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Can fatigue predict walking capacity of patients with Parkinson's disease?

A fadiga pode predizer a mobilidade e a capacidade de marcha em pacientes com doença de Parkinson?

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ABSTRACT

Although fatigue is an expressive symptom of Parkinson's disease (PD), few studies have investigated the association between fatigue, mobility and walking capacity of these patients. **Objective:** To investigate whether fatigue is an independent factor associated with mobility and the walking capacity in patients with PD. **Methods:** Forty-eight patients with PD (22 with fatigue) were tested for mobility and their walking capacity: Timed Up and Go (TUG), 10-Meter Walk Test (10MWT) at usual and fastest speed, and 6-Minute Walk Test (6MWT). Fatigue was measured with Parkinson's Fatigue Scale (PFS-16). Linear regression analysis was used to investigate if fatigue is an independent factor contributing to variance in mobility and walking capacity. **Results:** There was a positive correlation between PFS-16 and TUG (r_s=0.385; p=0.007). There was a negative correlation between PFS-16 and 10MWT at comfortable (r=-0.385; p=0.007) and fast speeds (r=-0.396; p=0.005), and 6MWT (r=-0.472; p=0.001). Linear regression analysis revealed that fatigue did not explain the variance of TUG and 10MWT. PFS-16, age and section III of UPDRS explained 49.6% (adjusted R^2; p<0.001) variance in the 6MWT, and fatigue was the most significant predictor (F=-32.1; p=0.022). **Conclusions:** Fatigue is an independent factor contributing to the distance covered during 6MWT in patients with PD. Our results highlight the importance of recognition and management of this symptom.

Keywords: Parkinson's disease; fatigue; mobility; gait speed; walking capacity.

RESUMO

Embora a fadiga seja um sintoma importante na doença de Parkinson (DP), poucos estudos investigaram a associação entre fadiga, mobilidade e capacidade de marcha nesses pacientes. **Objetivo:** Investigar se a fadiga é um fator independente associado à mobilidade e à capacidade de marcha em pacientes com DP. **Métodos:** Quarenta e oito pacientes com DP (22 com fadiga) foram avaliados com testes de mobilidade e capacidade de marcha: *Timed Up and Go* (TUG), Teste de Caminhada de 10 metros (T10m) na velocidade usual e máxima, Teste de Caminhada de Seis Minutos (TC6m). A fadiga foi medida pela Escala de Fadiga no Parkinson (PFS-16). A análise de regressão linear foi utilizada para investigar se a fadiga é um fator independente que contribui para a variação na mobilidade e capacidade de marcha. **Resultados:** Houve correlação positiva entre PFS-16 e TUG (rs=0,385; p=0,007). Houve correlação negativa entre PFS-16 e T10m na velocidade usual (r=-0,385; p=0,007) e máxima (r=-0,396; p=0,005) e TC6m (r=-0,472; p=0,001). Análise de regressão linear revelou que a fadiga não explicava a variância do TUG e T10m. A PFS-16, a idade e a seção III da UPDRS explicaram 49,6% (R2 ajustado, p<0,001) da variância no TC6m e a fadiga foi o preditor mais significativo (F=-32,1; p=0,022). **Conclusões:** A fadiga é um fator independente que contribui para a distância percorrida durante o TC6m em pacientes com DP. Nossos resultados destacam a importância do reconhecimento e manejo desse sintoma.

Palavras-chave: doença de Parkinson; fadiga; mobilidade; velocidade de marcha; capacidade de marcha.

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Parkinson's disease (PD)-related fatigue is one of the most common and disabling symptoms and affects approximately 50% of PD patients[1,2]. Patients report a significant reduction in energy levels or perception of increased efforts to perform daily activities. However, this symptom is distinct from sleepiness, lack of motivation, and depression. To be considered as a relevant symptom, it must be present for most of the day or nearly every day during the previous month[3].

Fatigue occurs since early stages of PD, including the pre-motor period, to more advanced stages of the disease[4]. Studies have shown that fatigue is correlated to other symptoms, such as depression, anxiety, and sleep disturbance[5-8]. The pathophysiology of fatigue has not been elucidated yet; however, increased circulating inflammatory cytokines, such as interleukin 6 (IL-6) may play a significant role[9]. Dysfunction in nigrostriatal and extrastriatal dopaminergic or non-dopaminergic pathways, and autonomic nerve system impairment are proposed as pathophysiological mechanisms of fatigue[4].

PD fatigue can be divided into peripheral and central. Peripheral fatigue occurs after repeated muscle contractions, involves decreased muscle strength and can be measured[10]. Peripheral fatigue is produced by changes in neuromuscular transmission, neuromuscular junctions, muscle cell membranes and factors within muscle fibers[11]. On the other hand, central or subjective fatigue can be further divided into physical and mental[10,12]. The effort to perform activities that depend on skeletal muscles to generate force and cognitive demands are reported in physical and mental fatigues, respectively[10,12]. Central fatigue is more often assessed using one or multidimensional questionnaires[13]. Parkinson Fatigue Scale (PFS-16) is designed to measure the physical aspects of subjective fatigue and its impact on daily activities, but it does not consider cognitive or emotional features[5,13].

Although fatigue is an important symptom in PD, only few studies have assessed its association with mobility, walking capacity, and physical activity in patients with PD[14-18]. Some studies have shown an association between fatigue severity and self-reported leisure activity, frequency of vigorous physical activity, and time spent moving[14]. A 12-week prospective cohort study presented a significant association between fatigue and dynamic activities[15]. Patients who experience higher levels of fatigue are less physically active in their daily lives[15]. Nonetheless, this symptom was not able to predict the level of physical activity in two proposed models by Lana, although fatigue was correlated with Human Activity Profile scores[16]. Physical activity, physical function, psychological well-being, and quality of life were reduced in PD patients with greater subjective fatigue[6-8]. Recently, Kader et al. showed that fatigue is the third strongest factor that independently contributes to perceived walking difficulties in people with PD, after freezing of gait and general self-efficacy[18]. This study aimed to investigate whether fatigue can predict mobility and walking capacity of patients with PD.

METHODS

The Research Ethics Committee of Universidade Federal de Minas Gerais, Brazil, approved the design of the cross-sectional study. Participants were recruited from the movement disorders outpatient clinic of Santa Casa Hospital, Belo Horizonte City, Brazil. Written informed consent was obtained from all subjects before their participation.

Forty-eight patients with PD diagnosis according to the United Kingdom Brain Bank Criteria were included[19]. Patients with cognitive dysfunction were excluded, according to the Mini-Mental State Examination (MMSE) adapted for the Brazilian elderly population[20], or with any other medical disorder that could potentially be associated with fatigue, such as heart and pulmonary diseases, renal and hepatic failure, or cancer. Only those subjects with a sedentary lifestyle with no regular exercises were recruited to avoid the confounding factor of physical activity levels.

Demographic data, medical history, and pharmacological treatment (disease duration, antiparkinsonian medication, and other treatment) were collected in a structured interview. L-dopa equivalent dose (LED) was calculated for each studied patient[21].

All patients were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS), which assesses different signs and symptoms of PD[22]. PD patients were tested during a clinical "on" status, with the more severe side being tested. The "tremor score" and the "non-tremor score" for each patient were calculated according to Lewis et al.[23]. The patients were classified: tremor-dominant type, akinetic-rigid or mixed type. The modified Hoehn and Yahr (HY) staging scale was used to establish the stage of PD[24], which ranges from stage I (unilateral involvement) to stage V (confinement to bed or wheelchair, unless aided). The modified Schwab and England activities of the daily living scale was used to assess daily routines.

The timed up and go test (TUG) was used to evaluate gait in a functional situation of their daily lives. It is a simple, quick and widely used clinical performance-based measure of balance and mobility. Walking aids were used, patients were asked to stand up from a standard chair, walk 3 meters at the easy and fast-paced, turn 180 degrees, walk back to the chair and sit down. The time to complete the task was measured with a stopwatch. Timing starts with the 'go' command and stops when the patient's back is positioned against the back of the chair after sitting down. The time taken to complete is recorded in seconds[25,26].

Comfortable and fast gait speeds were assessed using the 10-Meter Walk Test (10MWT), which was performed on a flat 14-meter corridor and the time required to cover the 10 intermediate meters was registered with a digital stopwatch. The first 2 meters were provided to reach the patient's usual gait speed and the last 2 meters to slow down and stop. This test was applied 2 times and the average value was

calculated. This test is a measure of overall walking performance but does not include an endurance component[26].

The 6-Minute Walk Test (6MWT) was used to measure the maximal distance that the patient can walk on a flat surface, as fast as possible, for 6 minutes. Patients were allowed to self-pace and rest as needed while they walked back and forth along a marked walkway. For some patients, it is a submaximal test of aerobic capacity[26].

Fatigue was assessed with the PFS-16, which is a self-report questionnaire of 16 statements regarding fatigue in which patients choose how much they agree or disagree with these statements. In this study, a cut-off point of 3.3 was used to identify patients with PD who perceive fatigue as a problem. Higher scores indicated more severe fatigue[5].

The categorical variables are described by the number of participants (percentage). Demographic and clinical features were described using mean and standard deviation or median and range (min, max). Pearson (r) or Spearman (rs) correlations were used to assess the association between the independent variable (fatigue) and mobility and walking capacity. A linear regression analysis was used to exclude confounding factors (age, cognitive function, UPDRS II and III, and HY stage). The significance level applied was <0.05. All statistical analyses were performed with the SPSS Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

A total of 101 patients were contacted, but 34 (33.7%) were not eligible due to the exclusion criteria, 11 (10.9%) declined to participate, and 8 (7.9%) patients did not attend the appointments or did not show PD drug effects. Therefore, the final sample consisted of 48 (of which 52.5% were men) participants. Three (6.3%), one (2.1%), 17 (35.4%), eight (16.7%) and 19 (39.7%) individuals were classified as stage 1, 1.5, 2, 2.5, and 3 according to the modified HY scale, respectively. Furthermore, 22 (45.8%) participants showed significant fatigue. Demographic and clinical features are shown in Table 1.

Table 1. Demographic and clinical characteristics of study population (n=48).

Variables	Participants (n=48)	Patients without fatigue (n=26)	Patients with fatigue (n=22)	p-value
Gender (men), n (%)	27 (52.5%)	15 (57.7%)	12 (46.2%)	0.529*
Age (years), mean (SD)	67.2 (10.0)	64.1 (7.1)	70.9 (11.8)	0.025
Education level (years), mean (SD)	8.3 (4.8)	9.3 (5.1)	7.1 (4.4)	0.114
MMSE (scores), mean (SD)	23.5 (4.4)	25.3 (3.6)	21.3 (4.3)	0.001
Onset of symptoms (years), mean (SD)	9.0 (5.3)	8.4 (3.9)	9.8 (6.6)	0.353
Disease duration (years), mean (SD)	7.4 (4.6)	7.1 (3.9)	7.7 (5.4)	0.641
LEDD — Levodopa (mg), mean (SD)	706.1 (308.1)	592.3 (269.7)	725.0 (255.2)	0.098
UPDRS, mean (SD) UPDRS I score UPDRS II score UPDRS III score UPDRS total score	3.0 (2.4) 15.7 (6.0) 27.0 (11.9) 45.7 (17.3)	2.5 (1.9) 13.5 (5.8) 22.4 (10.2) 38.4 (14.9)	3.6 (2.8) 18.2 (5.2) 32.6 (11.5) 54.4 (16.2)	0.093 0.006 0.002 0.001
Phenotype Tremor, n (%) Rigidic-ackinetic, n (%) Mixed, n (%)	2 (4.2%) 23 (47.9%) 23(47.9%)	1 (3.85%) 11 (42.3%) 14 (53.85%)	1 (4.55%) 12 (54.55%) 9 (40.9%)	0.669*
Hoehn and Yahr staging (scores), median (min-max)	2.5 (1.0-3.0)	2.0 (1.0-3.0)	3.0 (2.0-3.0)	0.025&
Schawb and England (scores), median (min-max)	70% (50-100)	80% (70-100)	70% (50-80)	0.008&

Continue...

Table 1. Continuation.

Variables	Participants (n=48)	Patients without fatigue (n=26)	Patients with fatigue (n=22)	p-value
TUG (s), median (min-max) Patients >16 s, n (%)	13.3 (7.1-97.0) 15 (31.2%)	11.9 (7.1-20.5) 3 (11.5)	17.5 (8.4-97.0) 12 (54.5%)	0.009[&]
10MWT (comfortable speed) (m/s), mean (SD)	0.94 (0.29)	1.05 (0.19)	0.80 (0.34)	0.004
10MWT (maximal speed) (m/s), mean (SD)	1.22 (0.38)	1.37 (0.30)	1.04 (0.39)	0.002
6MWT (meters), mean (SD)	359.0 (124.4)	418.6 (89.1)	288.5 (124.8)	<0.001
PFS-16 (scores), mean (SD)	3.2 (1.0)	2.4 (0.57)	4.2 (0.48)	<0.001

MMSE: Mini-Mental State Examination; UPDRS: Unified Parkinson's Disease Rating Scale; HY: Hoehn and Yahr Staging of Parkinson's disease; SE: Schawb and England Activities of Daily Living; 10MWT: 10-Meter Walk Test; TUG: Timed Up and Go; 6MWT: 6-Minute Walk Test; PFS-16: Parkinson's Disease Fatigue Scale. *Chi-square test. [&]Mann-Whitney U test. Student's t-test to other variables.

Patients with fatigue were older and had worse cognitive functions when compared to patients without fatigue. They had higher scores on UPDRS (II, III and total UPDRS scores) and more advanced stages of the disease, besides higher levels of functional dependence according to SE scale. This group spent more time in TUG. Comfortable and maximum gait speeds and distance covered during 6MWT were smaller in fatigue group.

Bivariate correlations between PFS-16 score and TUG, 10MWT, and 6MWT are shown in Table 2. The degree of fatigue was correlated with mobility and the walking capacity. Linear regression analysis revealed that age, PD symptoms (UPDRS III), and severity of fatigue (PFS-16) were independent contributors to 6MWT, and explained 49.6% of total variance of 6MWT (Table 3). Fatigue did not explain total variance of TUG and 10MWT (comfortable and fast gait speeds). In the first dependent variable (TUG), the model included age and severity of PD symptoms (UPDRS III) and explained 38.75% of total variance of TUG. For the second dependent variable (10MWT), the model included age and cognitive function (MMSE) and explained 35.9 and 41.2% of total variance of comfortable and fast gait speeds, respectively.

Table 2. Bivariate correlation between PFS-16 and mobility and exercise capacity.

Variables	PFS-16	
	r	p-value
TUG*	0.385	0.007
10MWT (comfortable speed)	-0.385	0.007
10MWT (maximal speed)	-0.396	0.005
6MWT	-0.472	0.001

TUG: Timed Up and Go; 10MWT: 10-Meter Walk Test; 6MWT: 6-Minute Walk Test; PFS-16: Parkinson's Disease Fatigue Scale. *Spearman's rank correlation coefficient. Pearson correlation coefficient to other variables.

Table 3. Linear regression.

Variables	6MWT		
	Beta (p-value)	*p-value*	*95% confidence interval*
Age	-4.4	0.002	-7.1/-1.7
UPDRS III	-4.1	0.001	-6.5/-1.7
PFS-16	-32.1	0.022	-59.4/-4.8
R^2 adjusted	49.6%		

6MWT: 6-Minute Walk Test; UPDRS: Unified Parkinson's Disease Rating Scale; PFS-16: Parkinson's Disease Fatigue Scale.

DISCUSSION

Frequency of fatigue (46%) observed here is consistent with those found in the literature (50%) for PD patients.[27]. Few studies investigated the impact of fatigue on mobility and walking capacity in individuals with PD[11,28,29]. Our results showed that patients with higher scores of PFS16 had worse performance in a basic mobility skill (TUG), gait speed over a short distance (10MWT), and endurance and ability to walk over longer distances (6MWT). TUG test may be a useful tool to assess patients with PD, because they normally exhibit difficulty in performing activities, such as walking and turning, and complex or dual tasks[25,26]. In elderly people, it is considered normal to spend ≤10s in the TUG[25]. For PD, patients who spend more than 16 seconds to complete the TUG have an increased risk of falling[30]. In our study, 31.2% patients spent

more than 16 seconds to perform this test. The 10MWT and 6MWT are common clinical gait assessment tools. The first test measures average gait speed at a single pace (i.e. comfortable or fast) over a short distance. In contrast, 6MWT measures their walking endurance at a self-determined pace over a long distance[25,26]. Our study showed that mean gait speed was 0.94 m/s in PD patients. This result corroborates findings of a previous study conducted by Paker et al.[31]. According to the literature, the gait speed is between 0.18 and 1.21m/s in PD patients. These values are much lower when considering the elderly patients who reach a speed of 1.30-1.36 m/s[28,31].

After linear regression analysis, considering fatigue as an independent variable, it did not explain the variance of reaction time (TUG) and gait speed (T10M). However, PFS-16, age, and section III of UPDRS explained variance in 6MWT and fatigue was the most significant predictor of 6MWT. This could be an important factor to increase patient's physical inactivity. In previous studies, associations between gait impairment and activity limitation in PD were described[31,32]. From a clinical perspective, our results suggest that fatigue may reduce functionality in everyday activities of PD patients and prolong periods of sedentary behaviors. This is particularly important seen that PD-related fatigue is one of the most common and disabling symptoms in these patients[2,3].

The study by Kader et al. found eight contributing factors for the perception of gait difficulty in individuals with PD: freezing, general self-efficacy, fatigue, PD duration, low limb function, orthostatic hypotension, bradykinesia, and instability postural[18]. Fatigue was the third strongest related factor. Those findings are in accordance to results found here, considering that fatigue is an independent factor that contributes to the perception of walking difficulty[18]. Santos et al. analyzed the effect of fatigue in lower limbs on gait parameters. They found that fatigue caused adjustments in gait parameters, and these adjustments were interpreted as adaptation strategies to maintain balance in response to the provoked fatigue[28]. Although the study also observed that level of a physical activity of individuals with and without PD did not affect gait performance after provoked fatigue, practice of physical activity is fundamental to improve gait of individuals with PD.

Fatigue has been linked to mobility and walking and aerobic abilities in people with multiple sclerosis and mild neurological disability[33]. These authors suggested that a better understanding of fatigue could lead to more effective management of this highly disabling symptom[32,33]. Nevertheless, according to Hoang et al., fatigue was not associated with physical parameters, including 10MWT and 6MWT[34].

An important point discussed in the literature is that mildly down-regulated thyroid function in elderly people may be protective and is associated to better physical function and lower mortality when compared with euthyroid individuals[35]. However, Vestergaard et al. showed that lower extremity function, walking speed, mobility, and instrumented activities of life are impairment for older people who report fatigue even after adjustment of their health behaviors, diseases, inflammatory markers, and thyroid function[36].

A limitation of this study was that antidepressant medication intake and nonmotor symptoms (mainly affective and sleep disorders), which are known to influence PD patients[29], could not be assessed. Moreover, the cross-sectional design of the study does not allow further exploration of causal relationship between studied variables. Hence, the result of this study should be interpreted within this context. The strength of the present study is that patients were investigated with validated instruments for PD and fatigue, and tests were mainly used to assess mobility and walking capacity of patients with PD. The findings of this study are important once fatigue is considered one of the most common and disabling nonmotor symptoms in PD patients and it harms their quality of life[27].

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