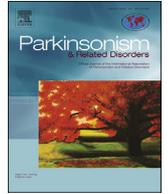




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Motor, behavioural, and cognitive correlates of fatigue in early, de novo Parkinson disease patients

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ABSTRACT

Introduction: Fatigue is one of the most common and disabling non-motor symptoms in Parkinson's disease (PD). The objective of this study was to determine prevalence and motor, behavioural, and cognitive correlates of distressing fatigue in early, de novo PD patients.

Methods: Eighty-one consecutive de novo PD patients (64% men; mean age 65.73 ± 8.26 years) underwent a comprehensive examination, including Parkinson's disease Fatigue Scale (PFS), Epworth Sleepiness Scale (ESS), Parkinson's Disease Sleep Scale (PDSS), Beck Depression Inventory (BDI), Parkinson's Anxiety Scale (PAS), and Apathy Evaluation Scale (AES). Moreover, all patients underwent a detailed neuropsychological evaluation exploring attention and working memory, executive functions, memory, visuospatial abilities and language. Score of patients with or without distressing fatigue (defined as a PFS score ≥ 8) were compared by Student's *t*-test or Pearson's chi-square test. Logistic regression analyses were performed to search for motor and non-motor features independently associated with presence of distressing fatigue.

Results: Twelve (15%) patients presented distressing fatigue. Logistic regression identified sleepiness ($p = 0.04$), "episodic anxiety" subscale of PAS ($p = 0.005$), and "cognitive apathy" subscale of AES ($p = 0.017$) as the main factors associated with distressing fatigue. No significant association was found between diagnosis of Mild Cognitive Impairment and distressing fatigue ($p = 0.745$).

Conclusion: In a sample of consecutive de novo PD patients, distressing fatigue is associated with episodic anxiety, cognitive apathy and sleepiness, but not with cognitive impairment. Our findings suggest possible shared pathogenic mechanisms underlying these non-motor symptoms and foster development of early combined therapeutic approaches.

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1. Introduction

Fatigue has been recently defined as a significantly diminished energy level or increased perception of effort that are disproportionate to attempted activities [1]. In Parkinson's disease (PD), fatigue is considered one of the most common and disabling non-motor symptoms, which may manifest even during premotor stages of PD [2], and leads to strong negative impact on patients' quality of life [3,4].

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Estimates about prevalence of fatigue in PD are quite variable, ranging between 33% and 58% [5]. The variability of prevalence estimates across studies may be attributed both to lack of a consensus definition and classification, and to different self-report scales employed to rate severity of symptoms [5]. Indeed, a comparison between two widely used scales, the Fatigue Severity Scale (FSS; [e-1]) and the Parkinson Fatigue Scale (PFS; [e-2]), It showed that they likely assess partially different aspects of fatigue, and are differentially associated with motor and non-motor symptoms [6].

In levodopa-treated PD patients the relationship between fatigue and motor symptoms is controversial. Indeed, several studies showed a correlation between disease severity, as assessed by

Hoehn and Yahr (HY) stage [e-3] or by the Unified Parkinson's Disease Rating Scale (UPDRS) [e-4], and fatigue [4,7–10], whereas others did not [11]. These discrepancies may be partially explained by the mediating effect of depression ([12]; see also [13]). Actually, fatigue may be associated with other common non-motor symptoms of PD, such as depression [4,7–12], anxiety [8,10,11], apathy [10,11,14], and sleep disorders [4,8], but not always at statistically significant levels (for a review, see Ref. [3]). Moreover, only a few studies supported significant associations between cognitive impairment and increased perception of fatigue [7,15], but these studies either assessed selected domains of cognitive functioning (e.g. executive functions) or employed only screening tests (e.g. Mini Mental State Examination), and also in these respects contrasting results have been reported [16].

The few available studies addressing fatigue in de novo PD patients provided quite variable findings. Prevalence of fatigue in these patients has been reported to range from 13.7% to 58% [17–22]. In such studies fatigue was consistently associated with depression, whereas a mixed pattern of associations was reported between fatigue and disease severity, sleep disorders, daytime somnolence or cognitive impairment. Three studies took into account apathy in de novo PD patients and did not observe an independent association of apathy with fatigue in multiple regression analyses [18,21,22], but they did not investigate single domains of apathy, as it has been done in levodopa-treated PD patients [11]. Moreover, none of these studies considered the potential association of fatigue with anxiety. Last, only Kluger et al. [21] investigated the association of distressing fatigue with impairments in selected cognitive domains, reporting a significant correlation with visuospatial impairments, but even in this case the authors employed a limited neuropsychological battery, not examining executive functions, attention and working memory, visuospatial abilities, and language in depth.

Based on the available literature, no strong conclusions can be drawn about prevalence and clinical correlates of fatigue in de novo PD patients.

In the present study we aimed to assess fatigue in a consecutive sample of de novo patients, and to systematically search for motor, behavioural, and cognitive correlates of distressing fatigue. For these purposes we used only validated scales assessing motor and non-motor symptoms, and when appropriate, we examined association of fatigue with single subscale scores rather than with total scores only. Moreover, to clarify the relationships between cognitive impairment and fatigue we used a comprehensive neuropsychological battery including two tests for each relevant cognitive domain, consistent with level II criteria for the diagnosis of mild cognitive impairment (PD-MCI) proposed by the Movement Disorder Society (MDS) Task Force [e-5].

2. Methods

2.1. Participants

For the present study, we screened all outpatients consecutively admitted for their first visit to the First Division of Neurology of the University of Campania "Luigi Vanvitelli" (Naples, Italy) between April 2015 and February 2017. To be enrolled in the study, patients had to fulfil the following inclusion criteria: 1) diagnosis of PD according to the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria [e-6]; 2) disease duration < 2 years from first appearance of PD symptoms; 3) modified HY stage \leq 2.5; 4) no current or previous exposure to anti-PD medications. Exclusion criteria were: 1) dementia associated with PD (PD-D) according to consensus criteria [e-7]; 2) global cognitive impairment, as evidenced by age- and education-adjusted MoCA score lower than or

equal to the Italian cut-off score (15.5) [e-8], to avoid any bias in responding to self-report scales; 3) diagnosis of atypical or secondary parkinsonism, hereditary forms of parkinsonism, history of psychosis; 4) history of relevant head injury or cerebrovascular diseases and major medical diseases (e.g., neoplasms, clinically relevant renal or hepatic insufficiency).

All participants underwent a 3-T brain Magnetic Resonance Imaging (MRI); white matter hyperintensity (WMH) load was calculated using MIPAV software [e-9].

All procedures were approved and supervised by the local Ethical Committee, in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

2.2. Assessment of PD severity

Severity of parkinsonian symptoms was rated using the motor portion of the UPDRS [e-4] and HY staging system [e-3]. Degree of asymmetry of motor dysfunction was determined using the formula suggested by Foster and colleagues [e-10]. The classification of PD subtypes was defined according to Jankovic et al. [e-11].

2.3. Assessment of fatigue and behavioural variables

Fatigue was assessed by PFS, and a cut-off score of ≥ 8 was used to identify the presence of distressing fatigue [e-2]. Sleep disorders and daytime sleepiness were evaluated by the Parkinson's Disease Sleep Scale (PDSS) [e-12], and Epworth Sleepiness Scale (ESS) [e-13]. Depressive and anxious symptoms were rated by the Beck Depression Inventory (BDI; [e-14,e-15]), and the self-rated version of Parkinson Anxiety Scale (PAS; [e-16,e-17]), respectively. The PAS consists of three subscales: one pertaining to persisting anxiety (PAS - Persistent), one to episodic anxiety (PAS - Episodic), and one to avoidance behaviour (PAS - Avoidance). Finally, apathy was evaluated by the Apathy Evaluation Scale [e-18,e-19], assessing four apathy domains: cognitive (AES - Cognitive), behavioural (AES - Behavioural), emotional (AES - Emotional), and other (AES - other).

2.4. Neuropsychological assessment

All PD patients underwent a comprehensive neuropsychological battery including two tests for each of the following five cognitive domains: *attention and working memory* (Trail Making Test-A and digit span backward), *memory* (prose recall test and Rey's Auditory Verbal Learning Test - delayed recall), *executive functions* (Modified Card Sorting Test - number of achieved categories and letter fluency task), *visuospatial abilities* (copying drawings and Judgment of Line Orientation test), and *language* (nouns denomination task and verbs denomination task) (for references, see [Supplementary Table 1](#)). Therefore, the present neuropsychological battery allowed discriminating between PD-MCI single domain (i.e., abnormalities on two tests within a single cognitive domain) and PD-MCI multiple domains (i.e., abnormalities on at least one test in two or more cognitive domains) [e-5]. Impairment on neuropsychological tests was defined as performance at least 1.5 standard deviation below the Italian norms (for references, see [Supplementary Table 1](#)).

2.5. Statistical analysis

All data were tested for normality, and values between -1 and $+1$ for asymmetry and kurtosis were considered acceptable. The comparisons between PD patients with and without distressing fatigue were performed by Student's *t*-test for continuous variables, and by Pearson's chi-square test (χ^2) for categorical

variables, with a significance level of $p < 0.05$. A logistic regression analysis (forward conditional method) was performed entering variables associated with presence of distressing fatigue in univariate analysis ($p < 0.05$), using subscale scores rather than total scores when applicable. Finally, a logistic regression analysis was run with presence of PD-MCI as the independent variable and distressing fatigue as outcome. All analyses were performed using IBM Statistical Package for Social Science (SPSS) version 20, with p value < 0.05 considered statistically significant.

3. Results

Asymmetry and kurtosis were acceptable for all continuous variables. A total of 81 de novo PD patients were enrolled: 12 (15%) had distressing fatigue.

Descriptive statistics are reported in Table 1. Mean PFS score was significantly higher in patients with distressing fatigue compared with those without. Clinical data, neuropsychological scores, and MRI findings did not significantly differ between the two groups. Among the demographic variables considered for the study, only education was significantly higher for patients with distressing fatigue.

In contrast, patients with distressing fatigue had more severe sleepiness (ESS), and depressive (BDI), anxious (PAS - Total), and apathetic (AES - Total) symptoms in comparison with patients without distressing fatigue. In particular, the two groups significantly differed on three subscales for anxiety (PAS – Persistent, PAS – Episodic, and PAS - Avoidance), and three subscales for apathy domain (AES- Cognitive, AES – Emotional, and AES – Other).

The nine variables associated with fatigue in univariate analysis were entered into the logistic regression analysis as independent variables with distressing fatigue as the dependent variable. The model identified the ESS, PAS – Episodic, and AES – Cognitive as the independent factors significantly associated with presence of distressing fatigue (Table 2).

The model was able to accurately distinguish patients with or without distressing fatigue in 90.1% of the cases.

Neuropsychological scores compatible with diagnosis of PD-MCI multiple domain were observed in 30 of 81 (37%) de novo PD patients, of which 4 of 12 (33%) patients with distressing fatigue, and 26 of 69 (38%) patients without distressing fatigue. Logistic regression did not show a significant association between diagnosis of PD-MCI and distressing fatigue ($\chi^2(1) = 0.106$, $p = 0.745$; Odds ratio = 1.238; 95% Confidence Interval = 0.339–4.525).

4. Discussion

We observed distressing fatigue in a relatively small proportion of our sample of de novo PD patients, and that it was significantly associated with sleepiness, episodic anxiety, and cognitive apathy, but not with neuropsychological scores or cognitive decline.

The relatively low prevalence of distressing fatigue in the present study was similar to that reported in the ADAGIO study (13.7%) including data of 1105 drug naïve PD patients [20], but was lower to that reported in most studies on de novo PD patients [17–19,21,22]. This discrepancy might be explained by the fact that we used the same self-rating scale (i.e., PFS) and cut-off values specifically validated for PD as that employed in the ADAGIO study, whereas the other studies adopted the FSS. It is interesting to underline that a similar difference in prevalence of distressing fatigue has been observed in previous studies adopting PFS or FSS in treated PD patients [4,10,11,18]. Therefore, the relatively low prevalence of distressing fatigue revealed by the PFS might be explained by the specific focus of this scale on the subjective perception of fatigue, rather than on performance fatigability, in line with the distinction

recently proposed by Kluger et al. [23]. Indeed, these authors suggested that fatigue, in terms of subjective sensation of exhaustion, should be distinguished from fatigability, an objective decrement in performance induced by continued activity and closely related to aging or disease severity [23]. Accordingly, our PD patients with distressing fatigue did not differ from non-fatigued patients with respect to demographic aspects, clinical data or cognitive performance, suggesting that fatigue complaints may be driven more by altered subjective perception than by ageing [7], motor symptoms [5,23] or cognitive decline [18].

In the present study, de novo PD patients with distressing fatigue showed higher sleepiness, depression, anxiety, and apathy scores, demonstrating that the presence of distressing fatigue, at least when assessed by PFS, was associated with a higher burden of non-motor symptoms [6]. The logistic regression analysis, however, demonstrated that sleepiness, cognitive apathy, and episodic anxiety were the only independent factors with the highest explanatory contribution for distressing fatigue.

The positive association between distressing fatigue and daytime sleepiness is consistent with studies on treated PD patients where fatigue was assessed by means of the PFS scale [6], but is at odds with previous studies on early, untreated PD patients [18–22] in which fatigue was assessed by FSS. These discrepancies may be explained by some overlap between items included in both PFS and ESS, whereas FSS seems to be less influenced by the confounding effect of sleepiness on fatigue [6]. However, we believe that the relationships between daytime sleepiness and fatigue are worth being investigated since PD-related neuronal loss and Lewy body accumulation involve brain regions, such as basal forebrain, brainstem, thalamus, and hypothalamus [24,25], which are thought to be associated with both sleep-wake regulation and fatigue [26].

The association between cognitive apathy and fatigue is a novel finding in de novo PD patients, but a similar association has been already described in levodopa-treated PD patients [10,11]. Cognitive apathy is defined as indifference, decrease in goal-directed thought content, and generalized loss of interest [e-18], ascribed to dysfunction of the fronto-striatal connections [27]. Indeed, growing neuroimaging evidence has demonstrated a close association between fatigue and changes in local metabolic activity and connectivity in prefrontal regions and basal ganglia [26,28]. Taken together, these findings would support the existence of common pathophysiological mechanisms involved in fatigue and in cognitive aspects of apathy, but further studies are needed to corroborate this hypothesis.

Another intriguing result is the association between episodic anxiety and fatigue. Episodic anxiety is described by the following symptoms: intense fear, shortness of breath, fast heart beating not related to physical effort, and fear of losing control [e-16]. A similar association has been reported in previous studies on levodopa-treated PD patients [10,16], and even in general population [29], but here we confirmed that episodic anxiety is associated with subjective perception of fatigue independently from other non-motor symptoms in early, untreated PD patients too. The nature of this association should be addressed by further studies, as it is plausible that episodic anxiety may contribute to subjective perception of fatigue, but it is also plausible that fatigue may contribute to development of anxiety or that both non-motor symptoms are related to underlying shared mechanisms.

As stated above, we did not observe any association between distressing fatigue and scores on single neuropsychological tests. This finding seems to be in contrast with a recent study in which fatigue, assessed by FSS, was associated with visuospatial impairments, detected by means of Silhouettes and Cube subtests from the Visual Object and Space Perception battery (e-20) in a large sample of early PD patients [21]. The divergences between the two

Table 1
Characteristics of patients with and without distressing fatigue, and summary of univariate analysis.

Variables	Total sample size (n = 81)	PFS ≥ 8 (n = 12)	PFS < 8 (n = 69)	p
<i>Demographics</i>				
Age	65.7 ± 8.2	62.7 ± 10.1	66.2 ± 7.8	0.17
Education, years	11.1 ± 4.8	13.9 ± 4.0	10.7 ± 4.8	0.03
Male sex	52 (64%)	6 (50%)	46 (67%)	0.26
<i>Clinical features</i>				
Age at onset	64.4 ± 8.2	61.2 ± 9.8	64.9 ± 7.8	0.15
Disease duration, months	15.6 ± 7.3	17.1 ± 6.5	15.4 ± 7.5	0.44
UPDRS III	22.2 ± 9.2	23.8 ± 9.2	22 ± 9.31	0.53
Tremor score	1.9 ± 2.3	2.5 ± 3.6	1.8 ± 2.1	0.33
Rigidity score	5.4 ± 3.9	5.8 ± 4.9	5.4 ± 3.8	0.74
Bradykinesia score	11.1 ± 5.9	10.4 ± 4.6	11.2 ± 6.1	0.65
Gait/Postural stability score	1.8 ± 2.5	3.5 ± 5.2	1.5 ± 1.5	0.23
Hoehn and Yahr stage	1.7 ± 0.4	1.7 ± 0.4	1.7 ± 0.4	0.94
Degree of asymmetry	0.09 ± 1.2	-0.07 ± 1.2	0.11 ± 1.2	0.60
Side of onset:				0.29
Left	36 (44%)	7 (58%)	29 (42%)	
Right	45 (56%)	5 (42%)	40 (58%)	
PD subtype classification:				0.58
Tremor-D	31 (38%)	3 (25%)	28 (41%)	
PIGD-D	38 (47%)	7 (58%)	31 (45%)	
Not determined	12 (15%)	2 (17%)	10 (14%)	
WMH	395.3 ± 558.9	283.2 ± 601.3	414.6 ± 554.0	0.47
<i>Neuropsychological measures</i>				
Attention/Working memory				
TMT-A	49.2 ± 30.5	46.0 ± 28.6	49.8 ± 31.0	0.69
Digit Span backward	3.1 ± .96	3.4 ± .669	3.1 ± 1	0.32
Memory				
Prose recall test	8.6 ± 4.0	10.2 ± 4.21	8.4 ± 3.9	0.15
RAVLT-delayed recall	6.6 ± 3.2	6.9 ± 3.14	6.5 ± 3.2	0.73
Executive functions				
MCST-achieved categories	3.7 ± 1.9	4.1 ± 1.9	3.6 ± 1.9	0.47
Letter fluency task	27.6 ± 11.5	28.1 ± 6.9	27.5 ± 12.2	0.89
Visuospatial functions				
Drawing copy	11.6 ± 2.3	12.2 ± 2	11.5 ± 2.3	0.37
Judgment of Line Orientation	18.9 ± 5.7	17.3 ± 6.0	19.2 ± 5.7	0.30
Language				
Nouns denomination task	9.7 ± .6	9.8 ± .5	9.7 ± .6	0.64
Verbs denomination task	8.6 ± 1.3	9.2 ± .9	8.5 ± 1.3	0.07
<i>Fatigue measure</i>				
PFS	15.39 ± 5.74	12.14 ± 2.1	4.62 ± 1.9	<0.0001
<i>Behavioural assessment</i>				
ESS	4.4 ± 3.2	7.1 ± 4.5	4 ± 2.6	0.001
PDSS	117.9 ± 21.6	116.4 ± 11.2	118.2 ± 23	0.79
BDI	8.8 ± 9.2	15.8 ± 13.1	7.6 ± 7.8	0.004
PAS - Total	9.7 ± 8.1	18 ± 11.7	8.3 ± 6.3	<0.0001
PAS - Persistent	6.5 ± 4.4	10.4 ± 5.4	5.8 ± 3.9	0.0008
PAS - Episodic	2.1 ± 2.8	4.9 ± 4.4	1.5 ± 2.2	<0.0001
PAS - Avoidance	1.2 ± 2.4	2.8 ± 3.9	0.93 ± 1.9	0.01
AES - Total	33.8 ± 8.8	42 ± 7.1	32.4 ± 8.4	<0.0001
AES - Cognitive	15.3 ± 4.7	19.5 ± 3.3	14.6 ± 4.6	0.001
AES - Behavioural	8.5 ± 2.7	9.9 ± 3.1	8.2 ± 2.5	0.05
AES - Emotional	3.8 ± 1.4	4.7 ± 1.1	3.7 ± 1.4	0.02
AES - Other	6 ± 1.9	7.7 ± 2	5.7 ± 1.8	0.0008

Note. Significant differences at $p < 0.05$ are shown in bold; values are means ± standard deviation for continue variables or counts and percentages for categorical variables; p values are derived from comparisons between patients with or without distressing fatigue analysed by Student t -test for continue variables or by Pearson's chi-square test (χ^2) for categorical variables; PFS, Parkinson's disease Fatigue Scale; UPDRS, Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; Tremor-D, Tremor-Dominant form; PIGD-D, Postural Instability Gait Disorder-Dominant; WMH, white matter hyperintensity; TMT, Trail Making Test; RAVLT, Rey's Auditory Verbal Learning Test; MCST (Nelson's modification), Modified Card Sorting Test; ESS, Epworth Sleepiness Scale; PDSS, Parkinson's Disease Sleep Scale; BDI, Beck Depression Inventory; PAS, Parkinson's Anxiety Scale; AES, Apathy Evaluation Scale.

studies might be explained by the differences in cognitive measures and in sample sizes. However, it is also possible that the divergences can be partially accounted for by the different scales adopted for assessing fatigue. Indeed, motor symptoms may play a higher role in FSS than in PFS [6], and it has been recently shown that severity of motor symptoms might be correlated with mild

cognitive deficits even at early stages of disease [30].

As we used a comprehensive neuropsychological battery fulfilling criteria for a level II diagnosis of PD-MCI [e-5], we could also directly investigate the relationship between presence of clinically relevant cognitive impairments and distressing fatigue. We detected PD-MCI in about one third of our sample, with a similar

Table 2

Logistic regression analysis (forward conditional method) of variables associated with the presence of distressing fatigue.

Variable	B (SE)	OR	95% CI	p
Constant	−9.051 (2.561)	0.000		<0.0001
ESS	0.371 (0.180)	1.449	1.018–2.064	0.040
PAS - Episodic	0.438 (0.155)	1.549	1.144–2.098	0.005
AES - Cognitive	0.243 (0.102)	1.275	1.045–1.556	0.017

Note. Model $\chi^2(3) = 26.347$, $p < 0.0001$, $R^2(\text{Nagelkerke}) = 0.489$; B, Beta; SE, Standard Error; OR, Odds ratio; CI, Confidence Interval; ESS, Epworth Sleepiness Scale; PAS, Parkinson's Anxiety Scale; AES, Apathy Evaluation Scale.

proportion of PD-MCI multiple domain among patients with or without distressing fatigue. The present prevalence rate is consistent with that reported in other cohorts of newly diagnosed PD patients [31]. The lack of association between PD-MCI and distressing fatigue, as assessed by PFS, would thus reinforce the idea that subjective feeling of effort are not explained by cognitive impairments in de novo PD patients. Moreover, it is noteworthy that the two groups of patients did not differ for WMH burden, which was found associated with fatigue in other pathological conditions [32].

The present study has several limitations mainly related to its cross-sectional and monocentric design, to the relatively small sample size, and to the low number of patients with distressing fatigue; it is also worth underlining that the two groups of patients differed in their educational attainment, although education did not result to be independently associated with presence of self-reported distressing fatigue. All these features might limit generalizability of our findings, but it is important to underline that we recruited a consecutive sample that could be considered as a relatively random representative of the untreated, early PD population.

Another limit might be related to the choice of the scale for assessing fatigue. Friedman et al. (e-21) reviewed available assessment instruments for fatigue and suggested that Multidimensional Fatigue Inventory (MFI; [e-22]) could allow assessing several specific fatigue domains, including mental fatigue [14]. However, we chose to employ PFS [e-2], that is the only tool, developed specifically for PD, allowing discrimination of patients with or without fatigue with a pre-determined risk of false positives and false negatives. Further studies addressing the relationships between behavioural and cognitive changes and fatigue in PD should consider exploring the cognitive, behavioural, and motor factors associated with different dimensions of fatigue (e.g., mental fatigue, physical fatigue) by means of specific assessment instruments (e.g., MFI). Moreover, to minimize the potential drawbacks related to misleading items encompassed in fatigue scales, future studies should rely on case definition criteria for diagnosis of Parkinson's disease-related fatigue, as those recently developed by Kluger et al. [23].

In conclusion, our findings demonstrate that cognitive apathy, episodic anxiety and, possibly, sleepiness, are commonly associated with distressing fatigue in de novo PD patients. Moreover, by using validated diagnostic criteria suggested by the MDS [e-5], we revealed, for the first time, no association between the presence of MCI and distressing fatigue.

Although the pathophysiology of these non-motor symptoms remains still largely unknown, plausible similarities in pathogenic mechanisms could explain their association in the early stages of PD. Thus, our study suggests that fatigue and associated non-motor symptoms should be better characterized to identify those patients who will most likely benefit from early combined therapeutic approaches.

Conflicts of interest

None.

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Authors' role

Mattia Siciliano contributed to the conception and design of the study, the acquisition, analysis and interpretation of data, drafted and revised critically the article for important intellectual content.

Luigi Trojano contributed to the conception and design of the study, the acquisition, analysis and interpretation of data, drafted and revised critically the article for important intellectual content.

Rosa De Micco contributed to the design of the study, the acquisition, analysis and interpretation of data, drafted and revised critically the article for important intellectual content.

Antonio Russo, Antonio De Mase and Federica Garramone contributed to the conception and design of the study, the acquisition and interpretation of data.

Gioacchino Tedeschi contributed to the design of the study, the acquisition, analysis and interpretation of data, drafted and revised critically the article for important intellectual content.

Alessandro Tessitore contributed to the conception and design of the study, the acquisition, analysis and interpretation of data, drafted and revised critically the article for important intellectual content.

All authors approved the final version of the article.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.parkreldis.2017.10.004>.

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