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Prevalence and Profile of Mild Cognitive Impairment in Parkinson's Disease

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Key Words
Parkinson's disease · Cognitive impairment · Epidemiology

Abstract
Background/Aims: The frequency of mild cognitive impairment (MCI) in Parkinson's disease (PD) ranges from 19 to 40%, and this is probably due to methodological differences between the studies. The aim of this study was to evaluate the frequency and profile of MCI in a large sample of nondemented PD subjects and neurologically healthy subjects (NHS). ***Methods:*** A total of 872 subjects (582 controls and 290 PD) were included. The association between MCI and PD was tested, using logistic regression models; odds ratios (OR) with 95% confidence intervals (CI) were calculated. ***Results:*** Fifty-three percent of PD subjects and 45% NHS met the criteria for MCI ($p = 0.001$). The PD subjects showed a higher frequency of nonamnestic MCI (naMCI), compared to NHS (23.8 vs. 14.4%, $p \leq 0.0001$). In comparison to NHS, PD was associated with a univariate OR of 1.9 (95% CI = 1.3–2.8) for naMCI, and this association was marginally significant after multiple comparisons (multivariate OR = 1.5, 95% CI = 0.96–2.3, $p = 0.077$). ***Conclusion:*** The association between PD and the impairment of nonmemory domains is probably due to frontal-subcortical involvement, which characterizes the disease.

Introduction

Mild cognitive impairment (MCI) is a nosological entity, which has been proposed as an intermediate state between normal aging and dementia [1]. The syndrome can be divided into two broad subtypes: amnestic MCI (aMCI) characterized by reduced memory, and nonamnestic MCI (naMCI) in which other cognitive functions rather than memory are mostly impaired. aMCI seems to represent an early stage of Alzheimer's disease (AD), while the outcomes of the naMCI subtypes appear more heterogeneous – including vascular dementia, frontotemporal dementia or dementia with Lewy bodies – but this aspect is still being debated [2].

In recent years, the MCI concept has also been applied to nondemented subjects with Parkinson's disease (PD). In a recent multicenter cohort of well-defined patients with PD, the frequency of MCI in PD ranged from 19 to 40% [3], probably due to methodological differences between samples. However, to date it is not well known which cognitive domain characterizes early cognitive decline in PD. Of interest, in the recommendations of the Movement Disorder Society for tests to be used in defining cognitive decline in PD, a variety of cognitive tasks (including those assessing memory, executive-attentive, language, praxis and visuospatial abilities) has been sug-

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gested [4]. Similarly, recent neuroimaging data of PD subjects with MCI revealed brain abnormalities in the frontal and temporal lobes, which are cortical regions linked to executive functioning, attention and memory [5].

The aim of this study was to evaluate the prevalence and profile of MCI in a large sample of nondemented PD subjects after having checked for demographic, disability and comorbidity variables.

Methods

Patients and Neurologically Healthy Subjects

All selected PD subjects were consecutively recruited from the outpatient movement disorders clinic of the Unit of Neurology and Cognitive Disorders, University Hospital, Palermo, Italy over a 9-year period (2001–2009). All patients underwent an extensive physical, neurological, and neuropsychological examination, laboratory testing and computed tomography or magnetic resonance imaging. From a total of 405 subjects with PD seen over the 9-year period, 32 were excluded due to their demented state and 83 due to missing data on neuropsychological examination or severe PD (i.e. Hoehn and Yahr scale stage IV) [6]. The remaining subjects thus comprised a group of 290 nondemented PD subjects, diagnosed according to the UK PD Society Brain Bank criteria [7], as included in this study. The motor assessment of PD included the Unified Parkinson's Disease Rating Scale – motor examination [8]. Only subjects with mild to moderate PD (Hoehn and Yahr scale stages I–III) [6] were included.

Neurologically healthy subjects (NHS) were consecutively recruited over the same 9-year period from subjects being referred to the memory clinic of our unit because of subjective cognitive complaints. With the aim of having a case:control study design ratio of 1:2, 582 NHS out of a total group of 2,150 were matched for age and education to cases selected from our database. The NHS and PD subjects belong to a larger, prospective, hospital-based study, which was carried out from 2001 up until now in our neurological unit and clinics, and which focused on normal and pathological aging (Cognitive Impairment through Aging, CogItA). The exclusion criteria for both groups were: a diagnosis of severe systemic disorder; the presence of psychosis; a history of significant head injury or substance abuse, and the presence of dementia according to DSM-IV criteria [9]. After a complete description of the study, written informed consent was obtained from all participants.

Neuropsychological Assessment

The neuropsychological battery included the Mini Mental State Examination [10], as a test of general cognition, and specific tests to assess the following 5 cognitive domains: *verbal memory* (Story Recall Test and the immediate and delayed recall of Rey's Auditory Verbal Learning Test) [11]; *language* (Token Test for verbal comprehension and the naming subtest of the Aachener Aphasie Battery) [12, 13]; *selective and divided attention* (Visual Search and Trial Making Test parts A and B) [12, 14]; *executive functions* (Phonemic Fluency Test, Raven's Colored Progressive Matrices and the Frontal Assessment Battery) [12, 15, 16], and *visuoconstructional abilities* (Copy Drawing Test and the position discrimination subtest of the Visual Object and Space Perception Battery) [12, 17]. Details regarding administration procedures and Italian normative data for score adjustment, based on age and education as well as normality cutoff scores (≥95% of the lower tolerance limit of the normal population distribution) were available for each battery test [11–16]. Different MCI subtypes were classified according to modified Petersen's criteria [18], as follows: (1) single, nonmemory MCI, subjects with a deficit in a single (other than memory) domain, defined as abnormal test performance (under normality cutoff) in 1 nonmemory test; (2) aMCI, subjects with selective memory deficits, defined as a pathological score in at least 1 standardized memory test, with no deficits in other cognitive tests; (3) aMCI multidomain, subjects with 1 abnormal test in at least 2 domains, one of which was memory impairment, and (4) naMCI multidomain, subjects with 1 abnormal test in at least 2 domains, excluding memory. The common criteria for all MCI subtypes were: (a) cognitive deterioration, representing a decline from a previously higher ability level (Clinical Dementia Rating = 0.5) [19]; (b) preserved general cognitive functions (Mini Mental State Examination age- and education-adjusted score ≥23.8) [10]; (c) no impairment or minimal impairment of the basic activities of daily living (ADL) [20] – regarding impairment of instrumental ADL [21], this occurs frequently in PD, being due to motor rather than cognitive impairment, and this feature was not adopted within the MCI criteria, and (d) no dementia according to the DSM-IV criteria [9]. Only a global aMCI (including aMCI and aMCI multidomain subtypes) versus naMCI classification (including single, nonmemory MCI and naMCI multidomain subtypes) was operationalized in the current analysis.

Covariates

The functional status was assessed with the basic ADL [20] scale, while somatic comorbidity was quantified by the Cumulative Illness Rating Scale (CIRS) severity index [22]. Lastly, depressive symptoms were evaluated with the Hospital Anxiety and Depression scale, depression subtest (HAD-D) [23].

Statistical Analysis

The descriptive data were analyzed by the t test or χ^2 test. The association between MCI and PD was tested using univariate and multivariate logistic regression models. The latter were adjusted for demographics, ADL scale score, CIRS index and HAD-D scores. The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for these analyses. All tests were two-tailed; the statistical significance was set at $p \leq 0.05$.

Results

As shown in table 1, males were significantly more represented than females among patients as compared with NHS (59.3 vs. 39.5%; $\chi^2 = 30.5$, $p \leq 0.0001$). Similarly, PD subjects presented higher numbers of ADL lost ($t = -7.2$, $p \leq 0.0001$), having a higher CIRS index ($t = -2.6$, $p = 0.010$) and HAD-D scores ($t = -4.5$, $p \leq 0.0001$) than NHS.

Table 1. Characteristics of subjects

Variables	NHS (n = 582)	PD (n = 290)
Gender (M:F)	230:352	172:118*
Age, years	68.3 ± 8.7	68.8 ± 8.4
Education, years	7.9 ± 4.8	7.5 ± 4.5
MMSE score	27.6 ± 2.2	27.5 ± 2.1
ADL lost, n	0.2 ± .0.4	0.5 ± 0.8*
CIRS index	1.9 ± 1.5	2.2 ± 1.4*
HAD-D score	6.94 ± 4.1	8.25 ± 4.0*
UPDRS-ME score	–	21.8 ± 12.8
Hoehn and Yahr stage	–	2.0 ± 0.6

Figures are means ± SD. NHS = Neurologically healthy subjects; PD = Parkinson's disease; MMSE = Mini Mental State Examination; ADL = activities of daily living; CIRS = Cumulative Illness Rating Scale; HAD = Hospital Anxiety and Depression scale; UPDRS-ME = Unified Parkinson's Disease Rating Score – Motor Examination. * $p \leq 0.010$ for all comparisons after t test or χ^2 analyses.

Table 2. Frequency of aMCI and naMCI in NHS and PD subjects

Variables	NHS (n = 582)	PD (n = 290)
Cognitively intact	318 (54.6)	134 (46.2)
aMCI	180 (31)	87 (30)
naMCI	84 (14.4)	69 (23.8)*

Figures are numbers with percentages in parentheses. aMCI = Amnestic mild cognitive impairment (MCI); naMCI = non-amnestic MCI; NHS = neurologically healthy subjects; PD = Parkinson's disease. * $p \leq 0.0001$ after χ^2 for trend.

The distribution of MCI subtypes significantly differed in PD patients compared to NHS, and these differences were primarily due to the naMCI frequency between groups (χ^2 for trend = 12.4, $p \leq 0.0001$), while that of aMCI was not (table 2). PD was associated with a univariate OR of 1.9 (95% CI = 1.3–2.8) for naMCI, and this result was marginally significant after multiple adjustments (multivariate OR = 1.5, 95% CI = 0.96–2.3, p = 0.077).

Discussion and Conclusion

Our findings suggest that impairment in a variety of nonmemory domains characterizes mild-moderate phases of PD, highlighting MCI as a key feature of PD. As previously reported [24], nearly 90% of PD subjects with naMCI showed an impairment of attentive-executive functions, thus underlying the fact that the frontal-subcortical involvement, which characterizes the disease, causes an impairment of these cognitive abilities. Of interest, areas of reduced gray matter were found in the left frontal and both temporal lobes in PD subjects with MCI, that is, the cortical regions linked to executive functioning, attention and memory [5]. In a recent multicenter pooled analysis of MCI in PD, which was conducted with 8 different samples, the authors described an MCI frequency ranging from 18.9 to 39.4% [3]. This difference is probably due to the heterogeneity of the cognitive assessment for diagnosing MCI, to differences in study setting and to differences in the duration and stage of PD included.

We believe that our study has several strengths, including the relatively large number of subjects included, and the use of a multidimensional standardized cognitive assessment. However, the inclusion of NHS with subjective cognitive complaints may have caused a degree of selection bias, thus explaining the high frequency of the MCI status in this group. Although we adjusted for major potential confounders, residual confounding is possible, given the observational design of the study. For example, we did not check for the use of dopaminergic drugs in the PD group, which have an impact on the frontostriatal circuit. Accordingly, we cannot be sure that the significant naMCI profile in PD that we found represents a truly prodromal phase of PD dementia or whether it is simply an ancillary aspect of the disease. Longitudinal studies are required to determine the prognostic role of the MCI condition in PD subjects. We have planned to verify and extend these findings in the ongoing follow-up of our sample.

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