Original Article

Cognitive profiles in Mild Cognitive Impairment (MCI) patients associated with Parkinson's disease and cognitive disorders

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Abstract

Background: Mild cognitive impairment (MCI) is rapidly becoming one of the most common clinical manifestations affecting the elderly and represents an heterogeneous clinical syndrome that can be ascribed to different etiologies; the construct of MCI in Parkinson's disease (PD) (MCI-PD) is more recent but the range of deficits is still variable. Early recognition and accurate classification of MCI-PD could offer opportunities for novel therapeutic interventions to improve the natural pathologic course. **Objective:** To investigate the clinical phenotype of amnestic mild cognitive impairment (aMCI) and in patients with PD and MCI (MCI-PD). **Materials and Methods:** Seventy-three patients with aMCI and in 38 patients with MCI-PD were enrolled. They all underwent Mini-mental State Examination (MMSE), the Rey auditory-verbal learning test and the immediate visual memory (IVM) item of the Mental Deterioration Battery, the Rey auditory-verbal learning test included the Rey-immediate (Rey-I), and the delayed recall of the word list (Rey test deferred, Rey-D). The Geriatric Depression Scale (GDS) was used for mood assessment. **Results:** The results of the Rey-I and Rey-D and of the IVM item showed statistically significant differences between the aMCI and the MCI-PD group. The mean Rey-I and Rey-D score was significantly lower as well as the IVM score was higher in patients with aMCI than in those with MCI-PD, aMCI patients showed greater impairment in long-term memory, whereas more aMCI than MCI-PD patients had preserved attention, computation, praxis, and conceptualization. **Conclusions:** Our findings demonstrate that the cognitive deficit profile is specific for each of the two disorders: Memory impairment was a typical feature in aMCI patients while MCI-PD patients suffered from executive functions and visuospatial attention deficits.

Key Words

Amnestic mild cognitive impairment, MCI-PD, Parkinson's disease

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Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are both associated with cognitive decline, but it is still unclear when they become functionally more similar over time. Most of PD patients develops dementia (PDD) in advanced stages of disease, but it affects over 80% of those with 20 years of disease[1] and a considerable number of them already shows cognitive deficits in the early stage so severe enough to be diagnosed as dementia.[2,3]

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The term mild cognitive impairment (MCI) was introduced in late 1980s and the concept of MCI has evolved from its initial use representing a stage in a global cognitive measure, to a cognitive syndrome with both clinical and research diagnostic criteria; it is associated with several different aetiologies.[4,5] Amnestic MCI (aMCI) is the most common type, and refers to a memory loss that is more pronounced than expected for age.[6] More recent definitions[7] have included deficits in memory and other domains (multiple-MCI or non-aMCI), if the patients do not meet the currently accepted criteria for clinically probable AD.

However, controversy exists as to how MCI can be best assessed and defined, as there is insufficient evidence to recommend specific tests or cut-off scores. In a clinical setting, the degree of impairment can be assessed neuropsychologically, but fulfilment of MCI criteria is ultimately determined through clinical judgement using information from these tests within a framework including other tools.[7]

Patients with aMCI usually progress to AD with high rate,[6,8] whereas patients with single, non-memory MCI (executive or visuospatial impairment) likely progress to a non-AD dementia, such as dementia with Lewy bodies, fronto-temporal dementia, Huntington's disease, or Parkinson-Dementia.[8,9]

Although not all MCIs progress to dementia, the construct of MCI implies that there is a continuum from normal cognition to dementia, with MCI representing a transitional or prodromal state. Up to date, only a few studies have focused on defining MCI in PD, nonetheless the concept of MCI-PD has become highly relevant in PD patients.[10,11] Despite the limited data, it has been demonstrated that MCI in PD lies between cognitively normal PD and PDD, and it may be defined applying criteria of MCI.[12] However, PD-MCI also appears to be common, even at the time of PD diagnosis before starting dopaminergic therapy.[13]

Studies suggest that MCI-PD may be the earliest stage of cognitive decline and a risk factor for developing dementia in PD,[11] thus representing an intermediate state between normal cognition and dementia in PD, similar in concept to aMCI and the subsequent development of AD. The biological validity of MCI-PD is supported by structural[14] and functional[15] neuroimaging, as well as by electroencephalography,[16] genetic,[17] cerebrospinal fluid,[18] and autopsy[19] studies, showing an association between a range neuropathophysiological variables and either cognitive impairment or cognitive decline in non-demented PD patients.

Recent neuropsychological studies studied whether the pattern of cognitive deficits in AD can be distinguished from that in PD[20,21] but the number of studies directly comparing these two patient groups was too small.[11,22-24] Frontal/executive dysfunction and amnestic deficit are the most frequently noted cognitive abnormalities in MCI-PD, while cognitive deficits in PD have traditionally been classified as deficits in executive (impaired planning and working memory),[25,26] visuospatial,[27] attentional,[28] memory,[29] and even language abilities.[30]

From a neuropathological point of view and against the background of disease-specific pathogenetic processes, it can be argued that MCI and MCI-PD patients show different patterns of cognitive deficits. For instance, according to the Braak stages in AD, the development of neurofibrillary tangles starts in the entorhinal cortex, extends into the hippocampus and then spreads to secondary association cortices.[31] In PD, neurodegeneration starts in the brain stem, extends into the midbrain, affecting the substantia nigra, and subsequently into cortical areas.[31] These findings may suggest that the two diseases are characterized by different patterns of cognitive deficits.

Materials and Methods

Patients

Seventy-three patients with aMCI and 38 patients with MCI-PD subscribed informant consent to participation were consecutively enrolled in the study.

The diagnosis of aMCI was based on clinical examination and neuropsychological assessment. Patients met the diagnostic criteria of the International Working Group on Mild Cognitive Impairment[7] and Petersen criteria.[5]

PD was clinically diagnosed along the lines of the UK brain bank criteria, the presence of two of three cardinal features (rest tremor, bradykinesia, and rigidity) without atypical features (early falls, early dementia, gaze palsy, etc.) or obvious secondary cause (arthritis, strokes, drugs, hydrocephalus, etc.).

The patients included in the MCI-PD group had to respect the Level I [according to the myelodysplastic syndrome (MDS) Task Force for the diagnosis of PD-MCI][32] and presented mini–mental state examination (MMSE) deficiency.

Patients with any other neurological or psychiatric disease unrelated to aMCI or MCI-PD were excluded from study participation.

Investigations

The severity of clinical symptoms was assessed using the Hoehn and Yahr scale[33] and motor status was evaluated with the Unified Parkinson's Disease Rating Scale part III (UPDRS-III).[34]

In our study, the diagnosis of MCI was based on clinical examination, neuropsychological assessment. For both groups (aMCI and MCI-PD), a sum score below 24 in the MMSE[35] was defined as cut-off score for diagnosing a dementia syndrome.[13]

This criterion was not the unique parameter for inclusion/exclusion of patients, but more clinical criteria according to the international consensus on MCI were considered.

The aMCI patients were:

1. patients evaluated not normal besides not fulfilling diagnostic criteria for dementia.
2. patients with functional activities mainly preserved, or at least with relative minimal impairment.

Patients demonstrated cognitive decline, themselves referred or family-related; associated with deficits on objective cognitive tasks, and/or evidence of decline over time on objective neuropsychological tests, which in our case were performed by screening with MMSE, analysing individual subitems; focusing Ray-test and immediate visual memory (IVM) of Mental Deterioration Battery).

The patients included in the MCI-PD group were present, in addition to a deficiency in the load of the global score of MMSE (defined as <24/30), also the response to at least the Level I (according to the MDS Task Force for the diagnosis of PD-MCI).[32]

At baseline, patients underwent a standard diagnostic examination, including medical history, physical and neurological examination, laboratory testing, brain imaging, electroencephalography, and laboratory tests (hematology and blood chemistry, thyroid function, vitamin B12, and folic acid).

The functional evaluation of patients was performed by assigning a score to the activities of daily living (ADL)[36] and to the instrumental activities of daily living (IADL).[37]

All participants underwent a neuropsychological examination that included the MMSE, the Rey auditory-verbal learning test,[38] and the immediate visual memory (IVM) item of the Mental Deterioration Battery.[39]

The Rey auditory-verbal learning test included the Rey-immediate (Rey-I) (reading aloud of a list of 15 words with the instruction to memorize the items) and the delayed recall of the word list (Rey test deferred, Rey-D). The Geriatric Depression Scale (GDS)[40] was used for mood assessment.

All patients underwent neuroimaging investigations.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 21.0 software (SPSS, Chicago, IL, USA) was used for data analysis. A paired *t*-test was used to compare the demographic and clinical characteristics between the cognitive impairment in aMCI and PD-MCI group. A P value < 0.05 was considered statistically significant.

Results

Table 1 summarizes the demographic data and the characteristics of the disease investigated (aMCI vs. MCI-PD). The two groups of patients with MCI were comparable in mean age, duration of the disease, ADL, and IADL score, also in the group of patients with aMCI was the most represented female sex compared to MCI-PD (58.3% female aMCI patients vs. 45.9% female PD-MCI patients). It should be noted that the patients with PD-MCI did not show a significant motor impairment (15.68 ± at 5:37 UPDRS III total score and 1.72 ± 00:36 at Hoehn and Yahr stage).

The neuroradiological imaging [analyses of brain magnetic resonance imaging (MRI)] showed differences between the aMCI and the MCI-PD group in according with MDS Task Force on mild cognitive impairment criteria:[39] Decreased gray matter in the precuneus, left frontal, left primary motor cortex (MCI-PD) compared to atrophy of the medial temporal lobe (MTL) structures, such as the hippocampus and entorhinal cortex (aMCI) (29% vs. 20%), non-specific subcortical microvascular disease (6% vs. 4%), atrophy of MTL structures associated, and reduced gray matter in the left frontal and bilateral temporal lobe regions with subcortical microvascular spread (20% vs. 5%) and non-specific pattern (17% vs. 8%) [Table 2].

As shown in Figure 1, the mean MMSE total score was comparable in the aMCI (mean ± SD: 25.07 ± 0.81) and in the MCI-PD group (mean ± SD: 24.97 ± 0.99). In the analysis of the MMSE subitems [Figure 2], statistically significant differences between groups were observed for long-term memory ($P = 0.046$), with higher mean score in the MCI-PD group than in the aMCI group, praxis ($P < 0.001$), and conceptualization ($P < 0.001$), with higher mean scores in the aMCI group than in and the MCI-PD group. Furthermore, higher mean scores (at the limit of statistical significance, $P = 0.06$) in the aMCI group than in and the MCI-PD group were observed for attention and computation.

The results of the Rey auditory-verbal learning test (Rey-I and Rey-D) and of the IVM item of the Mental Deterioration Battery [Figure 1] showed statistically significant differences ($P < 0.05$) between the aMCI and the MCI-PD group. The mean Rey-I and Rey-D score was significantly lower (i. e., patients committed more errors), as well as the IVM score was higher, in patients with aMCI than in those with MCI-PD.

The evaluation of the GDS showed that 51% of patients with aMCI was suffering from a depressive disorder compared with 36% of patients with PD-MCI, with a mean (± SD) total GDS score of 6.96 ± 6:08 and 3:05 ± 4:22, respectively in the two groups.

Discussion

Assessment of cognition in PD can be complicated by disease or medication-related effects, such as bradykinesia, fatigue, sleepiness, and mood disorders, which can adversely impact cognitive test results. Specifically, motor slowing (such as bradykinesia) and resting or intentional tremor may lead to impair performance in any type of test, while tremor can interfere with performance in tests requiring motor abilities. In this observational, cross-sectional study, we examined the frequency and clinical spectrum of aMCI and MCI-PD. Our

Table 1: Demographic data and disease characteristics by type of mild cognitive impairment (MCI) (aMCI vs. MCI-PD) and type of treatment in MCI-PD: Values are mean ± SD (median)

All Patients	aMCI (n = 73)	MCI-PD (n = 38)		
		Overall (n = 38)	Type of treatment	
			L-dopa (n = 30)	Monoamine oxidase B inhibitors. = 8)
Age, years	75.15±7.20 (76.00)	76.43±5.76 (76.00)	77.07±5.55 (76.00)	73.50±6.19 (72.00)
Education, years	5.47±2.31 (5.00)	4.62±1.52 (5.00)	4.52±1.70 (5.00)	4.38±1.77 (5.00)
Onset, years	20.89±10.71 (21.00)	24.24±12.35 (23.00)	24.48±13.86 (22.00)	24.38±3.34 (23.50)
Hoehn and Yahr stage	–	1.72±0.36 (2.00)	1.74±0.39 (2.00)	1.56±0.32 (1.50)
UPDRS-III, score	–	15.68±5.37 (14.00)	18.27±13.45 (15.00)	14.00±4.28 (13.00)
ADL, score	6.00±0.00 (6.00)	6.00±0.00 (6.00)	6.00±0.00 (6.00)	6.00±0.00 (6.00)
IADL, score	7.54±0.69 (8.00)	7.14±0.63 (7.00)	7.00±0.60 (7.00)	7.63±0.52 (8.00)

aMCI = Amnestic mild cognitive impairment, MCI-PD = Mild cognitive impairment in Parkinson's disease, SD = Standard deviation, UPDRS-III = Unified Parkinson's Disease Rating Scale part III, ADL = Activities of daily living, IADL = Instrumental activities of daily living

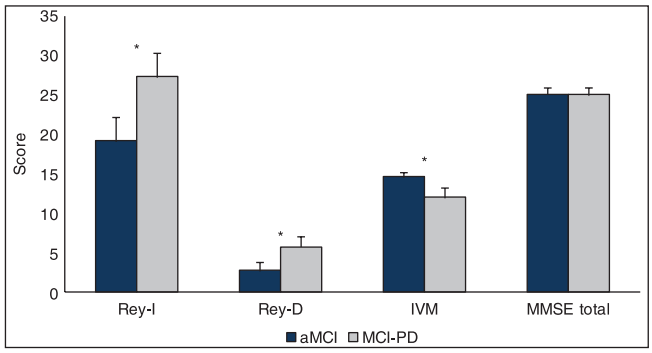


Figure 1: Results of the Rey auditory-verbal learning test (Rey-I and Rey-D), IVM item of the Mental Deterioration Battery, and MMSE total score by type of MCI (aMCI vs. MCI-PD): Data are means with SD in bars
***P* < 0.05 between groups**
aMCI = Amnestic mild cognitive impairment, MCI-PD = Mild cognitive impairment, IVM = Immediate visual memory, MMSE = Mini-mental state examination, SD = Standard deviation, MCI = Mild cognitive impairment

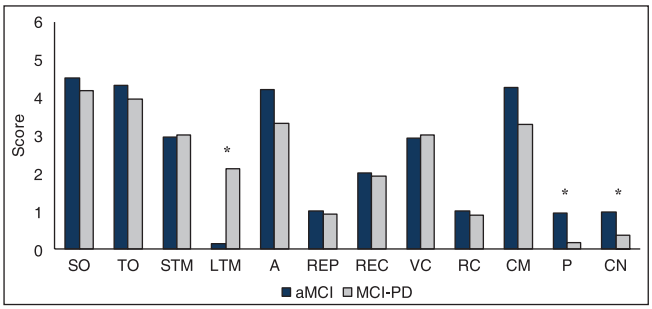
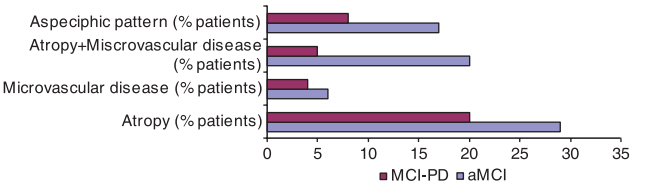


Figure 2: Results of MMSE subitems score by type of MCI (aMCI vs. MCI-PD): Data are means
***P* < 0.05 between groups**
A = Attention, CM = Computation, CO = Conceptualization, LTM = Long-term memory, P = Praxis, RC = Reading comprehension, REC = Recall, REP = Repetition, SO = Spatial orientation, STM = Short-term memory, TO = Temporal orientation, VC = Verbal comprehension, aMCI = Amnestic mild cognitive impairment, MCI-PD = Mild cognitive impairment, MMSE = Mini-mental state examination, MCI = Mild cognitive impairment

Table 2: Neuropathological findings (analyses of brain MRI)



MRI = Magnetice resonance imaging, aMCI = Amnestic mild cognitive impairment, MCI-PD = Mild cognitive impairment

data showed that aMCI is the most common type of MCI, while, consistently with findings of other previous studies,[12,13] MCI-PD is observed less frequently. As observed in precedent investigations,[12,41] MCI-PD patients suffered from attentional and visuoconstructive deficits, whereas memory impairments were typical features in aMCI subjects. However, deficits in attentional, praxis, conceptualization, and executive functions were possible findings of MCI-PD patients. Depressive mood was present in both disorders. Depressive mood was present in both disorders. The lack of difference in the GDS total score between the group of patients with aMCI and the group of patients with MCI-PD suggests that the depressive symptoms cannot account for group differences.

Dopaminergic pathway is in fact crucial also for cognitive process, such as working memory and attention,[42-44] usually associated with prefrontal functions. Dopamine level is reduced in prefrontal cortices of patients with PD.[42] Instead cholinergic system has been implicated in MCI-related cognitive impairment with degeneration of the nucleus basalis of Meynert, decreased cholinergic activity in the cortex, and reduced choline acetyltransferase activity in the frontal and temporal lobes in aMCI. These deficits may be linked to impairment in attention, learning, and memory in aMCI and could explain the diversity of the anatomical substrate between MCI and aMCI-PD.[45] Nevertheless, many patients in the MCI-PD group showed deficits in other areas of cognitive functioning we also found evidence of visuospatial deficits, which has not been reported by precedent studies MCI-PD patients,[19,22] therefore, represents an interesting to investigate in future study of patients with PD-MCI.

This study has some limitations, which consist mainly in relatively small number of patients and in the different sizes between the aMCI and the PD-MCI groups and the two treatment subgroups, as a result of a consecutive patients recruitment process. Moreover, the relative small sample size might compromise the statistical significance for some variables in the comparisons between groups. Indeed, significant statistical differences should be interpreted with caution, whereas blackberries relevance should be given to the direction and the extent of the observed differences.

Furthermore, assessment of cognition in PD can be complicated by disease or medication-related effects such as bradykinesia, fatigue, sleepiness, and mood disorders. Specifically, bradykinesia and resting or intentional tremor may impair precise manual skills.

After consulting with experts clinical neuropsychologists, we have decided not to use the Montreal Cognitive Assessment (MoCA) test because it is not easy to be administered in daily clinical practice, instead using selected subitems of Mental Deterioration battery and MMSE. MoCA test may be able to detect executive dysfunction compared to the MMSE; however, it may have limited diagnostic accuracy for MCI-PD.[46]

The heterogeneity of cognitive deficits reported here is not surprising, given the diverse pattern of neuronal degeneration associated with PD.[12,47] Evidence of abnormalities in other subcortical structures including the loss of noradrenergic neurons in locus coeruleus, serotonergic neurons in the dorsal raphé nucleus, and cholinergic neurons in the nucleus basal is of Meynert evident from the early stages of the disease process may represent a possible explanation.[48-50]

We believe important the identification of an MCI, a condition that often precedes the development of a greater cognitive decline, could avail of specific therapies for cognitive impairment, to be performed in the earliest stage, that is, the only real medical condition liable, if not improvement, of at least slowing the disease condition itself.

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