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ORIGINAL COMMUNICATION

Link between non-motor symptoms and cognitive dysfunctions in de novo, drug-naive PD patients

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Abstract Little is known about the relationship between cognitive dysfunctions and the non-motor complex in subjects with newly diagnosed untreated Parkinson's disease (PD). The aim of this study was to explore the association between non-motor symptoms (NMS) and cognitive dysfunctions in an incident cohort of de novo, drug-naive, PD patients. Sixty-six non-demented, early, untreated PD patients completed a semi-structured interview on NMS and a battery of neuropsychological tests that assess verbal memory, visuospatial abilities, and attention/executive functions. Scores were age- and education-corrected. Patients who failed at least two tests for each cognitive domain were diagnosed as having mild cognitive impairment (MCI). All but three (95.4%) PD patients complained of at least one NMS. A total of 37.8% was diagnosed with MCI. There was a relationship between sleep-NMS and cognitive dysfunctions. Specifically, both REM behavioral sleep disorders (RBD) and insomnia were associated with lower scores on several cognitive tests. Moreover, RBD was closely related to MCI. NMS and MCI are very common even in the early phase of PD, before patients are treated. Given the correlation between sleep disturbances and cognitive impairment, it is possible that sleep symptoms in PD patients might be considered as an early marker of dementia.

Keywords Parkinson's disease · Non-motor symptoms · Cognitive impairment · MCI · REM behavioral sleep disorders

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Introduction

Besides classical motor symptoms, patients with Parkinson's disease (PD) may also experience other complaints, which are commonly referred to as "non-motor symptoms" (NMS). Although NMS negatively affect the patient's quality of life and significantly contribute to institutionalization at an advanced disease stage [1, 2], they are not yet well recognized in clinical practice. NMS may already be present at disease onset and some, like hyposmia, depression, and REM behavioral sleep disorders (RBD), may occur even before motor symptoms [3, 4]. Besides NMS attributable to PD-related pathology, other NMS, such as orthostatic hypotension, nausea, psychosis or impulse control disorders may arise or worsen consequent to dopaminergic replacement during the course of disease [5, 6]. Cognitive impairment is very common in PD, even in the early stage of disease: patients who have been newly diagnosed with PD are twice as likely to develop cognitive dysfunctions [7] and between 20 and 57% of patients are affected by mild cognitive impairment (MCI) within the first 3–5 years after diagnosis [8].

Increasing evidence suggests that the cognitive deficits seen early in the course of PD might be a powerful predictor of the progression to dementia [9]. However, the rate and progression of cognitive decline is still poorly understood. Data from studies of advanced PD support a predictive association between cognitive impairment and such NMS as depression [10], apathy [11], hallucinations [12], and sleep disturbances [13]. Furthermore, dopamine replacement therapy has been reported to affect cognition in PD [14, 15].

Little is known about the link between cognitive dysfunctions and NMS in newly diagnosed untreated PD patients. Therefore, we explored the relationship between cognitive dysfunctions and NMS in an unselected cohort of newly diagnosed, drug-naive PD patients.

Patients and methods

Study design

We conducted a baseline evaluation to determine the prevalence of NMS and their correlation with cognitive dysfunctions in a cohort of newly diagnosed untreated PD patients. We clinically re-evaluated the patients 1 year later to better assess the diagnosis of PD. The study was approved by the local ethics committee and all patients provided written informed consent.

Data collection and methods

We enrolled de novo, drug-naive, patients with Parkinsonism consecutively referred to the Department of Neurological Science at the University of Naples "Federico II" between January 1, 2008 and June 30, 2009. Inclusion criteria were: presence of a parkinsonian syndrome according to United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria (bradykinesia plus one other sign, i.e., rigidity, resting tremor or postural instability) [16]; onset <2 years; age less than 70 years and no previous or current treatment with dopaminergic drugs. Additional criteria for inclusion were lack of significant cerebral lesions on MRI or CT. Exclusion criteria were: diagnosis of secondary (such as vascular and iatrogenic) or familial parkinsonism, diagnosis of atypical parkinsonism, namely, multiple systemic atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and dementia with Lewy bodies (DLB), according to current diagnostic criteria [17–20].

Detailed clinical information was obtained from the patient's history and neurological examination. Parkinsonism was diagnosed by movement-disorder specialists experienced in parkinsonian disorders and staged according to Hoehn and Yahr [21]. The Unified Parkinson's Disease Rating Scale III (UPDRS-III) was used to evaluate motor disability [22].

All patients completed the Non-Motor Symptoms Questionnaire (NMSQuest), a validated tool for detection of NMS in PD [23]. The NMSQuest consisted of nine NMS domain, each of which included 2–7 specific questions with dichotomous (yes/no) answers for a total of 30 items. Patients (and care-givers) were asked to report specific symptoms and domains as "present/absent" with reference to the month before the visit.

The patients were also administered a neuropsychological battery that consisted of evaluation of verbal episodic memory (immediate and delayed recall of the Rey Auditory Verbal Learning Test), visuospatial abilities (Constructional Apraxia Test, Benton judgment of line orientation test, the copy task of Rey's Copy Rey-Osterrieth Complex Figure Test and the Clock drawing test), attention/executive functions (Phonological fluency task, Stroop test, Trail making test, Corsi's block span, verbal span).

Scores were age- and education-adjusted, according to Italian normative data [24]. Major depression and dementia were diagnosed according DSM-IV criteria [25]. A cognitive domain (attention/execution, visuospatial, memory) was defined as "altered" when patients failed at least two tests of each domain. Non-demented patients were diagnosed with MCI if one or more (single vs. multi-domain) cognitive domain was altered, according to proposed criteria [26].

Patients underwent clinical re-evaluation 1 year later to assess the diagnosis of PD according to both exclusion and supportive criteria of the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria for PD.

Statistical analysis

Only fully completed scales were used for statistical analysis. The scores of neuropsychological tests were adjusted for age and education. Spearman's rank correlation coefficient was used to check associations: correlations were considered weak for coefficient values below 0.30; moderate for values between 0.30 and 0.59; and strong for values 0.60 or higher. Statistical comparisons between patients with or without cognitive impairment were performed with the χ^2 test or t test as appropriate, $p < 0.05$ were statistically significant. Multiple logistic regression analyses with forward stepping (likelihood ratio method) were applied to assess variables that were independent correlates of MCI. Variables attaining a significance level of $p < 0.01$ with MCI in the bivariate analysis were included in a subsequent multivariate logistic regression model, using the presence of MCI as the dependent

variable and sex, age, motor disability by mean of UPDRS III, and total number of NMS as independent variables.

Statistical analyses were done with the STATA software, version 11.0 (StataCorp LP, USA).

Results

We enrolled 66 de novo, drug-naive, patients: the demographics and clinical data are listed in Table 1. At 1-year clinical follow-up, no patient showed any clinical feature suggestive of atypical or secondary parkinsonism, all having a positive response to dopaminergic treatment, and thus PD was diagnosed in all subjects.

At least one NMS was identified in all but three patients (95.4%). The percentage of single NMS as flagged up by NMSQuest is shown in Table 2 with anxiety (56.1%), sad-blue (45.7%), acting out during dreams (37.9%), loss of interest (34.8%), and forgetfulness-memory (33.3%) being the most frequently reported (>30%).

Twenty-five patients (37.8%) fulfilled criteria for either single MCI (sMCI) or multi-domain MCI (mMCI): 12 (48%) were diagnosed with visuospatial sMCI; four (16%) with dysexecutive sMCI; eight (32%) with non-amnestic mMCI and one patient (4%) with amnestic mMCI. No one fulfilled the DSM-IV criteria for dementia.

Acting out during dreams was correlated with both immediate (Spearman's rho: -0.454; $p < 0.0001$) and delayed recall (Spearman's rho: -0.460; $p < 0.0001$) of Rey Auditory Verbal Learning Test, whereas insomnia was correlated with the Constructional Apraxia Test (Spearman's rho: -0.324; $p = 0.008$), the copy task of the Rey Copy Rey-Osterrieth Complex Figure Test (Spearman's rho: -0.351; $p = 0.004$), Stroop color-word test interference task (Spearman's rho: -0.343; $p = 0.005$); and the Benton judgment of line orientation test (Spearman's rho: -0.287; $p < 0.05$). Forgetfulness–memory was correlated with immediate recall of Rey Auditory Verbal Learning Test (Spearman's rho: -0.372; $p = 0.002$), whereas loss of interest was correlated with the Constructional Apraxia Test (Spearman's rho: -0.266; $p < 0.05$). No correlations were found for the other NMS.

Based on the proposed criteria for MCI, acting out during dreams was more frequently identified in patients with MCI (χ^2 test; $p = 0.001$), particularly with attention/executive MCI (χ^2 test; $p < 0.05$). No differences were found for the other NMS, but Mantel–Haenszel test showed an odds ratio of having MCI equal to 1.1 for a one unit increase in age ($p < 0.001$).

We run a regression model setting MCI as dependent variable and sex, age, UPDRS III, "acting out during dreams", "insomnia", "forgetfulness–memory", "loss of interest", and total number of NMS as covariates. The regression model showed a significant effect only for acting out during dreams (odds ratio 3.95; $p = 0.02$) as well as

Table 1 Demographics and clinical data of the 66 patients enrolled in the study

Total *n*: 66	
Men, *n* (%)	40 (60.6)
Age (years), mean (SD)	58.2 (8.6)
Onset (years), mean (SD)	57.7 (8.7)
UPDRS III, mean (SD)	15.1 (6.9)
Hoehn & Yahr stage, median (range)	1 (1–2)
MMSE, mean (SD)	25.7 (1.3)
Major depression (%)	0 (0)
Antidepressant drugs/sedatives (%)	0 (0)
Number of NMS per patient, mean (SD)	5.1 (3.8)

Table 2 Percentage of NMS in our cohort

NMS	Yes (%)
Dribbling	15 (22.7)
Taste/smelling	16 (24.2)
Swallowing	8 (12.2)
Vomiting	5 (7.5)
Constipation	15 (22.7)
Bowel incontinence	0 (0)
Bowel emptying incompl.	9 (13.6)
Urgency	13 (19.7)
Nocturia	10 (15.1)
Forgetfulness, memory	22 (33.3)
Loss of interest	23 (34.8)
Concentrating	15 (22.7)
Hallucinations	1 (1.5)
Delusions	0 (0)
Sad, blues	30 (45.7)
Anxiety	37 (56.1)
Sex drive	1 (1,5)
Sex difficulty	7 (10.6)
Dizzy	15 (22.7)
Falling	0 (0)
Daytime sleepiness	0 (0)
Insomnia	18 (27.3)
Intense, vivid dreams	9 (13.6)
Acting out during dreams	25 (37.9)
Restless legs	2 (3)
Pains	5 (7.5)
Weight	5 (7.5)
Swelling	8 (12.2)
Sweating	2 (3)
Diplopia	4 (6)

higher age (odds ratio 1.12; $p = 0.009$). The other covariates did not correlate with MCI and were therefore excluded from the model. The Hosmer–Lemeshow goodness-of-fit test supported our regression model as being valid.

Discussion

Many previous studies have highlighted that NMS are very common in PD, even in the early stage [27–30].

We found that nearly all patients with PD reported at least one NMS, with symptoms belonging to neuro-psychiatric (i.e., anxiety, sad-blue, loss of interest, and forgetfulness–memory) and sleep (i.e., acting out during dreams) domains being the most frequent. This result is consistent with previous data showing that neuropsychiatric features and sleep disturbances are very common early in the course of PD and might predate the onset of motor symptoms [3, 4, 31].

Few studies have evaluated cognitive dysfunctions in early untreated PD patients. The prevalence of cognitive impairment reported in newly diagnosed PD patients ranges between 18.9 and 36% [32–34]: deficits in executive functions, attention, visuospatial skills, and memory were reported, non-amnestic deficits being the most frequent. In our cohort, 25 patients fulfilled the criteria for MCI, thereby resulting in a prevalence of 37.8%, which is marginally higher than previously reported. This little discrepancy might be attributed to many factors including study design, methodology, and definition for MCI in PD.

Previous studies have identified such NMS as depression, apathy, hallucinations, and sleep disturbances [10–13] as being predictive risk factors for developing dementia in PD (PDD). These NMS have been demonstrated to be very common in PDD [35] and a recent data-driven approach using a cluster analysis to investigate the inter-relationships of these NMS reported the existence of five distinct subgroups of PDD patients, suffering respectively with hallucinations, depression, sleep disturbances, apathy-anxiety-depression and having the last cluster high scores across several non-motor domains [36]. Moreover, a study recently performed on non-demented PD patients demonstrated "DASH symptoms" (i.e., Depression, Anxiety, Sleep disturbances and Hallucinations) to be related to cognitive impairment, which in turn is associated with PDD [37]. However, this evidence came from studies conducted on treated PD patients and dopamine replacement has been demonstrated to arise or worsen such NMS as sleep disturbances and visual hallucinations [38]. Thus non-motor predictors of cognitive impairment in early untreated PD patients have never been investigated. To our knowledge, ours is the first study to look for correlations between cognitive functions and the whole NMS-complex in de novo, untreated PD patients. In our cohort, patients with sleep disturbances scored lower than patients without sleep disturbances on many cognitive tests, especially those exploring non-amnestic domains. In detail, we have found a strong correlation between "acting out during dreams" and impairment of verbal memory, whereas insomnia was associated with frontal and visuospatial dysfunctions. Moreover, patients with "acting out during dreams" were more frequently diagnosed as having MCI, particularly executive-MCI, also when adjusted for such confounding factors as gender, motor symptoms severity, other NMS belonging to cognitive or neuro-psychiatric domains and disease duration, age being the only other independent risk factor to develop cognitive impairment. In line with previously published studies, it is conceivable that "acting out during dreams" could refer to RBD phenomena [39]. In fact, in the work of Perez-Lloret et al., sleep-related items of the NMSQuest have been compared with data obtained from Parkinson's Disease Sleep Scale (PDSS), from sleep patients diary and from nocturnal actigraphy. Presence of RBD, as flagged up by item 25 of NMSQuest, was particularly related to increased nocturnal activity as measured by actigraphy. Moreover, the association we found between "acting out during dreams" and cognitive impairment coincides the previously reported close correlation between PD-related RBD and non-amnestic MCI [13, 40, 41].

Neuropathologic and neuroimaging studies revealed that PD patients with cognitive impairment and with RBD are affected by similar neural alterations in several brainstem nuclei and anomalies in their corresponding neurotransmitters (i.e., dopaminergic, cholinergic, noradrenergic, and serotonergic systems) [42, 43]. All these brainstem structures have widespread projections to the cerebral cortex and perturbations of these neural networks, particularly cholinergic deficit due to degeneration of the ascending pathways [44], may contribute to the development of cognitive impairment and dementia in PD patients, even before involvement of the neocortex. This "cascade" could partially account for the association we found between RBD and memory tasks, and supports the concept that sleep disturbances are an early risk factor for dementia.

This study represents the first attempt to investigate the whole spectrum of NMS and its correlation with cognitive functions in de novo, drug-naive PD patients. We acknowledge that it has some limitations: (1) the lack of normal controls to assess differences in NMS with PD patients and to compare results of the neuropsychological testing; however, we adjusted the results for age and education according to normative data; (2) although the NMSQuest is a validated tool to detect NMS in PD patients and sleep-related items of the NMSQuest have been further validated [39], the diagnosis of clinical RBD was based on interview and no sleep recording was obtained. However,

for RBD clinical recognition, we did not consider cases of somniloquy without limb or body movements, as reported by the care-givers; single and isolated episodes were also disregarded, while vivid dreams accounted for another item (i.e., item 24, intense vivid dreams).

Further studies are needed to better understand the mechanisms underlying the non-motor complex in PD. In particular, it is necessary to define the clinical relevance of the different MCI subtypes, their relationship with NMS and their prognostic value in terms of risk for developing dementia.

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References

1. Aarsland D, Larsen JP, Tandberg E, Laake K (2000) Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriatr Soc 48:938–942
2. Findley L, Aujla M, Bain PG et al (2003) Direct economic impact of Parkinson's disease: a research survey in the United Kingdom. Mov Disord 18:1139–1145
3. Shiba M, Bower JH, Maraganore DM et al (2000) Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. Mov Disord 15:669–677
4. Claassen DO, Josephs KA, Ahlskog JE et al (2010) REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. Neurology 75(6):494–499
5. Park A, Stacy M (2009) Non-motor symptoms in Parkinson's disease. J Neurol 256(Suppl 3):S293–S298
6. Pacchetti C, Manni R, Zangaglia R et al (2005) Relationship between hallucinations, delusions, and rapid eye movement sleep behavior disorder in Parkinson's disease. Mov Disord 20:1439–1448
7. Kehagia AA, Barker RA, Robbins WR (2010) Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. Lancet Neurol 9:1200–1213
8. Janvin CC, Larsen JP, Aarsland D, Hugdahl K (2006) Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. Mov Disord 21:1343–1349
9. Aarsland D, Andersen K, Larsen JP et al (2001) Risk of dementia in Parkinson's disease. Neurology 56:730–736
10. Santangelo G, Vitale C, Trojano L et al (2009) Relationship between depression and cognitive dysfunctions in Parkinson's disease without dementia. J Neurol 256(4):632–638
11. Pedersen KF, Alves G, Aarsland D et al (2009) Occurrence and risk factors for apathy in Parkinson disease: a 4-year prospective longitudinal study. J Neurol Neurosurg Psychiatry 80(11):1279–1282
12. Santangelo G, Trojano L, Vitale C et al (2007) A neuropsychological longitudinal study in Parkinson's patients with and without hallucinations. Mov Disord 22(16):2418–2425
13. Marion MH, Qurashi M, Marshall G, Foster O (2008) Is REM sleep behaviour disorder (RBD) a risk factor of dementia in idiopathic Parkinson's disease? J Neurol 255(2):192–196
14. Kulisevsky J, Garcia-Sanchez C, Berthier ML et al (2000) Chronic effects of dopaminergic replacement on cognitive function in Parkinson's disease: a two-year follow-up study of previously untreated patients. Mov Disord 15:613–626
15. Fera F, Nicoletti G, Cerasa A et al (2007) Dopaminergic modulation of cognitive interference after pharmacological washout in Parkinson's disease. Brain Res Bull 74:75–83
16. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) The accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinicopathological study. J Neurol Neurosurg Psychiatry 55:181–184
17. Gilman S, Wenning GK, Low PA et al (2008) Second consensus statement on the diagnosis of multiple system atrophy. Neurology 71(9):670–676
18. Litvan I, Agid Y, Calne D et al (1996) Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 47(1):1–9
19. Lang AE, Riley DE, Bergeron C (1994) Cortical-basal ganglionic degeneration. In: Calne DB (ed) Neurodegenerative diseases. WB Saunders, Philadelphia, pp 877–894
20. McKeith IG, Galasko D, Kosaka K et al (1996) Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 47(5):1113–1124
21. Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17:427–442
22. Fahn S, Elton RL, UPDRS program members (1987) Unified Parkinson's disease rating scale. In: Fahn S, Mardsen CD, Goldstein M, Calne DB (eds) Recent developments in Parkinson's disease, vol 2. Florham Park N, Macmillan Healthcare Information, pp 153–163
23. Chaudhuri KR, Martinez-Martin P, Schapira AHV et al (2006) An international multicentre pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord 21:916–923
24. Spinnler H, Tognoni G (1987) Standardizzazione e taratura italiana di test neuropsicologici. Ital J Neurol Sci 6(Suppl 8):8–20
25. American Psychiatric Association (1994) Diagnostic and statistical manual of mental health disorders, 4th edn. Washington, DC
26. Caviness JN, Driver-Dunckley E, Connor DJ et al (2007) Defining mild cognitive impairment in Parkinson's disease. Mov Disord 22(9):1272–1277
27. Chaudhuri KR, Naidu Y (2008) Early Parkinson's disease and non-motor issues. J Neurol 255(suppl 5):33–38
28. Dhawan V, Dhoat S, Williams AJ et al (2006) The range and nature of sleep dysfunction in untreated Parkinson's disease (PD). A comparative controlled clinical study using the Parkinson's disease sleep scale and selective polysomnography. J Neurol Sci 248:158–162
29. Müller B, Larsen JP, Wentzel-Larsen T et al (2011) Autonomic and sensory symptoms and signs in incident, untreated Parkinson's disease: frequent but mild. Mov Disord 26(1):65–72

30. Barone P, Antonini A, Colosimo C et al (2009) The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord 24(11):1641–1649
31. Iranzo A, Molinuevo JL, Santamaría J et al (2006) Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. Lancet Neurol 5:572–577
32. Aarsland D, Brønnick K, Larsen JP et al (2009) Cognitive impairment in incident untreated Parkinson disease: the Norwegian ParkWest study. Neurology 72(13):1121–1126
33. Foltynie T, Brayne CE, Robbins TW et al (2004) The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain 127(Pt 3):550–560
34. Muslimović D, Post B, Speelman JD, Schmand B (2005) Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 65:1239–1245
35. Aarsland D, Cummings JL, Larsen JP (2001) Neuropsychiatric differences between Parkinson's disease with dementia and Alzheimer's disease. Int J Geriatr Psychiatry 16:184–191
36. Bronnick K, Aarsland D, Larsen JP (2005) Neuropsychiatric disturbances in Parkinson's disease clusters in five groups with different prevalence of dementia. Acta Psychiatr Scand 112:201–207
37. Naismith SL, Lewis SJG (2011) "DASH" symptoms in patients with Parkinson's disease: red flags for early cognitive decline. J Clin Neurosci 18(3):352–355
38. Chaudhuri KR, Schapira AHV (2009) Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol 8:464–474
39. Perez-Lloret S, Rossi M, Cardinali DP, Merello M (2008) Validation of the sleep related items of the Non-motor Symptoms Questionnaire for Parkinson's disease (NMSQuest). Parkinsonism Relat Disord 14(8):641–645
40. Gagnon JF, Vendette M, Postuma RB et al (2009) Mild cognitive impairment in rapid eye movement sleep behavior disorder and Parkinson's disease. Ann Neurol 66:39–47
41. Vendette M, Gagnon JF, Décary A et al (2007) REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. Neurology 69(19):1843–1849
42. Emre M (2003) Dementia associated with Parkinson's disease. Lancet Neurol 2:229–237
43. Braak H, Rüb U, Jansen Steur EN et al (2005) Cognitive status correlates with neuropathologic stage in Parkinson disease. Neurology 64:1404–1410
44. Emre M (2004) Dementia in Parkinson's disease: cause and treatment. Curr Opin Neurol 17(4):399–404