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Mild cognitive impairment is common in Parkinson's disease patients with normal Mini-Mental State Examination (MMSE) scores

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Abstract

Purpose—Cognitive impairment occurs in the majority of Parkinson's disease (PD) patients, but little is known about detection of mild cognitive impairment (MCI) in this population. We report on the frequency and characteristics of cognitive deficits in PD patients with intact global cognition based on Mini-Mental State Examination (MMSE) performance.

Methods—One hundred and six PD patients with normal age- and education-adjusted MMSE scores (mean [SD] score = 29.1 [1.1]) were administered standardized neuropsychological tests assessing memory, executive function, and attention. Impairment on a cognitive domain was a low score (i.e., ≥1.5 SD below the published normative mean) on at least two measures or tests (for memory and executive abilities) or a single measure (for attention).

Results—Mild cognitive impairment was found in 29.2% of PD patients, with 17.9% demonstrating single domain and 11.3% multiple domain impairment. Memory and attention impairment were most common (15.1% and 17.0%, respectively), followed by executive impairment (8.5%). Depending on the measure of disease severity chosen, increasing age and disease severity, anti-anxiety medication use, and a suggestion for increasing severity of daytime sleepiness were independent predictors of cognitive impairment.

Conclusions—Cognitive deficits are common in PD patients with "normal" cognition based on MMSE performance, suggesting that MCI is under-recognized in clinical practice due to routine use of insensitive screening instruments. In contrast with some previous reports, early memory impairment may be as common as either executive or attentional deficits in PD. In addition, psychiatric medication use and daytime sleepiness may be reversible or treatable contributors to cognitive impairment.

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Keywords

Mild cognitive impairment; Parkinson's disease; Mini-Mental State Examination; Neuropsychology

1. Introduction

Cognitive impairment in the absence of frank dementia, typically called mild cognitive impairment (MCI), occurs frequently in Parkinson's disease (PD) [1,2], even among those newly diagnosed [3,4]. Impairments in executive function, attention, visuospatial skills and memory have all been reported, whereas language and praxis are thought to be relatively spared [3,5]. When a discrepancy in cognitive performance has been reported, greater impairment has been found on executive measures than memory measures [6,7].

Identification of MCI in PD is important, as it predicts future cognitive decline [2,5,8] and may eventually be a target for pharmacologic intervention to prevent or delay the development of dementia. Given the common occurrence of a range of cognitive deficits at all stages of PD, routine cognitive screening of all PD patients with a sensitive assessment is important.

The Mini-Mental State Examination (MMSE) [9] remains the "gold standard" screening instrument for global cognition. The MMSE is used extensively in PD, but its use in this population has been questioned [10,11], both because the MMSE assesses primarily memory and language skills (i.e., not broad enough), and because it may not be sensitive enough to detect many cases of MCI (i.e., instrument ceiling effect).

Given the existing limitations in our knowledge of MMSE performance in PD, we present results on the frequency and correlates of cognitive impairment in PD patients with intact global cognition based on MMSE performance.

2. Methods

2.1. Subjects

The study population consisted of a convenience sample of idiopathic PD patients recruited from movement disorders centers at the University of Pennsylvania and the Philadelphia Veterans Affairs Medical Center. Subjects completed an extensive psychiatric, neuropsychological, and neurological battery as part of a study on the frequency and correlates of psychiatric and cognitive complications in PD. The neuropsychological battery was chosen to focus on memory and executive function abilities, and an attention measure was included as well (Table 1). The research was approved by the Institutional Review Boards at both institutions, and all patients provided their own written informed consent prior to study participation.

Patients (N = 141) were administered the MMSE, specifically the version used to establish normative data [12], as part of the study screening process. For the purposes of these analyses, only subjects with a population-based age- and education-adjusted MMSE score in the top 75th percentile [13] were included, as this cut-off has previously been used to characterize individuals as having "intact cognition" [14] or as being the "best-performing" in a cohort, including in PD [8]. Of the original sample, 117 patients (83.0%) met our MMSE criterion for having intact cognition. In addition, we only included patients on whom we had complete data for the memory, executive, and attention measures, and some patients were either color blind and unable to complete the Stroop Color-Word Test (N = 9) or were unable to understand the instructions for or complete the Tower of London (N = 2). Thus, our final sample consisted of 106 patients with a mean (SD; range) MMSE score of 29.1 (1.1; 26–30).

2.2. Procedures

Trained research staff administered a focused neuropsychological battery to all subjects. The battery included standard measures of memory (Hopkins Verbal Learning Test-Revised (HVLT-R)) [15], executive function (Stroop Color-Word Test (STRP)) [16], semantic verbal fluency [17], Tower of London (TOL-DX)) [18], and attention (Digit Span) [19]. Patients were also assessed for severity of psychosis with the Parkinson Psychosis Rating Scale (PPRS) [20], a depression diagnosis (major depression, minor depression, or dysthymia) with the Structural Clinical Interview for Depression (SCID) [21] and depression severity with the Inventory of Depressive Symptomatology (IDS) [22], apathy severity with the Apathy Scale [23], severity of daytime sleepiness with Epworth Sleepiness Scale (ESS) [24], anxiety severity with the State Anxiety Inventory (SAI) [25], and olfaction with the University of Pennsylvania Smell Identification Test (UPSIT) [26].

Patients who scored ≥1.5 SD below the standardized mean on a given neuropsychological test were considered impaired on that particular instrument; the same cut-off has been used to define impairment on neuropsychological tests in a previous study of mild cognitive impairment in PD [8]. To be conservative in our classification of subjects, we required impairment on at least 2 of 3 components of the HVLT (immediate free recall total score, retention percentage, and recognition discrimination) for memory domain impairment and impairment on at least 2 of 3 executive function tests (the Color-Word condition of the STRP, semantic verbal fluency and total move score of the TOL-DX) for executive abilities domain impairment. As we only administered one test of attention, attentional domain impairment was defined as impairment on either the forward or backward digit span using the recommended cut-off scores for the elderly [27].

Each patient's performance on tests of neuropsychological function was categorized into one of three impairment classifications: (1) "No impairment"; (2) "Single Domain Only" cognitive impairment was defined as a sole deficit in either memory, executive function, or attention; or (3) "Multiple Domain" cognitive impairment was defined as deficits in any two or more cognitive domains. A fourth impairment classification, "Overall Impairment", was the sum of patients who had either single- or multiple-domain cognitive impairment.

2.3. Analyses

All statistical procedures were performed with SPSS 15.0 for Windows [28]. Independent demographic and clinical variables that suggested an association (p value ≤0.10) for "overall impairment" (i.e., MCI, versus patients with "no impairment") using univariate logistic regression analyses were entered into a multivariate logistic regression model. For the multivariate model a p value ≤0.05 was considered significant. Race was not used as an independent variable because nearly all subjects (94.3%) were white. In addition, anticholinergic medication use was not included as a variable due to its low frequency of use. Hoehn & Yahr stage [29], Unified Parkinson's Disease Rating Scale (UPDRS) motor score (Part 3) [29], and duration of PD were the three measures of PD severity; as Hoehn & Yahr stage and UPDRS Part 3 (i.e., motor) scores were highly correlated, we ran two multivariate analyses, one including Hoehn & Yahr stage and the other the UPDRS Part 3 score as the measure of disease severity.

To put the results for age, IDS score and levodopa daily dosage in a clinical context, scores were transformed so that the changes in the odds ratio were based on: (1) a 5-year change in age; (2) an 8-point change in IDS score (each increment corresponding roughly to a change in level of depression severity, i.e., no depression, mild depression, moderate depression, moderate–severe depression, and severe depression [22]); and (3) a 100-mg change in daily levodopa dosage.

3. Results

3.1. Frequency of impairment by neuropsychological test

Memory domain impairment was found in 15.1% of subjects, with 21.7%, 20.8%, and 14.2% demonstrating impairment on free recall, retention, and recognition discrimination subtests, respectively (Table 2). Executive function domain impairment was found in 8.5% of subjects, with 15.1% impaired on the TOL-DX, 11.3% on the STRP, and 7.5% on verbal fluency. Lastly, 17.0% of patients were impaired in attention, with 17.0% impaired in the backward digit span and 0.9% on the forward digit span.

3.2. Frequency of impairment by cognitive domain

A total of 17.9% of subjects demonstrated single domain impairment, and an additional 11.3% were impaired in multiple domains (Table 2); thus, a total of 29.2% of our sample had evidence for MCI. For patients with single domain deficits, attentional impairment was most common (8.5%), followed by memory impairment (5.7%) and executive dysfunction (3.8%). For patients with multiple cognitive domain impairments, memory plus attentional impairment was most common (6.6%), followed by memory plus executive impairment (2.8%) and executive and attention impairment (1.9%). None of the patients were impaired in all three cognitive domains.

3.3. Factors associated with MCI

On univariate analysis, correlates of MCI were increasing age (odds ratio = 1.34, 95% confidence interval (CI) 1.07–1.69, $p = 0.01$), higher Hoehn & Yahr stage (odds ratio = 2.70, 95% CI 1.33–5.49, $p = 0.01$), higher UPDRS motor score (odd ratio = 1.05, 95% CI 1.00–1.10, $p = 0.05$), anti-anxiety medication use (odds ratio = 3.35, 95% CI 1.03–10.97, $p = 0.05$) and increased ESS score (odds ratio = 0.92, 95% CI 0.83–1.02, $p = 0.10$) (Table 3).

On multivariate analysis with Hoehn & Yahr stage entered as the measure of disease severity, MCI was predicted by higher Hoehn & Yahr stage (odds ratio = 2.83, 95% CI 1.25–6.40, $p = 0.01$), with a trend finding for anti-anxiety medication use (odds ratio = 3.28, 95% CI 0.93–11.60, $p = 0.07$) and ESS score (odds ratio = 0.90, 95% CI 0.80–1.01, $p = 0.08$) (Table 3). Substituting UPDRS motor score for Hoehn & Yahr stage, MCI was predicted by increasing age (odds ratio = 1.29, 95% CI 1.00–1.66, $p = 0.05$) and anti-anxiety medication use (odds ratio = 3.60, 95% CI 1.01–12.78, $p = 0.05$).

4. Discussion

We found that mild cognitive impairment, either in single or multiple cognitive domains, occurs in almost one-third of PD patients with intact global cognition as defined by a normal score on the MMSE. In addition, memory deficits, including retrieval deficits, are as common as executive function and attention deficits at the initial stage of cognitive impairment. Finally, anti-anxiety medication use and excessive daytime sleepiness may be reversible or treatable contributors to mild cognitive impairment in PD.

Recent research focusing on mild cognitive changes in PD typically has defined the study populations as being either newly diagnosed [3,30], relatively recently diagnosed [31,32], or as not meeting clinical criteria for dementia [1,5,6]. However, newly or recently diagnosed patients have significant variability in actual disease duration and cognitive abilities. Moreover, PD patients not meeting clinical criteria for dementia have a wide range of global cognitive abilities, from being completely intact to being on the cusp of meeting criteria for dementia. By using a well-standardized cognitive screening instrument and a conservative cut-off point (i.e., excluding patients in the bottom 25th percentile based on their age- and education-adjusted

MMSE score), we helped ensure that our population did not have global cognitive impairment beyond the earliest stage.

In spite of these operationalized criteria to exclude patients with significant global cognitive impairment, almost one-third of our patients met criteria for MCI. This suggests that the MMSE is insensitive for detecting the earliest stage of cognitive impairment in PD. Although the MMSE has been criticized as being too insensitive and narrow when used in PD, to our knowledge this is the first report documenting the frequency and range of cognitive impairment in patients with normal age- and education-adjusted MMSE scores. As more extensive neurocognitive testing is typically not feasible in the day-to-day clinical practice of most movement disorder physicians, the use of a screening measure is often the only choice to assess cognition in a time-efficient manner. Recent research suggests that other screening instruments, such as the Montreal Cognitive Assessment (MoCA) [33], may be more sensitive than the MMSE in detecting MCI in PD [10].

We, like others before us, found that mild cognitive impairment is common in PD and occurs in a range of domains, including memory [1,5], executive function [1,5], and attention [34]. Reviewing recent studies, Janvin et al. [1] reported that 55% of non-demented PD patients had MCI, with half of those showing widespread cognitive deficits in visual memory, executive abilities, and visuospatial skills. Caviness et al. [5], using more stringent criteria similar to those applied by us, found that 25.4% of non-demented patients in a brain bank sample met criteria for MCI, with the most common deficits being in executive functioning and memory. Unlike some previous research in non-demented PD patients [6,7], we found that memory impairment is more common than executive impairment early in the course of cognitive decline, with impairment in recognition memory nearly as common as in free recall. This latter finding is different from what is commonly reported in the literature, although there is research reporting deficits in both encoding and retrieval in PD [35]. Memory deficits in PD, even early in the course of cognitive decline, are not surprising given the prominent diffuse cholinergic deficits that occur in PD [36] and the presence of neuropathology in both the basal forebrain and hippocampal formation relatively early in the disease course [37].

Impaired attention was as common as memory impairment. Impairment was almost exclusively on the backward digit span, which requires working memory as well as attention, while almost no impairment was seen on the forward digit span, which is thought to be more of a test of immediate recall [27].

Certain demographic (increasing age), PD-related (increasing Hoehn & Yahr stage and UPDRS motor score), and psychiatric (anti-anxiety medication use and increasing daytime sleepiness) variables were associated with MCI on univariate analyses. All of the aforementioned variables maintained at least a trend association with cognitive impairment on multivariate analysis. Interestingly, some of these variables have also been reported to be risk factors for the development of dementia in PD [38].

Anti-anxiety medications, particularly benzodiazepines, can be a cause of or contributor to cognitive impairment in the elderly [39], and use of non-benzodiazepine anti-anxiety agents (e.g., selective serotonin reuptake inhibitors (SSRIs)) or nonpharmacologic treatment approaches may lead to cognitive improvement in impaired patients. Likewise, better recognition and treatment of excessive daytime sleepiness (EDS) potentially could lead to an improvement in cognitive abilities. The etiology of EDS is complex [40], and management strategies include reducing overall exposure to dopaminergic replacement therapy as well as treatment with stimulants or modafinil.

There are limitations to our study. First, we did not have a non-PD control group, so it is not known if similar levels of cognitive impairment would be found in persons in the general

population with normal MMSE scores. The MMSE has also been found to be insensitive in the detection of pre-AD MCI, leading to the development of more sensitive instruments such as the MoCA. Second, our results may not be generalizable, as the majority of our patients were white and all were from specialty care centers. Third, we did not use formal criteria to diagnose MCI or exclude patients with dementia, so it is possible that a small percentage of our patients, in spite of having a high MMSE score, might have met clinical criteria for dementia. However, the mean MMSE score of our patients was similar to that reported in PD studies that only included patients who did not meet clinical criteria for dementia [1,41,42]. Fourth, our neuropsychological battery included memory, executive function and attention tests, but did not specifically assess visuospatial, language, or praxis abilities. Thus, we likely underestimated the frequency of cognitive impairment in our patients. Finally, the study was cross-sectional, and additional, longitudinal studies are needed to determine if particular cognitive deficits or clinical correlates of MCI also predict future development of PD dementia (PDD).

There is increasing evidence that PDD is common in advancing disease, affecting up to 78% of patients followed long term [43]. As MCI precedes the development of PDD, the cumulative prevalence of MCI in PD must be at least as high. In order to detect initial cognitive deficits in PD, all patients should undergo routine cognitive screening with a sensitive instrument that assesses a range of cognitive domains. Recognition of cognitive impairment at this stage will enable the treating doctor to educate the patient and family about prognosis and to make decisions about appropriate therapy.

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Table 1

Demographic and clinical characteristics

Variable	Mean (SD) or %
Age (# years)	64.6 (10.3)
Sex (% male)	69.8%
Race (% white)	94.3%
Education (# years)	15.6 (3.0)
PD duration (# years)	6.5 (5.8)
UPDRS motor score	18.4 (9.1)
Hoehn & Yahr stage	
Stage 1	15%
Stage 2	38%
Stage 3	46%
Stage 4	0%
Stage 5	1%
Levodopa dosage (mg/day)	504.4 (379.5)
Dopamine agonist use (% yes)	52.8%
Amantadine use (% yes)	19.8%
Anti-anxiety medication use (% yes)	12.3%
Antidepressant medication use (% yes)	34.9%
Antipsychotic medication use (% yes)	2.8%
History of DBS (% yes)	12.3%
Active depressive disorder (% yes)	42.5%
Inventory of Depressive Symptomatology (IDS) score	22.1 (14.2)
Parkinson's Psychosis Rating Scale (PPRS) score	5.6 (1.2)
Apathy Scale score[a]	13.8 (6.6)
Epworth Sleepiness Scale (ESS) score[b]	9.9 (4.8)
State Anxiety Inventory (SAI) score[c]	42.3 (15.4)
Penn Smell Identification Test (UPSIT)[d]	19.2 (7.2)

[a] $N = 90$.

[b] $N = 95$.

[c] $N = 103$.

[d] $N = 100$.

Table 2

Cognitive Impairment by Test and Domain

	% Impaired
TEST	
Memory	
Hopkins Verbal Learning Test	
Total Recall	21.7%
Retention	20.8%
Recognition Discriminability	14.2%
Any memory	**15.1%**
Executive Function	
Stroop Color-Word Test	11.3%
Semantic Verbal Fluency	7.5%
Tower of London-Drexel	15.1%
Any executive	**8.5%**
Attention	
Forward Digit Span	0.9%
Backward Digit Span	17.0%
Any attention	**17.0%**
DOMAINS	
Single domain only	
Memory, executive function, or attention	**17.9%**
Multiple domain	
Any two or more domains	**11.3%**
Overall impairment	
Single domain only þ multiple domain	**29.2%**

Table 3

Predictors of Mild Cognitive Impairment (logistic regression analysis)

Variable	Odds ratio (95% CI), *p* value		
	Univariate	Multivariate (with either Hoehn & Yahr stage or UPDRS motor score as measure of disease severity)	
		Hoehn & Yahr stage	UPDRS motor score
Age (# years)	1.34 (1.07–1.69), 0.01	1.22 (0.94–1.59), 0.14	1.29 (1.00–1.66), 0.05
Sex (male)	0.58 (0.22–1.54), 0.28	–	–
Education (# years)	0.99 (0.86–1.14), 0.84	–	–
PD duration (# years)	0.99 (0.92–1.07), 0.86	–	–
Hoehn & Yahr stage	2.70 (1.33–5.49), 0.01	2.83 (1.25–6.40), 0.01	N/A
UPDRS motor score	1.05 (1.00–1.10), 0.05	N/A	1.05 (0.99–1.10), 0.10
Levodopa dosage	1.02 (0.92–1.14), 0.67	–	–
Dopamine agonist use	0.78 (0.34–1.80), 0.56	–	–
Amantadine use	0.71 (0.24–2.14), 0.54	–	–
Anti-anxiety medication use	3.35 (1.03–10.97), 0.05	3.28 (0.93–11.60), 0.07	3.60 (1.01–12.78), 0.05
Antidepressant use	0.69 (0.28–1.70), 0.42	–	–
Antipsychotic use	5.10 (0.45–58.47), 0.19	–	–
History of DBS	1.09 (0.31–3.83), 0.90	–	–
Active depression disorder	1.69 (0.73–3.93), 0.22	–	–
IDS score	1.15 (0.90–1.45), 0.26	–	–
PPRS score	1.31 (0.94–1.82), 0.11	–	–
Apathy Scale score	0.99 (0.93–1.07), 0.87	–	–
ESS score	0.92 (0.83–1.02), 0.10	0.90 (0.80–1.01), 0.08	0.917 (0.82–1.02), 0.13
State Anxiety Inventory score	1.01 (0.98–1.04), 0.63	–	–
UPSIT score	0.99 (0.93–1.05), 0.64	–	–