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Autonomic dysfunction and fatigue in Parkinson's disease: a report from Kenya

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Abstract

Fatigue is a common non-motor symptom of Parkinson's disease (PD) that significantly impacts patient quality of life. However, the underlying mechanisms of fatigue in PD remain unclear. The present study aims to investigate the involvement of autonomic dysfunction, specifically cardiac sympathetic denervation, in the pathogenesis of fatigue in PD. Thirty-two Caucasian PD patients with a well-defined follow-up period and no depression or cognitive impairment were included in the study. Fatigue was evaluated using the Parkinson Fatigue Scale-16 (PFS-16), and autonomic function was assessed through MIBG scintigraphy and comprehensive autonomic function tests (AFTs). The results showed that fatigue is a prevalent issue in PD, with a prevalence of 48.15%, and is positively correlated with disease duration and reduced parasympathetic activity as measured by the deep breathing test. However, no significant correlations were found between fatigue and other AFT parameters related to sympathetic innervation or noradrenergic pathway dysfunction as measured by MIBG myocardial scintigraphy. The findings suggest that fatigue in PD has a multifaceted pathophysiology and cannot be solely attributed to dysfunction in a single neurotransmitter system. The study highlights the importance of recognizing fatigue as a significant aspect of PD and further investigating its underlying mechanisms to improve patient care and management.

Keywords: Parkinson's disease, Autonomic dysfunction, fatigue

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Introduction

Non-motor symptoms are becoming increasingly recognized as significant aspects of Parkinson's disease (PD). Among these symptoms, fatigue is a prevalent issue in both early and advanced stages of the disease (1). Previous studies have shown that the prevalence of fatigue in Parkinson's patients ranges from 33 to 58%. There is ongoing debate as to whether the severity of the disease is related to fatigue, and the underlying mechanisms of fatigue in Parkinson's disease remain unclear (2). Though some neuroimaging studies have suggested that striatal dopaminergic uptake may predict fatigue in mild Parkinson's patients, other studies have shown no significant difference in dopamine transporter uptake between fatigued and non-fatigued patients (3). In support of the potential role of non-dopaminergic pathways in fatigue generation, a recent PET study found decreased serotoninergic transporter uptake in fatigued patients compared to non-fatigued ones in the basal ganglia and associated limbic structures (4).

The primary focus of inquiry pertains to the potential involvement of autonomic dysfunction, specifically cardiac sympathetic denervation, in the pathogenesis of fatigue observed in PD (5). Previous research conducted by Nakamura and colleagues has established a direct connection between fatigue and cardiovascular sympathetic dysfunction, as determined by the 123Imetaiodobenzylguanidine (MIBG) heart-to-mediastinal uptake ratio. These findings suggest that certain PD phenotypes, characterized by greater involvement of the autonomic nervous system (ANS), may be more susceptible to experiencing fatigue (6).

Our investigation aims to assess the prevalence of fatigue amongst a group of Caucasian PD patients who possess a well-

defined follow-up period and are not affected by depression or cognitive impairment. Furthermore, we seek to examine the extent to which fatigue is related to disease duration and severity in this cohort. By leveraging results obtained via MIBG scintigraphy and comprehensive autonomic function tests (AFTs), we will also investigate for any significant correlation between autonomic dysfunction and fatigue in PD patients (7).

Material and methods

The present study involved the inclusion of 32 patients diagnosed with Parkinson's disease in accordance with the UK Parkinson's Disease Society Brain Bank criteria. The patients were recruited from the Parkinson's Disease Centre and their clinical records were used to obtain data on age, gender, and disease duration. At the time of inclusion, the patients were evaluated for disease severity using the Unified Parkinson's Disease Rating Scale (UPDRS) part III, which focused on motor examination, and the Hoehn and Yahr staging (H&Y) in the ON condition. Additionally, cognitive function was measured using the Mini-Mental State Examination (MMSE) and depressive symptoms were quantified using the Beck Depression Inventory (BDI). In order to be included in the study, patients were required to meet specific criteria, including having an MMSE score greater than 24 and a BDI score less than 8, as well as not being affected by heart failure, lung disease, or diabetes, or taking medication that influenced the autonomic nervous system. All recruited patients were receiving standard anti-parkinsonian therapy.

Fatigue was evaluated via employment of the Parkinson Fatigue Scale-16 (PFS-16), a self-reported questionnaire consisting of 16 items. Each item is rated on a scale from 1 to 5, encompassing the responses "strongly disagree," "disagree," "neither agree nor disagree," "agree," and "strongly agree," respectively. The PFS-16 mean score is computed as the average of all scores for each item. Distressing fatigue is defined as a PFS-16 mean score of ≥ 3.3.

Patients underwent the comprehensive assessment of AFTs in the morning between 8.00 and 10.00 a.m. prior to receiving their daily therapy, utilizing established methods as previously detailed. The AFTs included continuous non-invasive measurement of systolic and diastolic blood pressure (SBP, DBP) by an infrared photoplethysmograph (Finometer, Model-1 TNO Biomedical Instr., Amsterdam), ECG monitoring by standard means using Click EGC USB 3-12 Leads—ET Medical Devices SpA, and continuous monitoring of respiration rate with a nasal thermocouple respiration flow sensor (SleepSense®). The outcomes of each AFT were automatically obtained using Light-SNV software®.

All participants underwent a series of tests including the head-up tilt test (HUTT), Valsalva maneuver, deep breathing, and hand grip test. Prior to the HUTT, the participant rested in a supine position for 30 minutes, after which they were tilted up 65° for 10 minutes while changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured and expressed as Δ from the pre-HUTT baseline values. The Valsalva maneuver was performed by blowing through a mouthpiece attached to a manometer and maintaining a pressure of 40 mmHg for 15 seconds. Measures of autonomic activity were calculated, including the HR ratio between phases II and IV (VR) and the BP variations during phases II and IV (overshoot—OV). During the deep breathing test, the sinus arrhythmia was evaluated by calculating the difference between the maximum HR during inspiration and minimum HR during expiration (IE) in ten respiratory cycles. During the handgrip test, participants exerted 30% of maximal voluntary contraction of the dominant hand for 5 minutes on a dynamometer while BP was measured in the non-exercising arm at rest and at the third minute of the test.

The present study examined the function of both the sympathetic and parasympathetic nervous systems in a group of patients with Parkinson's disease. Measures of sympathetic function included blood pressure responses to head-up tilt test, Valsalva maneuvers, and handgrip test, while parasympathetic function was assessed through heart rate variation during deep breathing and with the use of the Valsalva ratio. In addition, all patients underwent cardiac-MIBG scintigraphy using a standard approach, with precautions taken to ensure that the results were not influenced by medication use or other factors known to affect MIBG uptake.

SPSS software was used for statistical analyses, and significant differences were defined as $p < 0.05$. Data were presented as mean and standard deviation, and correlation analyses were performed using Spearman's test.

Results

In this study, a total of 32 patients were included and their clinical characteristics can be seen in Table 1. The mean UPDRS-III score, which was assessed while the patients were in an ON condition, was found to be 27.12 ± 11.04 (mean, SD). This score was found to have a significant correlation with the duration of the disease ($R = 0.46$, $p < 0.001$). The mean PFS-16 score was 2.73 ± 1.03, and patients who scored ≥ 3.3 were classified as fatigued, resulting in the division of the patients into two groups - fatigued (n=18) and non-fatigued (n=14). Of the PD subjects The fatigued patients had a longer disease duration of 49.77 ± 29.82 months and a higher mean UPDRS-III score of 28.84 ± 13.45 compared to non-fatigued patients. However, no significant differences were observed in disease duration ($p = 0.17$), UPDRS-III ($p = 0.42$), MMSE ($p = 0,18$), and age ($p = 0.55$) between the two groups.

It is noted that there was a notable correlation between disease duration and PFS-16 score for the entire patient group ($R = 0.32$, $p = 0.011$). However, there was no significant correlation between fatigue score and either age ($R = 0.17$, $p = 0.35$) or UPDRS-III average score ($R = 0.05$, $p = 0.87$).

Additionally, the PFS-16 score had a negative correlation with the deep breathing test I-E, which measures the difference between maximum heart rate during inhalation and minimum heart rate during exhalation ($R = -0.46$, $p = 0.003$). Furthermore, there was a significant difference in deep breathing I-E between fatigued and non-fatigued patients ($p = 0.004$, as shown in Figure 1).

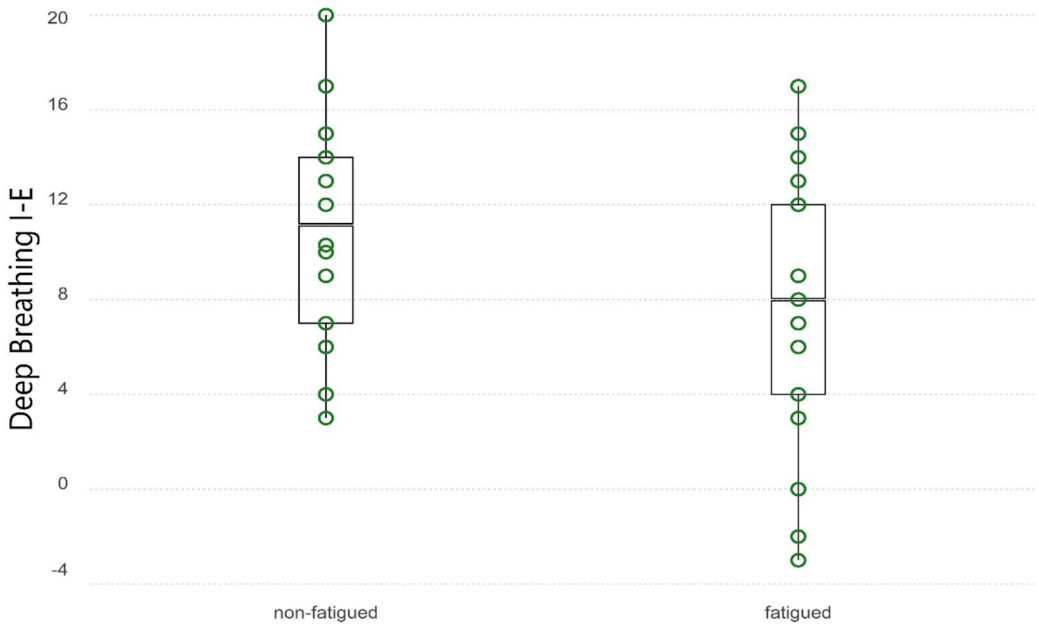

Figure1. deep breathing I-E test in fatigued and non-fatigued patients

Out of the 32 patients, eight met the criteria for orthostatic hypotension. However, all subjects underwent MIBG uptake analysis, and it was found that 16 patients with PD had decreased uptake (with 8 of those patients experiencing significant fatigue and 8 not experiencing fatigue). Fatigue did not have a correlation with the MIBG H/M ratios of both early and delayed images, but lower MIBG H/M ratios were found in fatigued subjects. A post hoc analysis was performed, dividing the group into milder and more severe disease, but no significant differences in PFS-16 score or MIBG H/M ratios were observed. However, subjects with more severe disease had lower MIBG H/M ratios.

Discussion

This study investigated the relationship between fatigue, which was measured using PFS-16 scoring, and ANS, which was assessed through MIBG scintigraphy and AFTs, in patients with Parkinson's disease. Our findings demonstrate that fatigue is a common symptom among individuals with Parkinson's disease, with a prevalence of 48.15%. Furthermore, our data indicate a positive correlation between PFS-16 score and disease duration. We also observed a significant positive correlation between PFS-16 score and deep breathing test score, but no significant correlations between fatigue and other AFTs parameters related to sympathetic innervation (8, 9).

The deep breathing test is a reliable way to examine the parasympathetic cardiovascular axis and can reveal reduced parasympathetic activity, which is a common feature of acute and chronic fatigue (10). In our study of PD patients, the deep breathing test was the most common indicator of neuro-vegetative impairment, although there was some overlap between fatigued and non-fatigued patients. It is difficult to determine how parasympathetic dysfunction affects physical performance, but studies are underway to investigate the relationship between the autonomic nervous system and performance during exercise and rehabilitation (11). Interestingly, we found no correlation between fatigue and noradrenergic pathway dysfunction as measured by MIBG myocardial scintigraphy (12, 13). This suggests that the noradrenergic pathway does not play a major role in fatigue. Additionally, our population did not often exhibit symptomatic orthostatic hypotension.

The absence of a relationship between fatigue and MIBG contrasts with a prior study that linked autonomic dysfunction and fatigue in PD (14, 15). The earlier study found that fatigued PD patients had greater pressor responses in both norepinephrine and dobutamine infusion tests, as well as a lower MIBG H/M ratio (both early and delayed images). The authors speculated that cardiac sympathetic denervation led to inadequate cardiac contractility during exercise, resulting in shortness of breath or fatigue in PD patients (11, 16). The differences in patient characteristics between our study and the Japanese study may account for this disagreement (17). The Japanese study had a higher incidence of orthostatic hypotension among their PD patients, and at least six non-fatigued patients had MIBG ratios of 2.5 or more, which is uncommon in Caucasian populations (18).

Several observations support the dopaminergic hypothesis as a potential cause of fatigue in Parkinson's disease (19, 20). For instance, the ELLDOPA trial revealed a significant worsening of fatigue in the placebo group compared to the L-dopa groups. Additionally, a double-blind, placebo-controlled

study indicated that L-dopa treatment could partially alleviate physical fatigue in PD, and more recent investigations suggest that dopamine agonists may also play a role in mitigating fatigue (21, 22). However, this study has some limitations, including a relatively small sample size of patients with advanced disease, which made it challenging to identify significant differences between fatigued and non-fatigued groups (15). Moreover, disease duration may have influenced the results.

In summary, our study's main findings allow us to propose the following hypotheses. Firstly, the absence of a connection between MIBG H/M ratios and PFS-16 score provides evidence that neither sympathetic innervation nor noradrenergic mechanisms play a significant role in PD-related fatigue. Secondly, the correlation between fatigue and disease duration suggests that dopaminergic denervation may contribute to fatigue in PD patients (although the association between disease severity and fatigue score was weak). Lastly, the link between PFS-score and deep breathing test supports the notion that fatigue in PD has a multifaceted pathophysiology and cannot be solely attributed to dysfunction in a single neurotransmitter system.

Declarations

Funding

We do not have any financial support for this study.

Conflict of interest

The authors have no conflicts of interest to disclose.

Availability of data

The datasets analyzed during the current study are available upon request with no restriction.

Code availability

Not applicable

Consent for publication

This manuscript has been approved for publication by all authors.

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