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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.

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].

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

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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 ≤ 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 l.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

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