Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-181117
IOS Press

Mild Behavioral Impairment in Parkinson's Disease: Data from the PArkinson's Disease COgnitive Impairment Study

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Handling Associate Editor: Patrizia Mecocci

Accepted 11 February 2019

Abstract. Neuropsychiatric symptoms (NPS) have been frequently described in Parkinson's disease (PD), even in the earliest stages of the disease. Recently the construct of mild behavioral impairment (MBI) has been proposed as an at-risk state for incident cognitive decline and dementia. The aim of the present study is to evaluate the prevalence and associated factors of MBI in PD. Cross-sectional data from 429 consecutive PD patients enrolled in the PArkinson's disease COgnitive impairment Study (PACOS) were included in the study. All subjects underwent neuropsychological assessment, according to the MDS Level II criteria. NPS were evaluated with the Neuropsychiatric Inventory. Multivariate logistic regression models were used to evaluate clinical and behavioral characteristics, which are associated with PD-MBI. PD-MBI was ascertained in 361 (84.1%) subjects of whom 155 (36.1%) were newly diagnosed patients (disease duration ≤1 year) and 206 (48.0%) had a disease duration >1 year. Furthermore, 68 (15.9%) out of 429 subjects were PDw (without MBI). Across the MBI domains, *Impulse Dyscontrol* was significantly more prevalent among PD-MBI with disease duration >1 year than newly diagnosed patients. The frequency of *Social Inappropriateness* and *Abnormal Perception* significantly increased throughout the entire PD-MBI sample with increasing Hoehn and Yahr (H&Y) stages. PD-MBI in newly diagnosed PD was significantly associated with H&Y stage (OR 2.35, 95% CI 1.05–5.24) and antidepressant drug use (OR 2.94, 95% CI 0.91–9.47), while in patients with a disease duration >1 year was associated with UPDRS-ME (OR 3.37, 95% CI 1.41–8.00). The overall MBI frequency in the PACOS sample was 84% and 36% among newly diagnosed patients. The presence of MBI mainly related to motor impairment and disability.

Keywords: Cognitive impairment, mild behavioral impairment, neuropsychiatric symptoms, Parkinson's disease, prevalence

INTRODUCTION

Neuropsychiatric symptoms (NPS) are frequent in dementia and mild cognitive impairment (MCI), relating to a worse prognosis [1, 2]. Similarly, NPS have been frequently described in Parkinson's disease (PD) even in the early, untreated phases of the disease, being associated with a reduced quality of life and advanced disease [3, 4]. Nearly 90% of patients with PD dementia had at least one NPS, with depression, apathy, anxiety, and hallucinations being the most prevalent symptoms [3]. Recently, the International Society to Advance Alzheimer's Research and

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Treatment (ISTAART) has proposed the new construct of mild behavioral impairment (MBI). This is characterized by later life-acquired NPS of different severity and it is considered an at-risk state for incident cognitive impairment and dementia [9]. Ismail et al. have identified five behavioral domains included within the MBI spectrum: *Decreased Motivation, Affective Dysregulation, Impulse Dyscontrol, Social Inappropriateness*, and *Abnormal Perception*. These behavioral changes interfere minimally with interpersonal relationships and affected individuals substantially maintain their independence regarding daily activities [9]. Subsequently, Sheikh et al. [10] have deployed ten behavioral symptoms rated to the Neuropsychiatric Inventory (NPI) [11] to operationalize the ISTAART-AA MBI domains. Currently, the concept of MBI is evaluated in subjects with subjective cognitive decline (SCD) and MCI, preclinical and a prodromal phase of Alzheimer's disease, respectively [12]. MBI is present in approximately 80% of the population, being more prevalent in MCI than in subjects with SCD (85.3 versus 76.5, respectively) [10]. Furthermore, the presence of MBI without cognitive impairment determines a higher risk of conversion to dementia than the presence of MCI without psychiatric complaints [13, 14].

Cognitive impairment and dementia have been described with a high frequency during the course of PD, being associated with age, disease duration, disease severity, and a poor outcome [3]. Validated clinical criteria for MCI in PD (PD-MCI) have been recently recommended [5], with a mean point prevalence for PD-MCI of nearly 27% [6]. PD-MCI has been found to be directly associated with age and motor impairment, while an inverse association has been observed between educational level and MCI [7]. PD-MCI subjects have a greater NPS burden than PD without cognitive impairment, and depression, sleep disturbance, anxiety, and apathy were the most common NPS in PD-MCI [8].

There are no studies evaluating the frequency and associated clinical features of MBI in subjects with PD, and thus the relationship between MBI and MCI in PD has not been evaluated. The aims of this study were: 1) to evaluate the prevalence and associated factors of MBI in PD subjects; 2) to investigate the relationship between MBI and MCI in PD patients; and 3) to examine whether the prevalence and risk factors of MBI differ according to disease duration (i.e., patients with a disease duration $\leq$1 year versus patients with a disease duration >1 year).

MATERIALS AND METHODS

The PArkinson's disease COgnitive impairment Study (PACOS) is a large, cross-sectional, hospital-based study, involving two Movement Disorder Centers in southern Italy (the University Hospitals of Catania and Palermo). The primary endpoint of the PACOS was to evaluate the burden of PD-MCI; the secondary endpoints were the evaluation of associated/risk factors and biomarkers for PD-MCI and its progression to PD dementia (PDD) [7]. With reference to the present study, 429 subjects with PD (according to the UK PD Society Brain Bank criteria [15]) were included and they had been consecutively evaluated for cognitive impairment over a 4-year period (2014–2017). The exclusion criteria were the presence of PDD [16], secondary parkinsonism and Parkinson-plus syndromes. All patients underwent an extensive physical, neurological, and neuropsychological examination, laboratory testing, and computed tomography or magnetic resonance imaging. Data relating to age at onset and disease duration in years were collected for each patient. Motor evaluation included the Unified Parkinson's Disease Rating Scale-Motor Examination (UPDRS-ME) [17] and the Hoehn and Yahr scale (H&Y) (stage I-III) [18].

According to the most prominent motor phenotype at onset of PD, patients were classified as: Postural Instability and Gait Difficulty, Tremor Dominant, or of a Mixed Type [19]. The Basic Activities of Daily Living (BADL) [20] and the Instrumental Activities of Daily Living (IADL) [21] were used to evaluate functional ability (scored as the number of items lost for each scale). The overall burden of dopaminergic drugs was evaluated with the total daily Levodopa Equivalent Dose (LED) [22]. The Cumulative Illness Rating Scale (CIRS) was used to evaluate somatic comorbidity, considering the *total score* and the *severity index* (number of systems with score $\geq$3) [23]. All PD subjects underwent a neuropsychological assessment when in "on" state. PD-MCI was diagnosed according to the Movement Disorder Society (MDS) Task Force, Level II criteria [5]. Subjects underwent a complete neuropsychological battery, exploring five cognitive domains: memory, attention, visuospatial and executive functioning, and language. The details of the cognitive assessment have already been described elsewhere [24]. Neuropsychological performance was considered as impaired when subjects scored two standard deviations below normality cut-off values.

NPS and their severity were assessed by the NPI, a fully structured caregiver interview measuring 12 behavioral symptoms [11]. Frequency and severity scores were multiplied for each symptom to obtain a composite score ranging from 0 to 12. As suggested by Sheikh et al., MBI domains were computed using NPI subscores as follows: 1) *Decreased Motivation* (NPI: apathy/indifference); 2) *Affective Dysregulation* (NPI: depression/dysphoria, anxiety, elation/euphoria); 3) *Impulse Dyscontrol* (NPI: agitation/aggression, irritability, liability, aberrant motor behavior); 4) *Social Inappropriateness* (NPI: disinhibition); and 5) *Abnormal Perception* (NPI: delusions, hallucinations) [10]. Just one behavioral symptom was sufficient to meet the MBI domain criteria. Thus, if at least one of the five domains was present, an MBI diagnosis was fulfilled. To fit the MBI construct, which requires six months of new onset symptoms, a modified reference range of six months was used to ascertain each NPI symptoms, as previously detailed. Regarding functional abilities, no impairment or minimal impairment of BADL was considered as inclusion criteria. Contrarily, IADL impairment occurs frequently in PD due to motor rather than cognitive impairment and this feature was not adopted for MBI classification [8]. Finally, patients were classified as follows: PDw (without behavioral impairment) and PD-MBI (with behavioral impairment), stratified by disease duration (newly diagnosed: patients with a disease duration $\leq$1 year and patients with a disease duration >1 year). All subjects provided written informed consent prior to entering the study, which was approved by the local Ethics Committee, in accordance with the Declaration of Helsinki.

Statistical analysis

Statistical analyses were carried out using STATA v14.2 software. Data cleaning was performed prior to data analysis, considering range and consistence checks. Normal distribution and homogeneity of variables were tested with Kolmogorov-Smirnov and Levene's test respectively. Mean data (Standard Deviation, SD) were compared using a one-way analysis of variance (ANOVA) with Scheffe's *post hoc* test for multiple comparisons, while medians (Interquartile Range, IQR) were analyzed with the Mann-Whitney test. The chi-square test was used to compare categorical variables.

In order to evaluate the possible predictors for MBI, an unconditional logistic regression analysis was performed using PDw as the reference category and stratifying subjects according to disease duration ($\leq$1 versus >1 year). Covariates, which were significantly associated with study outcomes (PD-MBI) after univariate analysis ($p < 0.1$), were entered into the multiple logistic regression, which includes the following as *a priori* confounders: age, sex, education, and MCI. Furthermore and to avoid collinearity between CIRS neurologic/psychiatric items and PD-MBI, the CIRS total score and severity index were calculated, excluding the neurological and psychiatric items.

The model was manually constructed, using the likelihood ratio test in order to compare the log-likelihood of the model with and without a specific variable. Whenever quantitative variables were dichotomized (UPDRS-ME and LED), the cut-offs were derived from the pooled distribution (median value of the pooled distribution). The possible interaction was also evaluated by the likelihood ratio test (test of violation of proportional odds). Regarding quantitative exposure, the test for linear trend was performed to evaluate the linear or trend effect. The results are presented as odds ratios (OR) with 95% confidence intervals (95% CI).

RESULTS

Clinical characteristics and descriptive features of MBI in PD patients

Four hundred twenty-nine PD patients were enrolled in the study (59.9% male, mean age 68.2 ± 9.4) with a mean disease duration of 2.9 ± 3.6 and a median UPDRS-ME of 21 (range 14–19) (see Table 1). Of the 429 enrolled patients, 361 fulfilled the criteria for MBI, providing an overall frequency of 84.1%. One hundred fifty-five (36.1%) of the 361 PD-MBI and 33 (48.5%) of 68 PDw were newly diagnosed patients (disease duration $\leq$1 year). Overall, there were 165 subjects (38.5%) with MCI (57% male, median education 5 [range 3–8]), mean age 70.5 ± 8.2, mean disease duration 3.3 ± 3.7 and median UPDRS-ME 25 [range 18–33]). Regarding the entire sample, a borderline significant higher frequency of MCI was recorded among PD subjects with MBI with respect to PDw (PD-MBI with MCI = 40% versus PDw with MCI = 27.9%, p-value 0.054).

The mean scores for each NPI symptom and the frequency of each MBI domain are depicted in Table 2. Specifically, *Affective Dysregulation,*

Table 1
Demographic and clinical characteristics of PDw, PD-MBI ≤ 1 *y*, and PD-MBI > 1 *y*

	Total *n* = 429 (100%)	PDw *n* = 68 (15.9%)	PD-MBI ≤ 1 *y* *n* = 155 (36.1%)	PD-MBI > 1 *y* *n* = 206 (48.0%)	*P*
Age (y), mean (SD)	68.2 (9.4)	66.0 (11.8)	68.1 (8.6)	69.0 (9.0)	0.079
Education (y), median (range)	5 (3–12)	6 (5–13)	6 (5–13)	5 (3–10)	0.482
Male, *n* (%)	257 (59.9)	46 (67.6)	91 (58.7)	120 (58.2)	0.364
Disease duration (y), mean (SD)	2.9 (3.6)	2.5 (3.5)	0.3 (0.5)	5.1 (3.6)	<0.001
Motor phenotype, n (%)					
-TD	116 (27.0)	24 (35.3)	47 (30.3)	45 (21.8)	0.156
-Mixed	48 (11.2)	6 (8.8)	19 (12.3)	23 (11.2)	
-PIGD	265 (61.8)	38 (55.9)	89 (57.4)	138 (67.0)	
H&Y, median (range)	2 (1.5–2.5)	2 (1–2.5)	2 (1.5–2.5)	2 (1–2.5)	0.032
UPDRS-ME, median (range)	21 (14–29)	17 (12–23)	19 (13–25)	25 (19–33)	<0.001
UPDRS-ME ≥ 21, *n* (%)	224 (52.2)	24 (35.3)	63 (40.6)	137 (66.5)	<0.001
Total LED mg/die, median (range)	300 (200–400)	300 (200–325)	250 (200—375)	375 (250–500)	<0.001
Total LED ≥ 300 mg/die, *n* (%)	261 (60.8)	35 (51.5)	75 (48.4)	151 (73.3)	<0.001
Antipsycotic drug use, *n* (%)	20 (4.9)	0 (0)	8 (5.2)	12 (5.8)	0.133
Antidepressant drug use, *n* (%)	115 (26.8)	9 (13.2)	47 (30.3)	59 (28.6)	0.021
Anxiolytics drug use, *n* (%)	112 (26.1)	10 (14.7)	48 (31.0)	54 (26.2)	0.039
CIRS total, mean (SD)	15.8 (2.6)	15.0 (2.3)	16.2 (2.7)	15.7 (2.5)	0.008
CIRS index, mean (SD)	1.2 (1.2)	0.9 (1.1)	1.4 (1.3)	1.2 (1.2)	0.019
MCI, *n* (%)	165 (38.5)	19 (27.9)	51 (32.9)	95 (46.1)	0.006

PD, Parkinson's disease; MBI, mild behavioral impairment; PDw, Parkinson's disease without MBI; PD-MBI ≤ 1 *y*, PD with MBI with disease duration ≤1 year; PD-MBI > 1 *y*, PD with MBI with disease duration >1 year; TD, tremor dominant; PIGD, postural instability gait difficulty; H&Y, Hohen and Yahr; UPDRS-ME, Unified Parkinson's Disease Rating Scale, Motor Examination; LED, levodopa equivalent dose; CIRS, Cumulative Illness Rating Scale; MCI, mild cognitive impairment.

Decreased Motivation, and *Impulse Dyscontrol* were in decreasing order the most prevalent MBI domains in both MBI groups. PD-MBI with disease duration >1 year revealed a significantly higher frequency of *Impulse Dyscontrol* than PD-MBI newly diagnosed (47.6% versus 35.5%, $p = 0.021$).

Thereafter, the frequency of each MBI domain in PD patients, stratified by motor disability according to H&Y stage (H&Y 1–1.5, H&Y 2–2.5, and H&Y 3) was evaluated. Overall, the impairment in each domain increases with increasing H&Y stage (see Fig. 1) except for *Affective Dysregulation.* However, significant differences were found only for *Social Inappropriateness* ($p \leq 0.001$) and *Abnormal Perception* ($p = 0.004$).

Table 2
Mean scores of NPI symptoms and frequency of MBI domains in PD-MBI ≤ 1 *y* and PD-MBI > 1 *y*

NPI symptoms	PD-MBI ≤ 1 *y* (*n* = 155) mean (SD)	PD-MBI > 1 *y* (*n* = 206) mean (SD)	*p*
Delusions	0.25 (1.29)	0.18 (1.04)	0.557
Hallucinations	0.34 (1.24)	0.53 (1.67)	0.230
Agitation	0.68 (2.05)	0.72 (1.75)	0.838
Depression	4.04 (3.07)	3.44 (3.26)	0.076
Anxiety	3.98 (3.20)	3.37 (3.24)	0.075
Euphoria	0.06 (0.66)	0.15 (0.83)	0.291
Apathy	2.61 (3.11)	2.54 (2.87)	0.831
Disinhibition	0.19 (1.28)	0.14 (0.90)	0.646
Irritability	1.50 (2.76)	1.53 (2.56)	0.908
Aberrant motor behavior	0.38 (1.60)	0.30 (1.27)	0.577
MBI domains	*n* %	*n* %	
DM	78 (50.3%)	111 (53.9%)	0.503
AD	142 (91.6%)	180 (87.4%)	0.200
ID	55 (35.5%)	98 (47.6%)	0.021
SI	4 (2.6%)	9 (4.4%)	0.367
AP	20 (12.9%)	33 (16,0%)	0.408

NPI, Neuropsychiatric Inventory; PD, Parkinson's disease; MBI, mild behavioral impairment; PD-MBI ≤ 1 *y*, PD with MBI with disease duration ≤1 year; PD-MBI > 1 *y*, PD with MBI with disease duration >1 year; DM, decreased motivation; AD, affective dysregulation; ID, impulse dyscontrol; SI, social inappropriateness; AP, abnormal perception.

Factors associated with PD-MBI

Univariate and multivariate analysis were conducted to explore associated factors for PD-MBI, considering PDw as the reference group and stratifying by disease duration (≤1 versus >1 year) (see Table 3). The univariate analysis relating to newly diagnosed patients revealed significant associations with age (OR 1.06, 95% CI 1.01–1.10), H&Y (OR 2.51, 95% CI 1.22–5.17), antidepressant drug use (OR 3.15, 95% CI 1.05–9.48), anxiolytics drug use (OR 2.51, 95% CI 0.91–6.90), CIRS total (OR 1.21, 95% CI 1.03–1.42), and CIRS index (OR 1.44, 95% CI 1.03–2.03). On the contrary, there was no association with MCI (OR 1.82, 95%CI

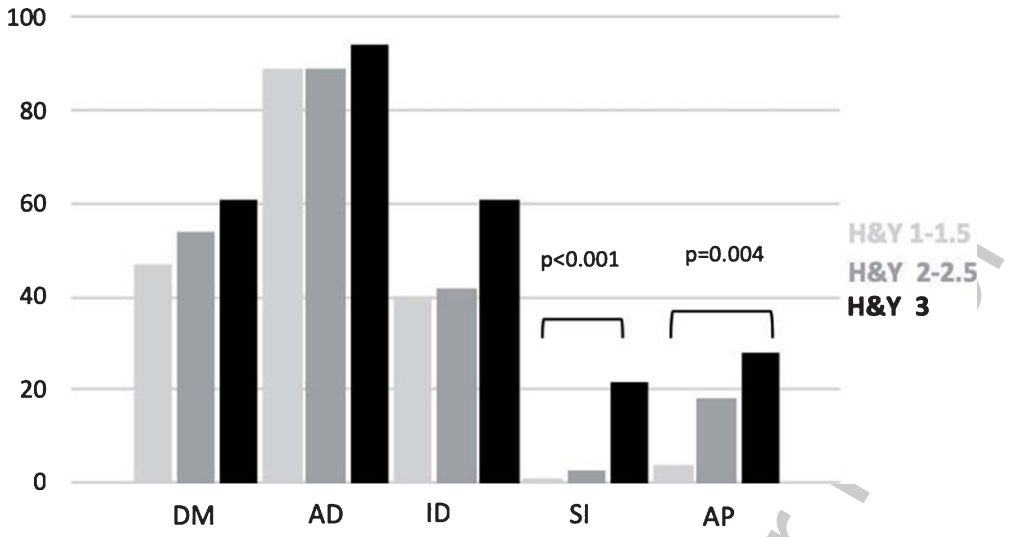

Fig. 1. Frequency of each MBI domains, stratified by H&Y stage MBI, mild behavioral impairment; H&Y, Hohen and Yahr; DM, Decreased Motivation; AD, Affective Dysregulation; ID, Impulse Dyscontrol; SI, Social Inappropriateness; AP, Abnormal Perception.

Table 3
Univariate and multivariate analysis of PD-MBI ≤ 1 *y* versus PDw and PD-MBI > 1 *y* versus PDw

	PD-MBI ≤ 1 *y* versus PDw ≤ 1		PD-MBI > 1 *y* versus PDw > 1 *y*	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Age, y (per y increase)	1.06 (1.01–1.10)***	1.04 (0.99–1.08)	1.01 (0.96–1.04)	0.99 (0.96–1.04)
Education, y (per y increase)	0.95 (0.88—1.03)	1.01 (0.92–1.10)	0.99 (0.92–1.08)	1.02 (0.94–1.12)
Gender, (male versus female)	0.53 (0.23–1.22)	0.70 (0.29–1.73)	0.82 (0.39–1.73)	0.83 (0.38–1.82)
Disease duration, y (per y increase)	1.93 (0.79–4.74)		1.04 (0.93–1.16)	
H&Y, (per unit increase)	2.51 (1.22–5.17)**	2.35 (1.05–5.24)**	1.88 (0.93–3.77)*	0.91 (0.39–2.08)
UPDRS-ME, median (per unit increase)	1.03 (0.99–1.07)		1.08 (1.03–1.13)***	
UPDRS-ME, (≥21 versus < 21)	1.20 (0.55–2.61)		3.81 (1.79–8.10)***	3.37 (1.41–8.00)***
Total LED mg/die, median (per unit increase)	1.01 (0.99–1.01)		1.01 (1.01–1.02)**	1.01 (0.99–1.01)
Total LED mg/die, (≥300 versus < 300)	1.27 (0.60–2.72)		1.83 (0.87–3.85)	
Antidepressant drug use	3.15 (1.05–9.48)**	2.94 (0.91–9.47)*	2.41 (0.89–6.50)*	1.80 (0.64–5.09)
Anxiolytics drug use	2.51 (0.91–6.90)*	2.19 (0.74–6.45)	2.13 (0.79–5.77)	
CIRS total	1.21 (1.03–1.42)**		1.12 (0.96–1.32)	
CIRS Index	1.44 (1.03–2.03)**	1.24 (0.88–1.75)	1.31 (0.93–1.85)	
MCI	1.82 (0.74–4.48)	1.10 (0.40–3.01)	1.64 (0.77–3.47)	1.34 (0.59–3.03)

PD, Parkinson's disease; MBI, mild behavioral impairment; PDw, Parkinson's disease without MBI; PD-MBI ≤ 1 *y*, PD with MBI with disease duration ≤1 year; PD-MBI > 1 *y*, PD with MBI with disease duration >1 year; H&Y, Hohen and Yahr; UPDRS-ME, Unified Parkinson's Disease Rating Scale, Motor Examination; LED, levodopa equivalent dose; CIRS, Cumulative Illness Rating Scale; MCI, mild cognitive impairment. *<0.1; **<0.05; ***<0.01. Age, sex, education, and MCI were considered as *a priori* confounders.

0.74–4.48). However, only H&Y (OR 2.35, 95% CI 1.05–5.24) and antidepressant drug use (OR 2.94, 95% CI 0.91–9.47) were still significantly associated with PD-MBI after multivariate analysis. The univariate analysis regarding patients with disease duration >1 year revealed significant associations with H&Y (OR 1.88, 95% CI 0.93–3.77), UPDRS-ME (OR 1.08, 95% CI 1.03–1.13), UPDRS-ME ≥ 21 (OR 3.81, 95% CI 1.79–8.10), total LED (OR 1.01, 95% CI 1.01–1.02), and antidepressant drug use (OR 2.41, 95% CI 0.89–6.50). Again, there was no association with MCI (OR 1.64, 95%CI 0.77–3.47). At multivariate analysis, only UPDRS-ME ≥ 21 (OR 3.37, 95% CI 1.41–8.00) was still significantly associated with PD-MBI.

MCI was marginally significantly associated with MBI throughout the whole PD-MBI group only at the univariate analysis, giving an unadjusted OR of 1.75 (95% CI 0.99–3.09), which disappear after controlling for covariates (OR 1.29, 95% CI 0.68–2.42). However, when the MBI sample was stratified by disease duration (≤1 versus >1 year), MCI was not significantly associated with PD-MBI in either group (see Table 3).

DISCUSSION

This study evaluated the frequency and associated factors of MBI in PD subjects. The main results were: 1) the frequency of MBI was 84.1% throughout the whole sample of PD and 36.1% in newly diagnosed patients; 2) with reference to a specific behavioral domain, *Affective Dysregulation* and *Decreased Motivation* were in decreasing order the most frequent domains, while *Impulse Dyscontrol* was significantly more prevalent in PD-MBI with a disease duration >1 year, compared to newly diagnosed PD-MBI; 3) MBI showed a tendency to increase with disease progression, particularly for *Social Inappropriateness* and *Abnormal Perception*; 4) when compared to PDw, the presence of MBI in newly diagnosed patients was significantly associated with motor disability and antidepressant treatment, while in patients with a disease duration >1 year PD-MBI was associated with motor impairment; 5) lastly, there was no association of MCI with MBI, also after stratifying by disease duration.

There are currently no data regarding MBI in PD after stratification by disease duration: about half of the subjects with disease duration >1 year had MBI, which was also found in over one/third of newly diagnosed PD. Overall, these data indicated a cumulative prevalence of MBI in PD of 84.1% (95% CI 80.3–87.5), thus confirming previous reports in nondemented, non-PD subjects [10].

The result of the present study confirmed that MBI domains, including depression and anxiety (i.e., *Affective Dysregulation*), and apathy (i.e., *Decreased Motivation*), are very frequent in nondemented subjects with PD with and without MCI [8, 25]. Depression and anxiety have been described as significant factors, which are associated with cognitive decline [25, 26], both representing the strongest predictors of a poor quality of life in PD patients [27]. Apathy, which is often associated with lower global cognition and depression in PD [28], in subjects with PD-MCI is significantly related with executive functioning [29]. This indirectly supports the hypothesis that the presence of motivational disorders in these patients is related to frontal-striatal dysregulation [29].

When stratifying PD subjects according to disease duration (in order to evaluate differences in MBI domains), those with longer duration of disease displayed a significantly higher percentage of symptoms, which were related to irritability, agitation, and aberrant motor behavior (i.e., *Impulse Dyscontrol*) when compared to newly diagnosed PD-MBI individuals. There are few data in the literature describing the frequency of these neuropsychiatric symptoms in PD: in a Serbian study, irritability was present in 19.4% of PD patients, agitation in approximately 10.8%, and aberrant motor behavior in a very small percentage (2.5%). The authors of this study also observed that the cluster of neuropsychiatric symptoms (including agitation, irritability, disinhibition, and psychosis) was associated with a higher UPDRS-ME score [30]. Regarding the four other MBI domains (i.e., *Decreased Motivation*, *Affective Dysregulation*, *Social Inappropriateness*, and *Abnormal Perception)*, the two PD-MBI samples (newly diagnosed versus patients with a disease duration >1 year) did not show any significant difference. Overall, the above results suggest that MBI, as a surrogate measure of neuropsychiatric symptoms in PD, has poor specificity for the identification of the early phase of the disease.

MBI domains across H&Y stages in PD were also evaluated. Excluding *Affective Dysregulation* (i.e., depression, anxiety, and euphoria), very frequent and early nonmotor symptoms in PD [25], MBI showed a tendency to increase with disease progression and disability, with significant results appearing for *Social Inappropriateness* and *Abnormal Perception.* The results of the present study confirm previous findings, demonstrating that neuropsychiatric symptoms are more frequent in advanced disease, and that the main correlates/risk factors for psychosis in PD are increasing severity and duration of PD [3].

Thereafter, associated factors for MBI in PD were examined: a significant association of MBI with H&Y score and antidepressant drug use was observed in newly diagnosed subjects, while in patients with a disease duration >1 year MBI related only to UPDRS-ME. Overall, the results of the present report are in line with those previously described, confirming that NPS (including depression, anxiety, and psychosis) are associated with motor impairment [31].

Lastly, the association between MBI and MCI was evaluated. Although the latter was more prevalent overall in PD-MBI with a disease duration >1 year versus PDw and newly diagnosed PD-MBI subjects, it was significantly associated with MBI only at univariate analysis and in the whole MBI group. However, multivariate analysis did not reveal any significant association with MCI and MBI for the whole group as well as when PD-MBI was stratified according to disease duration. These results suggest that, even showing a minor association, MCI and MBI

represent very frequent non-motor features of early PD, which could have different etiologies and determinants. Nonetheless, we cannot exclude a possible lack of statistical power, type II error, when analysis was stratified for disease duration due to the small number of PDw patients included. Accordingly, future prospective research conducted in larger cohorts is required in order to clarify the association between MCI and MBI in nondemented PD patients, their risk factors, and their effects on PD prognosis.

This study has several strengths. It was designed to specifically evaluate the prevalence and correlates of MBI in a relatively large sample of PD patients, including newly diagnosed patients. Patients underwent a comprehensive cognitive and behavioral assessment using: level II MDS diagnostic criteria for PD-MCI [5] and the NPI, a widely used and validated questionnaire for cognitive impairment-related behavioral symptoms, in order to define the MBI construct [11].

However, there are some methodological issues. Firstly, since the sample was drawn from a specialized setting, a selection bias (i.e., an overestimation of MBI frequency) cannot be excluded. Secondly, the use of NPI—a caregiver-based interview—has raised the possibility of reporting bias (i.e., under- or overestimation of behavioral information). Thirdly, MBI was defined using the NPI as previously suggested [10]. This definition takes little account of those symptoms belonging to the impulse dyscontrol spectrum, which are specific of PD. Therefore, the frequency and relationships of this cluster of neuropsychiatric symptoms in individuals with PD may be underestimated in this study. Fourthly, although analyses were adjusted for major confounders, unmeasured confounding (i.e., premorbid personality traits) cannot be excluded. Fifthly, concerning the potential role of dopaminergic treatment, it was not possible to evaluate the prevalence of MBI in drug naïve PD subjects due to the small sample included. Nonetheless, LED was not associated with MBI in newly diagnosed PD, but, as expected, after univariate analysis it was associated with PD-MBI in PD patients with disease duration >1 year. However, this result disappeared after multivariate analysis. Future studies conducted on large untreated populations are required to evaluate the role of dopaminomimetics in determining MBI profiles in PD subjects. Lastly, the cross-sectional study design precludes making causal inferences about the relationship between putative associated factors and the study outcome.

In conclusion, the results of this study suggest that MBI in subjects with PD is rather frequent, occurring in over 80% of subjects and in approximately one-third of newly diagnosed patients. Behavioral impairment in PD subjects is probably linked to motor progression and disability, in the absence of a significant relationship with MCI. Due to the relative high frequency of MBI in newly diagnosed patients, its early identification, characterization and appropriate treatment should be implemented. However, the MBI construct seems to be rather unreliable for PD, due to its low specificity in characterizing the early phase of the disease. Further analysis, with the recently proposed MBI Checklist [32], conducted in large prospective cohorts will clarify the role of MBI in predicting conversion to dementia in PD.

ACKNOWLEDGMENTS

The study was partially supported by a grant from the Italian Ministry of Health to Roberto Monastero (Project for Young Researcher 2007, GR-2007-686973).

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/18-1117r1).

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