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Is fatigue associated with cognitive dysfunction in early Parkinson's disease?

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ABSTRACT

Introduction: Fatigue is a common and disabling symptom which may be seen in early Parkinson's disease (PD). Our understanding of the phenomenology and etiology of fatigue in PD is limited. The objective of this study was to determine whether fatigue was related to cognition in early PD patients.
Methods: The study is part of the Norwegian ParkWest project, a population-based cohort study, comprising 184 de novo, drug-naïve patients with PD. PD was diagnosed according to the Gelb criteria. Fatigue was assessed by the Fatigue Severity Scale (FSS). Cognition was assessed by a battery of tests evaluating functions in the domains of verbal memory, processing speed, executive function and visuospatial abilities.
Results: 107 of the cohort had moderate to severe fatigue (FSS $\geq$ 4). In univariate correlation analyses high fatigue score was correlated to disease severity, presence of sleep problems, depressive symptoms, apathy, reduced processing speed and reduced visuospatial abilities. In a multiple regression analysis only disease severity (measured by the UPDRS part 3), sleep problems, depressive symptoms and reduced visuospatial abilities contributed to the model.
Conclusion: Fatigue is associated with visuospatial function in early PD patients. Further studies are needed to determine the pathophysiologic relevance of this association.

1. Introduction

Fatigue is a common and highly disabling symptom in Parkinson's disease (PD), affecting approximately half of all PD patients [1]. Despite its impact, we currently do not understand the etiology of fatigue in PD and have no effective therapies [2]. Fatigue complaints do not appear to be a simple consequence of motor symptoms as they are often seen in early PD [3], may precede motor symptoms, do not correlate with objective motor fatigability and do not reliably respond to dopaminergic or surgical therapies [2,4–8]. Regarding potential secondary causes of fatigue in PD, fatigue is consistently associated with depression [9]. However, these symptoms frequently exist independently and fatigue may persist following successful treatment of depression [10]. Fatigue in PD is also inconsistently associated with sleep disorders or sleep quality and is dissociable from daytime somnolence [11–14]. There is preliminary evidence that fatigue may be associated with cognitive impairment, particularly frontal executive dysfunction, but these studies were small and utilized only a single measure of cognitive function [15,16]. The objective of the current study was to evaluate the potential association of multiple domains of cognition with fatigue in a large cohort of non-depressed patients with early PD. Advantages of studying fatigue in this population include minimizing the potential confounds of depression, medications and high symptom burden and capturing early cognitive changes [17].

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2. Materials and methods

2.1. Participants

The present study is part of the Norwegian ParkWest project, a population based cohort study of incident PD, aiming to assess the development of motor and non-motor symptoms over time. A total of 212 patients with newly diagnosed, untreated PD were recruited from four counties in Western and Southern Norway between November 1, 2004, and August 31, 2006 [e−1]. During follow-up, reassessment of the diagnosis led to the exclusion of 20 patients, leaving 192 patients for the present analyses. One further patient was excluded due to missing fatigue severity scale (FSS) data and seven additional patients were excluded because of Mongomery and Aasberg Depression Rating Scale (MADRS) scores over 14, indicating significant depressive symptoms [18]. The remaining 184 patients were included in the baseline analyses. All included patients fulfilled the Gelb criteria for the diagnosis of PD [e−2].

The study was approved by the Regional Committee for Medical Research Ethics, Western Norway. All participants signed written informed consent.

2.2. Evaluation

A semi-structured interview was performed by a trained member of the study group to obtain information concerning demographic data and clinical history.

2.3. Parkinson disease severity and staging

Disease severity was measured by the motor subscale of the Unified Parkinson Disease Rating Scale (UPDRS) [e−3] and disease staging by the Hoehn and Yahr scale [e−4].

2.4. Measures of fatigue and potential confounds

Fatigue was measured using the Fatigue Severity Scale (FSS) [e−5], which is recommended for use in PD by a Movement Disorders Society task force [e−6]. Sleep problems were measured using the Parkinson's Disease Sleep Scale (PDSS) [e−7]. The severity of depressive symptoms was measured by the MADRS [e−8], and apathy was measured by the Starkstein Apathy Scale (SAS) [e−9].

2.5. Neuropsychological testing

The Mini-Mental State Examination (MMSE) was used to assess global cognitive functioning [e−10]. Four additional domains of cognitive function were chosen: processing speed, verbal memory, executive function and visuospatial abilities. Tests were chosen to assess each domain (Table 1). These particular tests of cognitive function were chosen because they were considered to be independent of motor function and cover aspects of cognition known to be affected in PD. As many different non-motor symptoms are assessed in the study, the number of tests within each field had to be limited. For each test z-scores were computed and a composite z-score within each domain was calculated.

2.6. Statistical analysis

All data analyses were performed SPSS 21 (IBM Corp. Armonk, NY), Comparison of means between the group of patients with high versus low FSS score were analyzed using Student's t-test for independent samples or Fisher's exact test where appropriate. Correlation analyses, corrected for age, gender and years of education, are given by Pearson's correlation coefficient.

The relationship between fatigue as measured by the FSS and demographic and clinical variables were analyzed with multiple linear regression for continuous outcomes and logistic regression analysis for binary outcomes. The independent variables included were age, gender, years of education, UPDRS motor score, PDSS, MADRS, SAS, processing speed, executive function, verbal memory and visuospatial abilities. The regression coefficients that are given are standardized β and partial correlation coefficients. All p-values are two-tailed and p-values <0.05 were considered statistically significant.

3. Results

3.1. Participant demographic and disease characteristics

184 participants were enrolled (mean age 67.9 (9.3); 114 males). Mean fatigue severity score was 4.4 (SD 1.6) 107 of the cohort had moderate to severe fatigue (FSS $\geq$ 4). See Table 2 for a summary of demographic and disease characteristics.

3.2. Relationship of fatigue with neuropsychological testing

When comparing participants with low (FSS $<$ 4) and moderate to high (FSS $\geq$ 4) score, patients with moderate or high FSS score were older and had more advanced disease, measured by both UPDRS motor and Hoehn and Yahr scores. The presence of depressive symptoms was low in both groups and statistically, but not clinically, significantly higher in the high fatigue group. Patients with moderate to high fatigue also reported more sleep problems and apathy. Global cognitive function, as assessed by the MMSE, was slightly lower in the group with FSS $\geq$ 4. A logistic regression model with FSS $<$ 4 vs FSS $\geq$ 4 as the dependent variable and age, gender, UPDRS motor score, PDSS, MADRS score, SAS and the four computed variables assessing verbal memory, processing speed, executive function and visuospatial abilities as independent variables showed a significant effect for visuospatial abilities (odds ratio 0.673, 95%CI: 0.504−0.898, p = 0.007) and executive function

Table 1
Neuropsychological domains and tests.

Cognitive domain	Tests	Ability measured
Processing speed	Stroop Word reading + Stroop Color naming [41]	To read as many color names as possible in 45 s, then to name as many color dots as possible in 45 s.
Verbal memory	California Verbal Learning Test - II total 1.-5th trial + CVLT-II Short delay free recall + CVLT-II Long delay free recall [42]	To recall a list of 16 words being read aloud to the subject 5 consecutive times, then following an interference list and lastly after a 20 min interval.
Executive function	Semantic verbal fluency [43] + Stroop Interference [41]	To name as many words as possible within a given category in 60 s, then to name as many words printed in colored ink as possible in 45 s.
Visuospatial abilities	Silhouettes and Cube subtests from the Visual Object and Space Perception battery [44]	To recognize as many of 30 silhouette pictures as possible, then to analyse as many of 10 cube pictures as possible.

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