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Mild Cognitive Impairment in Parkinson Disease: A Neuropsychological Study of 25 Patients

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Abstract

Parkinson's disease (PD) is associated with an increased incidence of cognitive impairment and dementia. Population-based cohort of 25 patients with incident PD underwent a large neuropsychological battery. Executive functions were the most affected cognitive domain including particularly initiation, mental flexibility and inhibition. Episodic memory and visuo-spatial functions were less affected. We found that 92% of patients were classified as having Mild Cognitive Impairment (MCI); most of them experienced PD-MCI Single-Domain (17 patients) with disturbances on executive functions. Less frequently, we identified a group of patients with multiple-domain PD-MCI demonstrating deficits on executive functions as well as on episodic memory and/or visuospatial capacities.

Keywords

MCI, PD, Neuropsychological Study, Executive Functions, Episodic Memory, Visuospatial Capacities

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease [1], characterized by its motor features including rigidity, bradykinesia and postural instability. Cognitive impairment and dementia are nowadays well known and mentioned among the most prevalent and disabling non-motor symptoms in PD [2]. Cognitive disorders are frequent in early PD even in the absence of cognitive complains [3]. They are noted in 30% of patients at the moment of diagnosis [4]. Executive functions are particularly

affected. They refer to brain processes underlying: response initiation, inhibition, control ability in set-switching, complex problem solving, retrieval abilities, organizational strategies, concept formation, working memory, attention decision-making and perseveration [5].

Several studies demonstrated that PD-Mild Cognitive Impairment (MCI) can represent the earliest stage of cognitive decline and is a risk factor for developing dementia. PD-MCI is a heterogeneous entity with different phenotype, timing and progression. It includes deficit of many cognitive domains. When a single domain is involved, it is mostly a non-amnestic MCI subtype. However, subtypes with predominant deficits in attention, memory, executive function, psychomotor speed and visuospatial abilities are more frequent and they frequently involve deficits across multiple cognitive domains [3].

With the development of new scales used to measure subjective and objective cognition, such as the Clinical Dementia Rating and the Global Deterioration Scale for Ageing and Dementia, an intermediate phase between normal ageing and dementia became more widely recognised. Therefore, PD-MCI may be an intermediate state between normal cognition and dementia, similar to the concept of amnestic MCI observed in Alzheimer's disease [6]. Dementia is frequent among subjects with advanced PD, occurring in 27% to 78% of patients; its prevalence depends on the duration of the disease. Patients have been shown to have six fold risk of developing dementia compared to those without PD [7].

The goal of our cohort was to evaluate cognitive disorders and to study the neuropsychological profile of MCI in PD patients using Moroccan version tests.

2. Materiel and Methods

We analyzed the neuropsychological profile of 25 patients, recruited from the department of Neurology A and Neuropsychology in Rabat Specialties Hospital from 2016 to 2018. All patients were followed in outpatient consultation by two neurologists specialized in movement disorders and PD management. The sample size was chosen to allow a first experience in our Moroccan population. Inclusion criteria included patients with PD evolving for at least 5 years, diagnosed according to the criteria of The United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB), Arabic speakers, and having at least 3 years of formal education. Additional 15 healthy adult normal controls were also included in the study. We excluded patients with a history of major depression. Controls with medical histories for diabetes, high blood pressure, neurological disease or injury, neurosurgical procedures, depression or psychiatric disorder, were excluded. Controls were selected to match age, gender and education level of the patients.

To diagnose dementia, we used the Clinical Diagnostic Criteria for Dementia Associated with PD established by Movement Disorder Society (MDS). A probable PD-dementia was defined by the presence of insidious dementia with slow progression, developed in the context of established PD. The diagnosis was based on history, clinical, and mental examination, associated with impairment

in more than one cognitive domain, not attributed to motor or autonomic symptoms. Attention should be impaired in spontaneous and focused attention with poor performance in attentional tasks that may fluctuate during the day and from day to day. Impairment in executive functions must be noticed in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance and mental speed. Impairment in visuospatial functions should be present in tasks requiring visualspatial orientation, perception, or construction. Memory deficit must be demonstrated in free recall of recent events or in tasks requiring learning new materials and usually improves with cueing leading to a better recognition than free recall [8].

To identify PD-MCI patients, we used the new criteria of the Movement Disorder Society. PD-MCI is defined as an insidious decline in cognitive abilities reported by patient or informant or observed by the clinician. Within the level I (Possible PD-MCI), impairment must be present on a scale of global cognitive abilities or at least two out of a limited battery of neuropsychological tests. For the level II, deficits are noted in at least two tests for each of the five cognitive domains (attention and working memory, executive functions, language, memory and visuospatial capacities). Level I criteria provide less diagnostic certainty in contrast to level II which allows more exact assessment. We defined testing abnormalities according to level II results.

We also classified our patients in 2 subgroups: PD-MCI single-domain (abnormalities on two tests within a single cognitive domain, with other domains unimpaired) and PD-MCI multiple-domain (abnormalities on at least one test in two or more cognitive domains) [9].

Cognitive exploration was performed by one neuropsychologist. The following tests were administered in Moroccan Arabic (Moroccan versions): Mini-Mental State Examination (MMSE) [10] [11], Montreal Cognitive Assessment (MoCA) [12] [13], Mattis Dementia Rating Scale (MDRS) [14] [15], Raven's progressive Matrices [16], Frontal Assessment Battery (FAB) [17], Trail making test (TMT) [18] [19], Stroop test [20], semantic and phonemic fluency, Memory Impairment Screen (MIS), and Benton judgment of line orientation (JLO) [21]. We used language sub-tests of MMSE and MoCA. Instrumental activities of daily living (IADL) and Montgomery-Åsberg Depression Rating Scale (MADRS) were also administered to the patients and controls (**Table 1**).

SPSS 13.0 software was used for the statistical processing of our data. Quantitative data were expressed in mean ± standard deviation (SD), Pearson test was used to analyse the effect of different demographic variables. And, in order to compare patients and controls performances in the neuropsychological tests, results were compared using paired-t test.

3. Results

All participants were native Arabic speakers, and had at least 3 years of formal education and aged between 36 and 77 years old. We studied 25 PD patients and

Table 1. Neuropsychological tests used in our study according to the corresponding cognitive domains.

Attention and working memory	Digit span (MDRS subtest) Attention and Calculation (MMSE) Atention (MoCA subtest)
Executive functions	FAB (Frontal Assessment Battery) TMT Stroop Initiation/Perseveration and Conceptualisation (MDRS) Abstraction (MoCA subtest) Visuospatial/Executive Clock Test (Moca subtest) Phonemic fluency
Episodic memory	Memory Impairment Screen (MIS) Memory (MDRS subtest) Memory (MOCA subtest)
Semantic memory	Semantic Fluency (animals) Market and Clothes (MDRS item)
Visuospatial function	Benton's Judgment of Line Orientation Construction (MDRS subtest) Drawing Copy (MMSE subtest)) Cube Copy (MOCA subtest)
Autonomy	Instrumental Activities of Daily Living (IADL)
Depression	Montgomery-Åsberg Depression Rating Scale (MADRS)

15 controls. Mean age of patients was 58 years and 59 years for controls. Mean educational level was 11 years in both groups (Table 2).

Results of our neuropsychological testing are summarized in Table 3. Cognitive decline has been noted in 92% (n = 23) of patients: 56% (n = 14) of patients had deficits in attention, 92% (n = 23) in flexibility and inhibition, 24% (n = 6) in episodic memory, 28% (n = 7) in phonemic verbal fluency, 12% (n = 3) in semantic fluency and 36% (n = 9) in visuospatial abilities. Mean disease duration was 12 (±5.79) years. However, we didn't observe any cognitive deficit in controls.

Concerning the global cognitive efficiency, the following mean scores were noted in patients in respectively MDRS, MoCA, MMSE and PM: 129 ± 8.91, 22 ± 3.83, 26 ± 3.06, 24 ± 6.88.

Controls exhibited better mean score in all these tests: MDRS: 134 ± 4.07, MoCA: 25 ± 2.60, MMSE: 27 ± 1.90, PM: 28 ± 3.41. Lower scores in the MDRS affected particularly the Initiation/Perseveration and Conceptualization subscales where patients obtained a mean of 30 ± 4.44 in Initiation/Perseveration and 32 ± 4.08 in conceptualisation while controls had means scores of 36 ± 0.45 and 37 ± 1.35: whereas, Memory and Calculation subtests in MMSE and PM showed a difference between patients and controls.

Results of the executive functions evaluation showed differences between patients and controls on every specific test. Patients had lowest scores on executive functioning. Indeed, the mean score patients on FAB was 14 ± 2.86 vs controls

Table 2. The socio-demographic characteristics of patients and control subjects.

	Age	Educational Level	Gender	
			Female	Male
P	58 (±10.56)	11 (±4.22)	5	20
C.S.	59 (±10.13)	11 (±3.88)	5	10

P = Patients, C.S. = Control subjects.

Table 3. Mean scores of study population on different neuropsychological tests.

Tests	PD	Controls
MMSE	26 ± 3.06	271 ± 0.90
MDRS	129 ± 8.91	134 ± 4.3
MOCA	22 ± 3.83	25 ± 2.60
PM	24 ± 6.88	28 ± 3.41
FAB	14 ± 2.86	16 ± 1.14
MIS	14 ± 198	150 ± 0.91
TMT B-A	71 ± 52.99	54 ± 43.10
Stroop test	124 ± 38.4	98 ± 44.5
P.F	9 ± 4.34	11 ± 545
S.F	16 ± 6.23	21 ± 4.84
JOLB	24 ± 4.23	26 ± 2.05.
IADL	14 ± 5.52	8 ± 0.84

MDRS = Mattis Dementia Rating Scale MMSE: Mini Mental Examination. MOCA = Montreal Cognitive Assessment. PM = Raven's Progressive Matrices. FAB = Frontal Assessment Battery. TMT = Trail Making Test. Stroop = Stroop Test. S.P. = Semantic Fluency. P.F. = Phonemic Fluency. MIS = Memory Impairment Screen. JLO = Benton Judgment of Line Orientation. IADL = Instrumental Activities of Daily Living.

16 ± 1.14. The mean time of TMT B-A PD participants was 71 ± 52.99 seconds vs 54 ± 43.89 seconds for healthy subjects. The mean time of completion for the Stroop was 124 ± 38.4 seconds for patients vs 98 ± 44.5 seconds in controls group. Mean of phonemic verbal fluency was 9 ± 4.34 in PD subjects and 11 ± 5.45 in controls.

The other specific tests used for long term memory (semantic and episodic) demonstrated that healthy subjects experienced better scores than patients. The mean score of phonemic verbal fluency was 16 ± 6.23 in patients and 21 ± 4.84 in controls. On visuospatial activities, patients had lower scores in JLO. They had a mean score of 24 ± 4.23 while controls had 26 ± 2.05. They also showed lower performance in other tests subtests exploring this cognitive domain as Visuospatial/Executive subtest in the MOCA (Copy cube) and Copying in Language and Praxis subtest in the MMSE. Performances of patients were therefore lower than controls.

According to the MDS criteria for MCI and dementia previously described, we classified our patients into 3 groups: first group (n = 17) was diagnosed as

MCI single-domain, the second group (n = 6) as PD-MCI multiple-domain and the third group (n = 2) was classified as being cognitively healthy. Therefore no one had dementia.

Concerning daily activities, PD patients showed a mean of 14 ± 5.52, 48% (n = 12) of them were identified as having functional disability. We didn't find a significant correlation between the IADL score and performance in neuropsychological evaluation (p = 1).

However, no patient was diagnosed as having depression, the mean of MADRS scale was 6 ± 3.56. So the impact of depression on cognitive performance can't be evaluated.

Pearson correlations Analysis yielded no significant educational level on the majority of tests except for MOCA and FAB, we found that the less educated and the older participants in both groups had lower scores. Age effect was noted in MDRS. However, no significant impact was observed in the other neuropsychological tests. Also, women performed as well as men (absence of influence of gender on the scores).

In addition, analyses demonstrated significant differences emerged among the PD subjects and controls in all of the neuropsychological tests performances ($P < 0.001$) (**Table 3**).

4. Discussion

In our study, we identified neuropsychological disorders in all patients except two. The majority of the cognitive disorders affected executive functions**.** Episodic memory and visuospatial functions were less disturbed. PD-MCI was noted in 92% of patients. Single-domain PD-MCI subtype was identified in 68% of them with impairment in executive functions particularly attention, initiation, flexibility and inhibition. Multiple-domain PD-MCI was demonstrated in 24% of subjects with deficits affecting executive, episodic memory and/or visuospatial functions.

Ours results gather data from several studies that showed marked impaired working memory, flexibility, inhibition process and verbal fluency [22] [23]. The study of Piscassia and colleagues (2018) [24], demonstrated that 25.5% of newly diagnosed PD patients had executive function disorders. Cognitive impairments without dementia have affecting executive function, psychomotor speed, visuospatial abilities, language and memory. In 2014, Hong *et al.* [25] found lower scores in patients with PD in visual memory, semantic fluency and naming compared to control subjects. No case of dementia was observed in our series. Reasons may be related to the level of education being higher than 11 years in most of our subjects, mean disease duration of only 12 years, a relatively young mean age of patients (58 years old) and finally, a small number of participants.

Prevalence of cognitive impairment in both the general population and in PD patients is known to increase with age. Fewer years in formal education has previously been reported to be a risk factor for cognitive deterioration in the general

population and in patients with PD. In our study, educational level and age influenced performances in the neuropsychological testing of cognitive decline in patients and controls, but gender did not have influence.

Statistical analysis showed that performance on the cognitive evaluation was not related to performance on daily activities. Otherwise, patients with a short disease course performed better than others, those with <10 years had better scores than those with ≥10 years of disease duration. The difference was statistically significant ($P < 0.001$). The importance of the duration of the disease was also reported by Pigott *et al.* (2015) [26], in a recent study followed 141 patients with PD with normal cognition at baseline over a period of 2 - 6 years, finding that nearly half of participants developed cognitive impairment within 5 years, and that 100% of individuals who developed MCI progressed to dementia within 5 years.

Nonsomatic depressive features, such as excessive pessimism, tearfulness, hopelessness, negative ruminations and guilt, help distinguish depressed from non depressed PD patients. Non depressed PD patients may limit their usual pursuits because of motor symptoms. Some studies indicate that self-blame, negative self-attitude, delusions, and suicidality are less common in major depression in PD patients [27]. In 1995 a study showed that analyses of neuropsychological testing results revealed no significant differences among patients with Parkinson's disease who currently had depression and those without depression groups' test scores [28]. In our data no patient was diagnosed as having depression, the mean of MADRS scale was 6 ± 3.56. So the impact of depression on cognitive performance can't be evaluated.

Executive deficits are subtle in early clinical patients and can be confused with depression or apathy [5]. This suggestion was not evaluated in our cohort as PD duration was at least five years.

Executive function is an important feature which includes the ability to organize, initiate, plan and regulate goal-directed behaviour and relies on frontal-striatal circuitry containing prefrontal regions such as the dorsolateral prefrontal cortex and its connections to the basal ganglia [29]. Executive disorders may be attributed to either degeneration of dopaminergic nigrostriatal or mesocortical pathways. Moreover, implication of medications has been analyzed in PD dementia, but not PD-MCI. Indeed, hypodopaminergic states have been related with executive dysfunction, decline of mental flexibility and working memory. Dopaminergic drugs have effects on cognition, with improvement in executive function tasks in some PD patients [6]. Shrag *et al.* (2017) suggested that amyloid deposition might be an important contributor to the development of cognitive impairment in early PD and that the nigrostriatal alteration, which underlies the motor symptoms, is not the sole driver of cognitive changes seen in PD. In addition, cognitive decline in non-demented PD have been considered as a result of neurochemical alterations in dopaminergic and cholinergic networks. Neuropathological evidences of Lewy bodies in limbic and cortical areas and also

presence of neurites, amyloid deposition and neurofibrillary tangles contribute also to these neuropsychological changes [30].

New emerging imaging showed potential for detecting subtle cognitive involvement in PD.

The role of the functional MRI (fMRI) is to understand the mechanisms of brain adaptation and plasticity to damage related to clinical symptoms in PD and also to explain the functional significance of pathological disorders in this disease. A disrupted functional connectivity of the default mode network since the early phases of PD has been demonstrated by different studies, which seems to be predictive of cognitive changes in cognitively normal patients. Default mode network alteration is the more reliable fMRI biomarker to predict cognitive decline development in PD patients. In PD MCI patients, deterioration of executive functions, working memory and attention is associated with a disrupted functional connectivity of the fronto-parietal network. Memory and visuospatial decline are supported by specific functional connectivity deterioration in brain networks including parietal, temporal and occipital regions [31]. As in several studies, our cohort had limitations. The major limitation was the small sample size of the PD group and the control group. The other limitation was the absence of a neuropsychiatric inventory.

5. Conclusion

In our cohort, executive functions were the most affected cognitive domain including particularly initiation, mental flexibility and inhibition. Episodic memory and visuospatial functions were less affected. Most of our patients experienced PD-MCI. Single-domain PD-MCI subtype was predominant. Nevertheless, we identified a group of patients with multiple-domain PD-MCI demonstrating deficits in also episodic memory and/or visuospatial capacities.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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