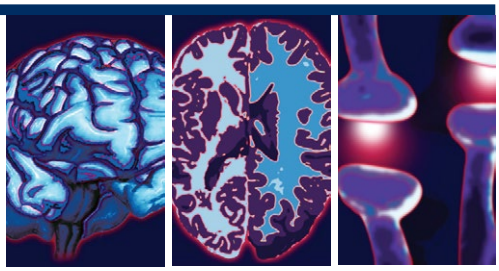

Clinical Factors Associated with Fatigue in Parkinson's Disease

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Abstract

Background

Fatigue is one of the common non-motor symptoms in patients with Parkinson's disease (PD). This study aimed to explore the associated clinical factors on fatigue in PD.

Methods

This prospective study enrolled 141 adult idiopathic PD patients. Fatigue were classified in accordance with Fatigue Severity Scale (FSS) with a threshold of means score ≥5.

Results

Fatigue occurred in 66 (66/141, 46.8%) patients. FSS total score is positively correlated with age, diseases duration, levodopa equivalent dose (mg), Unified Parkinson's Disease Rating Scale (UPDRS) I, UPDRS II, UPDRS III, total UPDRS, and Geriatric Depression Scale but negatively correlated with education years, striatal dopamine transporter uptake ratios, and Mini-Mental State Examination. Total mean UPDRS score remained independently associated with the presence of fatigue. Any increase one point in mean URDRS score one point will increase 6.2% of presence of fatigue rate. The area under the ROC curve for the mean URDRS score was 0.859 and the cut-*o*ff value to predict presence of fatigue was 41.5

Conclusions

Higher mean URDRS score (>41.5), which may imply an increase in the severity of PD, was associated with higher risk of fatigue. Preventing fatigue and develop developing therapeutic

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strategies in the high-risk PD group is an important safety issue and highly relevant for their quality of life.

Keywords

Fatigue, Idiopathic Parkinson's disease, Risk factors

Introduction

Parkinson disease (PD) is the second most common neurodegenerative disease, after Alzheimer disease, and results in both motor and non-motor dysfunction [1]. The main motor symptoms of PD are muscular rigidity, rest tremor, akinesia, and postural/ balance disorders. Fatigue, the non-motor symptom, is one of most debilitate symptoms of PD and accounted for more than half in these patients though the prevalence of fatigue is also 18-25% in general population [2-4]. For research on fatigue in PD, one recent study showed that the prevalence of fatigue in PD is different in different areas [5]. The prevalence seems to be lower in Northern Europe than in Western Europe [6-8], the prevalence is 37% in USA, 72.5% in Canada [9], and ranges from 27.1% to 64.8% in Asia [10,11].

For PD with fatigue, the most commonly used instruments included Fatigue Severity Scale (FSS), followed by Parkinson's Fatigue Scale, Multidimensional Fatigue Inventory, and Functional Assessment of Chronic Illness Therapy-Fatigue [12-15]. Fatigue is highly prevalent and has a negative impact on quality of life and performance in a variety of disorders. The 9-item FSS is one of the most commonly used self-report questionnaires to measure fatigue, but has only been validated in small sample-sized studies and in single disorders [16], and it was an adequate tool to assessment the association fatigue in PD [16].

The relationship between PD-related fatigue and depression remained controversial [17,18]. Although one study demonstrated fatigue and depression are associated in both PD and geriatric patients [17], the other Japanese study was not [18]. Furthermore, another study showed fatigue and daytime sleepiness was related with cognitive impairment [19].

Fatigue was a critical non-motor symptom and might affect quality of life and health care cost for PD patients. This hospital-based study aimed to provide accurate information on the severity and duration of PD, daily dose of anti-Parkinsonian agents, and functional outcome. Besides, we further confer to analyze the clinical features and scientific clinical scores to determine potential clinical factors associated with fatigue in patients with PD. Given the importance of fatigue to disease burden, determining the risk factors associated with presence of fatigue should receive preventive intervention is warranted.

Materials and Methods

■ Study design

This single-center prospective, case-control study was conducted at Chang Gung Memorial Hospital-Kaohsiung, a tertiary medical center and the main referral hospital serving a population of 3 million in southern Taiwan.

Inclusion and exclusion criteria

This study evaluated 180 patients with a definitive diagnosis of idiopathic PD [17] who were followed-up at the Neurology Out-Patient Clinic for more than six months after titration of their daily anti-Parkinsonian agents to a steady dose in accordance with their clinical symptoms. Patients were excluded if they had (1) newly diagnosed PD or were on follow-up for less than six months since their daily dose of anti-Parkinsonian agents was still under adjustment; and (2) other pyramidal signs, impaired consciousness or motor weakness or any neurological sign not related to PD. Thus, only 141 patients were finally included in the analysis. The hospital's Institutional Review Committees on Human Research approved the study protocol and all of the patients or their relatives provided written informed consent.

■ Clinical data collection

An experienced neurology nurse specialist (K.-Y. C), who was blinded to the patients' clinical and biochemical data was trained to measure these functional scores at the time of enrollment. The clinical features recorded were age at disease onset (or age at the time of the first reported symptom attributable to the disease), years of education, disease duration (time from onset until follow-up) and other underlying diseases other than PD. In this study, exercise habituation was defined as

patients engaged in physical activity of at least 30 minutes of moderate-intensity physical exercise more than twice per week. These patients underwent cranial magnetic resonance imaging (MRI) scan, 99mTc-TRODAT-1 SPECT/CT, and Region of Interest Analysis in accordance with previously published methods [20].

The FSS consists of 9 statements for evaluating the impact of the fatigue [12,21,22]. The subject was asked to rate the severity of the fatigue symptoms experienced in the last week using a numeric scale ranging from 1 (strong disagreement with the statement) to 7 (strong agreement with the statement). The total score has been calculated by averaging the scores of each item. In this study, a threshold of FSS means score ≥5 were defined as severe fatigue in accordance with the earlier studies with slightly modification [21,22]. The severity of PD was graded according to the scores of the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr staging [23,24]. The daily dose of anti-Parkinsonian agents was converted into the equivalent dose of levodopa [25]. In fluctuating patients, the UPDRS and Hoehn and Yahr scales were administered in off situation (8-10 hours after patients stopped their usual anti-Parkinsonian treatment) to evaluate the possible influence of disease severity. The Mini-Mental State Examination (MMSE) was used to assess general intellectual function [26], and the ability to perform digit forward span was assessed. Executive functions were evaluated using the digit backward span and design fluency test [27]. Cognitive outcomes were assessed by using the Clinical Dementia Rating (CDR) scale, since it scores the functional capacity of participants independently of physical disability [28]. The Geriatric Depression Scale (GDS) [29,30] consists of 30 questions; each with 2 possible answers scored either 0 or 1, and gives a maximum score of 30 and severities of depression were classified as follows: no depression (GDS<10) and depression (GDS ≥ 10)

Three separate statistical analyses were performed. First, the effects of individual variables, including sex, underlying diseases, levodopa equivalent dose, and mean functional score on depression were analyzed by Univariate logistic regression. Second, significant variables (p<0.05) found to be associated with a presence of fatigue (FSS means score ≥ 5) were entered into a forward stepwise logistic regression analysis model, which allowed for simultaneous control of multiple factors. Third, the receiver operating characteristic (ROC) curves were generated for significant predictor variables for presence of fatigue. All statistical analyses were conducted using the SAS software package, version 9.1 (2002, SAS Statistical Institute, Cary, North Carolina).

Results

The demographic features of 141 idiopathic PD cases were 65 males and 76 females **(Table 1)**.The mean age was 67.0 ± 10.9 years old. Their education years were 6.9 ± 5.0 years. The diseases duration was 4.2 ± 2.3 years. The body mass index was 23.9 ± 10.9 kg/m^2. The fatigue severity scale total score was 4.1 ± 1.9. The mean MMSE and GDS were 22.8 ± 6.2 and 13.9 ± 6.1, respectively. Meanwhile, the motor examination, activity of daily living, mention, behavior and mood and total of UPDRS were 30.8 ± 17.9, 14.1 ± 10.1, 4.7 ± 3.5 and 49.7 ± 30.1, respectively. The levodopa equivalent dose was 398.4 ± 291.7 mg. The striatal dopamine transporter uptake ratios were 1.4 ± 0.2. Twenty-two patients had exercise habituation while the other 119 had not. The underlying comorbidities of patients were listed in **Table 1**. The descriptive characteristics of each item for internal consistency of the FSS questionnaire in PD were listed in **Table 2**.

Correlation analysis of the effects of clinical factors on FSS total score

Correlation analysis was used to test the influence of clinical factors on FSS total score **(Table 3)**. FSS total score is positively correlated with age, diseases duration, levodopa equivalent dose (mg), UPDRS I, UPDRS II, UPDRS III, total UPDRS, and GDS but negatively correlated with education years, striatal dopamine transporter uptake ratios, and MMSE. The statistical results (correlation coefficient, *P*-value) were as follows: Age (r=0.263, P=0.002), education years (r=-0.287, P=0.001), disease duration (r=0.445, P<0.0001), levodopa equivalent dose (mg) (r=0.562, P<0.0001), striatal dopamine transporter uptake ratios (r=-0.358, P<0.001), MMSE (r=-0.420, P<0.0001), UPDRS I (r=0.739, P<0.0001), UPDRS II (r=0.740, P<0.0001), UPDRS III (r=0.724, P<0.0001), and total UPDRS (r=0.747, P<0.0001), and GDS (r=0.718, P<0.0001).

■ Clinical factors associated with fatigue

The clinical factors associated with fatigue were listed in **Table 4**. Statistical analysis of the baseline clinical manifestations and functional

Table 1: Characteristics of patients with Parkinson's disease.

	***n*=141**
Age, years	67.0 ± 10.9
Sex (men/women)	65/76
Education, years	6.9 ± 5.0
Fatigue severity scale total score	4.1 ± 1.9
Body mass index (kg/m^2)	23.9 ± 10.9
Disease duration, years	4.2 ± 2.3
Levodopa equivalent dose (mg)	398.4 ± 291.7
Striatal dopamine transporter uptake ratios	1.4 ± 0.2
Mini-Mental State Examination	22.8 ± 6.2
Unified Parkinson's Disease Rating Scale (UPDRS)[α]	49.7 ± 30.1
Clinical Dementia Rating (CDR)	
CDR=0	63
CDR=0.5	58
CDR=1	12
CDR=2	8
UPDRS I [β]	4.7 ± 3.5
UPDRS II [γ]	14.1 ± 10.1
UPDRS III [δ]	30.8 ± 17.9
Geriatric depression scale	13.9 ± 6.1
Exercise habituation	22
Underlying conditions	
Hypertension	40
Diabetes mellitus	59
Hyperlipidemia	25
Chronic obstructive pulmonary diseases	1
Chronic neuropathic pain	7
Knee osteoarthritis	9

†= Figures are mean+/-SD or number (%)

α="Total UPDRS" score is the combined sum of parts I, II, and III. Theoretical minimum and maximum values are 0 and 176, respectively (176 represents the worst disability and 0 no disability)

β= I. Mentation, behavior, and mood. Theoretical minimum and maximum values are 0 and 16, respectively. (16 represents the worst disability and 0 no disability)

γ= II. Activities of daily living (ADL). Theoretical minimum and maximum values are 0 and 52, respectively. (52 represents the worst disability and 0 no disability)

δ= III. Motor examination. Theoretical minimum and maximum values are 0 and 108, respectively. (108 represents the worst disability and 0 no disability)

Table 2: Descriptive characteristics of each item for internal consistency of the Fatigue severity scale questionnaire in Parkinson's disease patients.

Statement of each item[§]	**mean score (*n*=141)**
My motivation is lower when I am fatigued.	5.6 ± 2.1 [†]
Exercise brings on my fatigue.	5.1 ± 2.2
I am easily fatigued.	4.7 ± 2.3
Fatigue interferes with my physical functioning.	4.3 ± 2.3
Fatigue causes frequent problems for me.	3.9 ± 2.2
My fatigue prevents sustained physical functioning.	3.9 ± 2.2
Fatigue interferes with carrying out certain duties and responsibilities.	3.7 ± 2.1
Fatigue is among my three most disabling symptoms.	2.7 ± 1.6
Fatigue interferes with my work, family, or social life.	2.8 ± 1.9

†= Figures are mean+/-SD or number (%)

§=Patients are instructed to choose a number from 1 to 7 that indicates their degree of agreement with each statement where 1 indicates strongly disagrees and 7 strongly agree.

score findings between fatigue and non-fatigue groups revealed that PD duration (p<0.0001), education years (P=0.019), mean MMSE (P=0.001), mean levodopa equivalent dose (P<0.001), mean UPDRS score (*p*<0.0001), mean striatal dopamine transporter uptake ratios (*p*=0.002), mean geriatric depression scale (P<0.001), exercise habituation (P=0.028), and the underlying condition with chronic neuropathic pain (P<0.001) were significant variables. These variables were then used in the stepwise logistic regression model. After analysis, only UPDRS score (*p=0.001,* OR=1.062, 95% CI 1.025-1.101), remained independently associated with the presence of fatigue. Any increase one point in mean URDRS score one point will increase 6.2% of presence of fatigue rate. The area under the ROC curve for the mean URDRS score was 0.859 (95% CI 0.798-0.920; p<0.0001) and the cut-off value to predict presence of fatigue was 41.5 *(*sensitivity 83.3% and specificity 81.3%).

Discussion

Differences in the relative prevalence and risk factors associated with fatigue in patients with idiopathic PD vary with case determination and inclusion criteria, fatigue rating scales, disease severity and duration, length of follow-up, PD-related comorbidities (e. g., mood disorder, and cognitive decline and degenerative joint diseases or osteoarthritis, and cardiopulmonary functions), and PD medication-related complications (e.g., constipation, dry eye, dry mouth, and drowsy) [12-15, 17-19]. In the present study, the frequency of fatigue in patients with PD was 47.8% (66 out of 141) in a threshold of FSS means score ≥ 5.

The present study examined the risk of depression and produced three major findings. First, FSS total score is positively correlated with age, diseases duration, levodopa equivalent dose (mg), UPDRS I, UPDRS II, UPDRS III, total UPDRS, and GDS but negatively correlated with education years, striatal dopamine transporter uptake ratios, and MMSE. Second, total mean UPDRS score remained independently associated with the presence of fatigue. Any increase one point in mean URDRS score one point will increase 6.2% of presence of fatigue rate. The area under the ROC curve for the mean URDRS score was 0.859 (95% CI 0.798-0.920; p<0.0001) and the cut-off value to predict presence of fatigue was 41.5 *(*sensitivity

83.3% and specificity 81.3%). In other words, a higher mean URDRS score, which may imply an increase in the severity of PD, was associated with higher risk of fatigue. There are several studies also had the same conclusions and showed that significant correlations between the total score of the FSS and total scores of UPDRS scores in PD patients [4,31-33].

PD is a slowly progressive neuro-degenerative disorder. One study demonstrate that gender differences are not apparent on motor and other non-motor symptoms except early untreated female PD patients might be more depressed and have worse performance on cognition [34]. Another study demonstrated that fatigue symptom in patients with PD became worsened significantly more in the placebo group than in the levodopa groups over the 42 weeks of follow-up [35]. The other study also showed that the dosage of levodopa affected the health-related quality of life among PD patients with fatigue [4].

Cognitive impairment and fatigue association maybe dysfunction in the basal ganglia and frontal lobes. Neuroimaging studies revealed reducing cerebral blood flow in the frontal lobe in PD with fatigue [18], and our recent study also demonstrates that dopaminergic therapy modulates cortical perfusion in patients with PD with and without dementia [36]. One multicenter study had showed that Patients with cognitive impairment reported more frequently apathy, attention/memory deficit, and psychiatric symptoms [8], and out study also demonstrated that patients with lower mean MMSE had a higher tendency of fatigue.

Patients with PD associated with depressive mood are well documented and the prevalence is up to 40% [37,38]. Depression in PD is related with a specific loss of dopamine and noradrenaline innervation of cortical and subcortical components of the limbic system [34]. Meanwhile, PD patients with both motor impairment and depressed mood are associated with sleep/fatigue and sleep/fatigue also had a major impact factor on health-related quality of life [39]. Furthermore, one study focuses on the effects of encouraging recreational intimacy, and educational programs to promote positive mood and adjustment among people with PD [40]. Although the effects of strength training on fatigue in PD patients remained controversial [41-43], most studies confirmed that endurance exercise training improves physical conditioning in PD patients but there is insufficient evidence to include endurance exercise training as a specific treatment for PD [43].

Table 3: Correlation analysis of the effects of risk factors on Fatigue Severity scale total score.

Variables	Fatigue Severity scale total score	
	r	*P* value
Age, years	0.263	0.002
Education, years	-0.287	0.001
Body mass index (kg/m^2)	-0.039	0.650
Disease duration, years	0.445	<0.0001
Levodopa equivalent dose (mg)	0.562	<0.0001
Striatal dopamine transporter uptake ratios	-0.358	<0.001
Mini-Mental State Examination	-0.420	<0.0001
UPDRS [α]	0.747	<0.0001
UPDRS I [β]	0.739	<0.0001
UPDRS II [γ]	0.740	<0.0001
UPDRS III [δ]	0.724	<0.0001
Geriatric depression scale	0.718	<0.0001

Abbreviations

r= Correlation coefficient; UPDRS =Unified Parkinson's disease Rating Scale

†= Figures are mean+/-SD or number (%)

α="Total UPDRS" score is the combined sum of parts I, II, and III. Theoretical minimum and maximum values are 0 and 176, respectively (176 represents the worst disability and 0 no disability)

β= I. Mentation, behavior, and mood. Theoretical minimum and maximum values are 0 and 16, respectively. (16 represents the worst disability and 0 no disability)

γ= II. Activities of daily living (ADL). Theoretical minimum and maximum values are 0 and 52, respectively. (52 represents the worst disability and 0 no disability)

δ= III. Motor examination. Theoretical minimum and maximum values are 0 and 108, respectively. (108 represents the worst disability and 0 no disability)

Although our study demonstrated that a higher mean URDRS score, which may imply an increase in the severity of PD, was associated with higher risk of fatigue, our study had several limitations. First, as a prospective cross-sectional observation study, it may be subject to bias of unmeasured factors. Our study did not exclude those patients who had mild to moderate cognitive decline or depressive mood from our study. The symptoms of fatigue in some patients may be more related to depressive mood other than the severity of PD itself. Second, we did not assess the effects of dopaminergic therapy, endurance exercise training (e.g. postural stability, balance training, and exercise aimed at improving balance), and educational programs on fatigue

Higher mean URDRS score (>41.5), which may imply an increase in the severity of PD, was associated with higher risk of fatigue. Considering the co-morbidities of non-motor symptoms (e.g. cognitive decline and depression) associated with fatigue, towards developing

Table 4: Clinical factors associated with the presence of fatigue†.

	Non-fatigue (n=75)	Fatigue (n=66)	OR$^{\delta}$	95 % CI $^{\delta}$	p value $^{\delta}$
Sex (Women/male)	32/33	35/25	1.44	0.71-2.93	0.308
Body mass index (kg/m^2)	24.0 ± 2.7	24.0 ± 3.9			0.807
Age, years	65.7 ± 11.8	68.4 ± 9.7			0.356
PD duration, years	2.7 ± 2.3	5.8 ± 4.6			<0.0001
Education years	7.2 ± 5.1	5.2 ± 4.1			0.019
Levodopa equivalent dose	232.2 ± 37.2	601.9 ± 228.2			<0.001
Striatal dopamine transporter uptake ratios	1.5 ± 0.2	1.3 ± 0.2			0.002
Mini-Mental State Examination	24.0 ± 6.0	20.3 ± 5.8			0.001
UPDRS	36.1 ± 20.7	69.8 ± 20.3			<0.001
Geriatric depression scale	11.3 ± 5.5	17.6 ± 6.7			<0.001
Exercise habituation	46	31	0.44	0.21-0.92	0.028
Underlying conditions					
Hypertension	40	37	0.90	0.46-1.74	0.746
Diabetes mellitus	59	54	0.82	0.36-1.89	0.64
Hyperlipidemia	50	46	0.87	0.43-1.77	0.70
Chronic obstructive pulmonary diseases	1	6	7.40	0.87-63.16	0.051
Chronic neuropathic pain	7	23	5.20	2.05-13.15	<0.001
Knee osteoarthritis	9	13	1.80	0.71-4.53	0.21

OR= odds ratio; CI= confidence interval;
δ: OR, P value and the 95 % CI and odds ratio was calculated by Univariate logistic regression
†= Figures are mean+/-SD or number (%)

therapeutic strategies including adjust the dosage of levodopa, endurance exercise training (e.g. postural stability, balance training, and exercise aimed at improving balance), and recreational intimacy, and educational programs, are important issues highly relevant for the quality of life of patients in terms of their daily activities.

Abbreviations

PD: Parkinson's disease

FSS: Fatigue Severity Scale

UPDRS: Unified Parkinson's Disease Rating Scale

MRI: Magnetic resonance imaging

MMSE: Mini-Mental State Examination

CDR: Clinical Dementia Rating

GDS: Geriatric Depression Scale

ROC: receiver operating characteristic

Acknowledgements

The authors thank all of the subjects who participated in this study. None of the authors have any commercial association, such as consultancies, stock ownership, or other equity interests or patent-licensing arrangements.

Competing interests: The authors declare that they have no competing interests.

Ethics approval

The study was approved by Chang Gung Memorial Hospital's Institutional Review Committee on Human Research (IRB 101-0215C).

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