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Association between autonomic dysfunction and fatigue in Parkinson disease

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Abstract

Objective—Fatigue is a disabling non-motor symptom in Parkinson disease (PD). We investigated the relationship between autonomic dysfunction and fatigue in PD while accounting for possible confounding factors.

Methods—29 subjects with PD (8F/21M; mean age 61.6 ± 5.9 ; mean disease duration 4.8 ± 3.0 years), underwent clinical assessment and completed several non-motor symptom questionnaires, including a modified version of the Mayo Clinic Composite Autonomic Symptom Score (COMPASS) scale and the Fatigue Severity Scale (FSS).

Results—The mean modified COMPASS was 21.6 ± 14.2 (range 1.7–44.2) and the mean FSS score was 3.3 ± 1.6 (range 1.0–6.7). There was a significant bivariate relationship between the modified COMPASS and FSS scores ($R = 0.69$, $P < 0.0001$). Stepwise regression analysis was used to assess the specificity of the association between the modified COMPASS and FSS scores while accounting for possible confounder effects from other variables that were significantly associated with autonomic dysfunction. Results showed that the modified COMPASS ($R^2 = 0.52$, $F = 28.4$,

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$P<0.0001$) was highly associated with fatigue, followed by ESS ($R^2=0.13$, $F=8.4$, $P=0.008$) but no other co-variables. Post-hoc analysis exploring the association between the different modified COMPASS autonomic sub-domain scores and FSS scores found significant regressor effects for the orthostatic intolerance ($R^2=0.45$, $F=21.2$, $P<0.0001$) and secretomotor sub-domains ($R^2=0.09$, $F=4.8$, $P=0.04$) but not for other autonomic sub-domains.

Conclusions—Autonomic dysfunction, in particular orthostatic intolerance, is highly associated with fatigue in PD.

Keywords

Parkinson disease; Fatigue; Autonomic dysfunction

1. Introduction

Fatigue is a common non-motor symptom of Parkinson disease (PD), with a reported prevalence of up to 58% of patients [1]. Over 50% of PD patients consider fatigue to be one of the most debilitating symptoms of the disease [2], yet the causal mechanisms underlying fatigue are poorly understood.

We recently reported that the best clinical predictor of fatigue in PD was the Movement Disorders Society-revised Unified PD Rating Scale (MDS-UPDRS) non-motor experiences of daily living (nM-EDL) subscore [3]. The MDS-UPDRS nM-EDL subscore assesses several non-motor symptoms of PD, including fatigue, sleep, neuropsychiatric and autonomic symptoms. However, it remains unclear which of the various non-motor symptoms of the MDS-UPDRS nM-EDL are more specifically associated with fatigue. The clinical overlap between fatigue, mood and sleep problems are well recognized, but fatigue has also been associated with cardiovascular sympathetic denervation in PD [4] and with orthostatic hypotension in other patient populations [5,6], suggesting a link between autonomic dysfunction and fatigue. We therefore wanted to further explore the relationship between autonomic symptoms and fatigue in PD.

2. Methods

2.1 Subjects and Assessments

This was a cross-sectional analysis involving 29 PD subjects (21M/8F) originally recruited for a PET imaging study on non-motor symptoms in PD (ClinicalTrials.gov Identifier: NCT01565473). For that study, subjects had to meet UK PD Society Brain Bank Research Center clinical diagnostic criteria for PD¹⁶ and complete [¹¹C]dihydrotetrabenazine (DTBZ) vesicular monoamine transporter type 2 (VMAT2) PET imaging. Subjects with dementia (defined as MMSE < 24), subjects taking cholinesterase inhibitors or pure anticholinergic drugs, and subjects with diabetes mellitus were not eligible.

The 29 subjects in this study all underwent striatal DTBZ PET imaging and completed the Fatigue Severity Scale (FSS)[7] as well as the Mayo Clinic Composite Autonomic Symptom Score (COMPASS 31)[8]. The FSS contains 9 items and is self-administered. Items are rated on a 7-point Likert scale and the average score of all 9 items gives a total FSS score. The

COMPASS 31 is a 31-item self-administered questionnaire of autonomic symptoms, split into 6 domains (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor). The maximum raw score is 75 and the maximum weighted score is 100. Our subjects did not consistently answer item 31 due to the textual lay-out of the questionnaire form used in this study, so we calculated a modified COMPASS score that includes only the first 30 items and report the raw score (maximum 72). Other clinical assessments included the MDS-UPDRS (scored the morning after stopping dopaminergic medications overnight), modified Hoehn-Yahr (H-Y), Montreal Cognitive Assessment (MoCA), Epworth Sleepiness Scale (ESS), Insomnia Severity Index (ISI), Beck Depression Inventory (BDI), and the Marin Apathy Evaluation Scale (AES). Three subjects were not on any PD medications, 2 were on dopamine agonists only, 14 were on levodopa only and 10 were on both levodopa and agonist therapy.

2.2 Standard protocol approvals, registrations, and patient consents

All subjects gave written informed consent. The study was approved by the Institutional Review Boards of the University of Michigan.

2.3 Imaging Techniques and Data Analysis

The [^{11}C]DTBZ PET imaging protocol has been described previously [9]. The bivariate relationship between the modified COMPASS, striatal DTBZ binding and other clinical assessments was evaluated using Pearson correlation coefficients. Stepwise regression analysis using the FSS as the outcome parameter and significant variables of the bivariate analysis was performed. Finally, post-hoc stepwise regression using the FSS as outcome parameter and the modified COMPASS domain subscores was performed. All analyses were conducted using SAS version 9.3, SAS Institute, Cary, NC.

3. Results

Table 1 shows the demographic and clinical variables for the cohort. The mean modified COMPASS was 21.6 ± 14.2 (range 1.7-44.2).

Table 2 shows the correlations between the modified COMPASS and the clinical and PET assessments. After Holm-Bonferroni correction, there were not only significant correlations between the modified COMPASS and the FSS but also with age, ISI, ESS and the somatic subscale scores of the BDI (Table 2).

In order to further evaluate the specificity of the association between the modified COMPASS and the FSS scores, we performed a multivariate analysis using a stepwise regression model with the FSS as the outcome parameter, the modified COMPASS score as regressor and the significant variables from table 2 as co-regressors. This model demonstrated a significant regressor effect for the modified COMPASS ($R^2=0.52$, $F=28.4$, $P<0.0001$), followed by ESS ($R^2=0.13$, $F=8.4$, $P=0.008$) with a significant overall model ($R^2=0.72$, $F_{3,24}=15.1$, $P<0.0001$).

In a post-hoc analysis, we explored associations between the different modified COMPASS autonomic sub-domain scores (orthostatic intolerance, vasomotor, secretomotor,

gastrointestinal, bladder and pupillomotor functions) and the FSS. We found a significant overall model $R^2 = 0.54$, $F_{3,24} = 11.1$, $P < 0.0001$ and significant regressor effects for the orthostatic intolerance ($R^2 = 0.45$, $F = 21.2$, $P < 0.0001$) and secretomotor scores ($R^2 = 0.09$, $F = 4.8$, $P = 0.04$) but not for the other autonomic sub-domain scores.

4. Discussion

We found a robust correlation between autonomic symptoms (as measured by the modified COMPASS) and fatigue in PD (as measured by the FSS). In a stepwise regression model that controlled for confounding variables such as sleep and mood, the modified COMPASS had the strongest association with fatigue. Excessive daytime sleepiness, as measured by the ESS, was also associated with fatigue, though not surprising given that up to 50% of PD patients with fatigue report excessive sleepiness [1].

In a previous paper, we found that the MDS-UPDRS nM-EDL subscore, which includes questions on autonomic function (urinary problems, constipation, lightheadedness with standing) as well as cognitive, mood and behavioral symptoms was a strong clinical predictor of fatigue[3]. However, few studies in the literature have specifically examined the relationship between fatigue and autonomic symptoms in PD. Nakamura and colleagues reported a significant correlation between cardiac sympathetic denervation (using the heart-to-mediastinal [H/M] uptake ratio of ^{123}I -metaiodobenzylguanidine [MIBG]) and fatigue in 33 PD patients[4]. Zuo and colleagues evaluated 102 PD patients and split them into fatigued and non-fatigued groups based on a cutoff of 4 on the FSS[10]. The fatigued patients had significantly higher Scale for Outcomes in Parkinson's disease for Autonomic Symptoms (SCOPA-AUTO) scores, suggesting worsened autonomic dysfunction. Our results not only confirm their findings, but extend them by demonstrating that certain sub-domains of autonomic function (orthostatic intolerance and secretomotor function) are significantly associated with fatigue.

The COMPASS 31 is 31-item scale that rates autonomic dysfunction[8]. It was recently reduced and refined from the validated 84-item COMPASS and provides both raw and weighted scores. Our subjects did not consistently complete the last item of the questionnaire, so we calculated a modified COMPASS score from the first 30 items. The last item evaluates amount of improvement/decline in the most troublesome visual symptom, such as focusing or light sensitivity. Because these types of symptoms are not prominent complaints in the PD population, we feel that our modified COMPASS results are valid.

The orthostatic intolerance (frequency, severity and change over the past year in orthostatic symptoms) and secretomotor (sweating, dry eyes and dry mouth) domains were significantly associated with fatigue in our analysis. The association of secretomotor function with fatigue has not been previously reported to our knowledge, and a similar study in non-PD fatigued subjects with comparison to age-matched healthy controls will be needed to validate the PD specificity of these results. Both orthostatic intolerance and secretomotor domains, however, involve the peripheral sympathetic nervous system and support its role in the underlying pathophysiology of fatigue. Orthostatic intolerance has previously been linked to fatigue in PD and other patient populations. In the same paper that demonstrated a correlation between

cardiac MIBG uptake and fatigue in PD, Nakamura and colleagues also reported that a greater proportion of fatigued PD patients had orthostatic hypotension than non-fatigued PD patients, and that fatigued PD patients had a higher pressor response to norepinephrine infusion[4]. This response reflects denervation super sensitivity in peripheral vessels and supposedly predicts orthostatic hypotension. The COMPASS 31, and in particular the orthostatic intolerance sub-domain, strongly correlates with the FSS in multiple sclerosis patients[6]. Orthostatic hypotension is also present in patients with chronic fatigue syndrome, and fatigue in that condition may improve with treatment of the hypotension [5].

This was a cross-sectional sample of a predominantly male, relatively early PD cohort with mild to moderate disease severity, so the results may not have generalized applicability. Other factors affecting both autonomic function and fatigue, such as polypharmacy and reduced mobility, could also be playing a role rather than intrinsic autonomic nervous system changes. Nevertheless, there is a growing literature linking fatigue with autonomic dysfunction, especially orthostatic intolerance. Future research should examine the relationship between more objective measures of autonomic function and fatigue in PD as well as explore whether treating orthostatic hypotension can improve fatigue. There is also an ongoing movement to subtype PD on the basis of non-motor features. Autonomic features seem to occur more commonly in non-tremor-dominant subtypes of PD, at least early on in the disease [11]. Therefore, further study is needed to determine whether fatigue is another non-motor symptom that commonly goes along with the non-tremor-dominant PD motor subtype.

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Highlights

- We investigated the relationship between autonomic dysfunction and fatigue in PD.
- Autonomic dysfunction (measured by the modified COMPASS) was highly associated with fatigue, followed by sleepiness (measured by the Epworth Sleepiness Scale).
- Of the autonomic sub-domains of the modified COMPASS, orthostatic intolerance had the strongest association with fatigue, followed by the secretomotor sub-domain.

Table 1
Baseline characteristics of the cohort (n=29)

	Mean $\pm$ SD
Age (years)	61.6 $\pm$ 5.9
Gender	21M/8F
Disease duration (years)	4.8 $\pm$ 3.0
Levodopa Equivalent Dose (mg)	580.0 $\pm$ 351.9
Modified Hoehn-Yahr stage	2.3 $\pm$ 0.4
Fatigue Severity Scale	3.3 $\pm$ 1.6
Montreal Cognitive Assessment	26.6 $\pm$ 1.9
MDS-UPDRS	
Motor	29.2 $\pm$ 12.1
Modified COMPASS	21.6 $\pm$ 14.2
Epworth Sleepiness Scale	8.2 $\pm$ 4.3
Insomnia Severity Index	7.6 $\pm$ 6.8
Beck Depression Inventory	
Total score	8.3 $\pm$ 6.8
Affective subscale	1.9 $\pm$ 2.5
Somatic subscale	6.4 $\pm$ 4.9
Apathy Evaluation Scale	24.1 $\pm$ 6.9
Striatal DTBZ PET	1.96 $\pm$ 0.28

MDS-UPDRS = Movement Disorders Society-revised Unified PD Rating Scale Modified COMPASS = the first 30 items of the Composite
Autonomic Symptom Score DTBZ = [^{11}C] dihydrotetrabenazine

Table 2
Pearson correlations between the modified COMPASS, clinical and PET assessments

	Modified COMPASS	
	r	p-value
Levodopa Equivalent Dose (mg)	0.17	0.40
Fatigue Severity Scale	0.69	<0.0001 *
Montreal Cognitive Assessment	0.024	0.90
Age	-0.56	0.0022 *
Duration of motor disease	0.12	0.53
MDS-UPDRS		
Motor	0.26	0.18
Epworth Sleepiness Scale	0.54	0.003 *
Insomnia Severity Index	0.77	<0.0001 *
Beck Depression Inventory		
Total score	0.34	0.08
Affective subscale	-0.015	0.94
Somatic subscale	0.50	0.009 *
Apathy Evaluation Scale	0.16	0.4
Striatal DTBZ PET	-0.20	0.3

MDS-UPDRS = Movement Disorders Society-revised Unified PD Rating Scale COMPASS = Composite Autonomic Symptom Score DTBZ = [¹¹C] dihydrotetrabenazine

* Significant after Holm-Bonferroni correction for multiple testing.