impairment in PD has also been observed in several other studies [46–48]]. However, no study has investigated adherence in patients with PD-MCI. Only Straka et al. stated that the presence of subjective cognitive complaints in PD significantly predicted non-adherence [48]. This study found no difference in adherence based on self-report between the PD-MCI and PD-NC groups. These results can be explained either by a decrease in insight or by the environmental factors. Performance-based measures, such as the MMAA test, are objective methods and are therefore superior to self-reporting methods. An important advantage of performance-based measures is that they are free of the informant biases or lacunae in knowledge; consequently, they may be effective tools for detecting MCI [49]. Previous studies have shown that people with MCI can overestimate their functional abilities in self-reporting when compared to performance-based measures because of had poor insight [34]. Therefore, an adherence scale based on patient information may not be sufficiently effective for use on patients with

PD-MCI. Moreover, cognitive impairment may be compensated for by external factors, such as caregiver support or the use of reminders. Medication management is only a patient-dependent cognitive and functional activity, while adherence is a complex behavior that depends on various internal (patient-related) and external (treatment and environmental) factors in daily life [50]. Performance tests such as MMAA can give us information about the effect of the patient's cognitive status on medication management, but we cannot predict the adherence in daily life based on the MMAA score. This study focused only on the internal factors associated with adherence. Future studies that evaluate external supports (caregivers or use reminders) and use aim adherence methods (e.g., electronic monitoring systems) can explain the relationship between medication management and adherence more clearly.

The limitations of our study include the self-reporting assessment of adherence, a small sample size, and a low number of PD-MCI patients with single-domain impairment. Our assessment of prospective memory is also limited. Due to the lack of a standardized test in Turkish population, we developed a variety of practical tasks for patients to perform. Adherence to pharmacotherapy is a complex behavioral process determined by several interacting factors including attributes of the patient, the patient's environment (e.g., health care system), and characteristics of the disease and its treatment. This study is limited due to evaluating patient-related factors only.

In conclusion, our results suggest that mild cognitive impairment in patients with PD adversely affects medication management. Additional measures, such as providing more detailed, clearer instructions on medication, increasing family and caregiver support, and providing reminder devices, should be taken to improve medication management in patients with PD-MCI.

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Data availability The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of interest The authors have no conflict of interest to report.

Ethical approval Ethis approval was obtained from the Ethics Committee of Istanbul Faculty of Medicine, Istanbul University (22.12.2017/21).

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