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Chapter 3

Is impact of fatigue an independent factor associated with physical activity in patients with idiopathic Parkinson's disease?

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Abstract

Objective To investigate the longitudinal association between fatigue and physical activity in Parkinson's Disease (PD) and determine whether this association is distorted by potential confounders.

Methods Data from baseline, 3-, 6-, and 12-week assessments in a single blind randomized clinical trial with cross-over design were used (N = 153). The Multidimensional Fatigue Inventory (MFI) was used to assess fatigue and an activity monitor to measure amount of physical activity (defined as % dynamic activity during each monitoring session). Time-independent and time-dependent factors were investigated for their possible bivariate association with dynamic activity. Random coefficient analysis was applied. Candidate confounders were successively added to the longitudinal association model to determine if the association between dynamic activity and fatigue was distorted. A proportional change beyond 15% was considered to be significant.

Results Fatigue was significantly associated with physical activity (β = -0.099, SE = 0.032, p = 0.002). This association was not significantly distorted by type of intervention, age, gender, social support, disease duration, disease severity, motor impairment, cognition, anxiety or medication intake. Depression caused proportional change of 22.2% in the regression coefficient of MFI. After controlling for depression, a significant association between MFI and dynamic activity remained (β = -0.121, SE = 0.036, p = 0.000).

Conclusion The association found between fatigue and dynamic activity suggests that patients who experience higher levels of fatigue are less physically active. However, the total explained variance of dynamic activity by fatigue alone was small, suggesting that fatigue is only a minor factor in the complex of behavioral aspects that affect the amount of physical activity in patients with PD.

Introduction

Fatigue is common in many patients with idiopathic Parkinson's disease (PD) and has a negative impact on health related quality of life (HRQOL) [1-3]. Prevalence rates reported in the literature range from 32% to 50% [4, 5]. Fatigue is often believed to be an independent factor that is negatively associated with activities in patients with PD [3]. Although patients with PD often complain that fatigue limits their physical activities [6], only a few studies have investigated the association between fatigue and actual physical activity performed in patients' daily lives [6-8].

Garber et al. investigated the cross-sectional association among fatigue, physical activity, and physical functioning in PD [6]. The authors found a significant association between fatigue severity and self-reported leisure activity, frequency of vigorous physical activity, and the time spent moving [6]. Thus far, most studies used self-report questionnaires for assessing patients' activity level; however, these scales are vulnerable to recall bias and providing desirable answers. In contrast, an activity monitor (AM) is a more objective method of measuring the actual amount and type of 'real world' activities performed in patients' own home environments [9]. Hoff et al., for example, investigated whether the self-reported reduction in activity associated with fatigue could be quantified using an AM [8]. The authors found that patients with fatigue did not differ with regard to their activity level, the mean duration of sustained activity, and the mean duration of immobility periods, when compared with patients without fatigue. In a cross-sectional analysis, Rochester and colleagues investigated the association between gait-related activities and fatigue [7]. In this study, the authors applied an AM to quantify activity and found no significant difference in activity between 20 patients with PD and healthy-age matched controls. In addition, no clear association was found between fatigue and level of physical activity in patients with PD. However, the study population was small [7].

Unfortunately, research done so far is based on cross-sectional analysis in which the time-dependent fluctuations with respect to activities and perception of fatigue are considered to be random, whereas fatigue and real life performance are known to be time-dependent [4]. Therefore, longitudinal models with repeated measurements in time may more appropriately reflect the association between fatigue and actual observed levels of physical activity.

The aim of the present study was to investigate the longitudinal association between fatigue and physical activity measured with an AM. We hypothesized that the impact of fatigue is significantly and negatively associated with physical activity in patients

with PD. Subsequently, we investigated if the identified longitudinal association was distorted by potential confounders such as age, gender, social support, disease duration [4], disease severity [4], motor impairment [4], cognition [4, 10], anxiety, depression [4, 11] and medication intake [12, 13].

Subjects and methods

Population and design

This prospective cohort study was part of a single-blind, randomized clinical trial (the 'Rescue' trial) about the effects of cueing training on gait and gait-related activity in patients with PD [14]. In this study, 153 patients with PD were recruited from three European centers: Northumbria University, Newcastle upon Tyne (UK); Katholieke Universiteit Leuven, Leuven (Belgium) and the VU University Medical Center, Amsterdam (The Netherlands). The study was approved by the ethics committee of each participating center. All patients gave written informed consent. Patients were randomly allocated to an early or late intervention group by an independent person not involved in the study. A cross-over design was used to offer all patients the experimental treatment. Further details about design and outcome of the study have been published previously [14]. Data from the Rescue trial were used for analysis.

Subjects

Patients were recruited according to the following criteria: 1) age 18-80; 2) diagnosis of PD, defined by the UK Brain Bank Criteria [15]; 3) Hoehn and Yahr (H&Y) stage II-IV [16]; 4) stable drug usage and 5) mild-to-severe gait disturbance (score > 1 on the Unified Parkinson's Disease Rating Scale (UPDRS) item 29) [17]. Patients were excluded if they had undergone deep brain stimulation or other stereotactic neurosurgery; had cognitive impairment (Mini Mental State Examination (MMSE) < 24) [18]; had disorders interfering with participation in cueing training, including neurological (stroke, multiple sclerosis and brain tumor), cardiopulmonary (chronic obstructive disorders, angina pectoris) and orthopedic (osteoarthritis, rheumatoid arthritis and back pain) conditions; had unpredictable and long lasting off periods (score 1 on item 37 and score > 2 on item 39 of the UPDRS) [17] or had participated in a physiotherapy program two months before starting the trial.

Measuring physical activity

The Vitaport AM (VAM) was used to measure physical activity. (Vitaport 3, Temec Instruments b.v., Kerkrade, The Netherlands.) The VAM is a reliable and valid instrument to measure functional activity in patients with mild-to-moderate PD [19, 20]. In the present study (N = 77), the VAM showed excellent test-retest reliability for measuring dynamic activities (ICC = 0.76-0.81). The VAM set up consisted of five accelerometers connected to a portable data recorder. The accelerometers were attached to the body [19]: one on each leg (saggital plane) and three accelerometers on the lower third of the sternum (sagittal, longitudinal and transverse planes). All accelerometers were attached to the data recorder by cables that ran under the clothes. Patients wore the VAM for a period of approximately 8 hours on weekdays in the home and community environment. They were instructed to continue with their usual daily routine. Patients were kept naive about the function of the VAM to avoid reactivity effects. Data were sampled at a frequency of 256 Hz and stored at 32 Hz. The sampled data were analyzed using the software program Vitagraph which classified activity into the percentage time static activity (including standing, sitting and lying) and percentage time dynamic activity (including walking and periods of walking exceeding 5 seconds) [21] (Vitagraph, Temec Instruments b.v., Kerkrade, The Netherlands). These voluntary activities can be distinguished from dyskinesias because they tend to have other frequency content than dyskinesias and are more coordinated [22].

Measuring fatigue

The Multidimensional Fatigue Inventory (MFI) [23] was used to assess fatigue. The MFI is a self-report questionnaire that assesses five dimensions of fatigue, that is, general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation. The score within each dimension ranges from 4 (absence of fatigue) to 20 (maximum fatigue). The MFI has been widely used for patients with PD [1, 2, 11, 24]. In the present study (N = 77), the MFI proved to be a reliable instrument to assess fatigue (ICC = 0.70-0.87).

Measuring potential confounders

To establish whether the longitudinal association between fatigue and physical activity was confounded, various time-independent and time-dependent variables were measured. Time-independent variables were treatment allocation [14], age, gender, social support, medication intake, disease duration, disease severity and cognitive functioning. Disease severity was assessed with the H&Y scale [16], and cognitive functioning was assessed with the Brixton Test [25] and the MMSE [18].

The time-dependent variables were motor impairment, anxiety and depression. Motor impairment was assessed with the UPDRS part III [17]. The Hospital Anxiety and Depression Scale (HADS) [26] was used to assess anxiety and depression. The HADS is a self-report questionnaire that consists of seven anxiety and seven depression items. The total score in each subscale ranges from 0 (absence) to 21 (maximum). The HADS is a reliable and valid screening instrument for anxiety and depression in PD [27].

Procedure

All variables were assessed at baseline (t1). The time-dependent variables were also measured at week 3 (t2), 6 (t3) and 12 (t4). One observer from each center, blinded to treatment allocation and not involved in data analysis, performed all assessments in the patients' homes. Each patient was assessed at the same time of the day in the on phase, approximately 1 hour after medication intake. Fatigue, motor impairment, anxiety and depression were assessed preceding the period of activity monitoring. All patients carried the VAM with a belt around the waist.

Statistical analysis

The longitudinal association between fatigue and physical activity was evaluated by means of random coefficient analysis (RCA) [28] (MLwiN version 2.02, Multilevel Models Project Institute of Education, London, UK). In this two-level hierarchical model, repeated measurements are nested within subjects. Dependent on distribution by visual plot, linear multilevel models were applied.

First, bivariate longitudinal analysis was conducted with dynamic activity as dependent variable and several candidate determinants, including all dimensions of fatigue, as independent variables. The regression coefficients between dynamic activity and fatigue were calculated and adjusted for treatment allocation. Subsequently, candidate confounders were successively added to the longitudinal association model to determine if the β value between dynamic activity and fatigue was significantly influenced after controlling for time-independent and time-dependent covariates. If the regression coefficient of fatigue changed more than 15% after controlling for the added variable in the model, the added covariate was considered to be a confounder. If the relationship between fatigue and dynamic activity was still significant after controlling for the confounder of interest, new candidate confounders were added to the model. The likelihood ratio test was used to evaluate the necessity for allowing random coefficients into the model. A two-tailed significance level of 0.05 was used for all tests.

Results

Table 3.1 presents the demographic characteristics of the 153 included patients with PD. Most patients had mild-to-moderate disease severity as 46% (N = 71) of patients were in H&Y stage II, 42% (N = 64) in stage III and 12% (N = 18) in stage IV. The median

Table 3.1 Patient characteristics at baseline (N = 153)

	Median (IQR)
Demography	
Male/female[a]	88/65
Age (years)	68 (11)
Partnered[a]	123
PD characteristics	
Disease duration (years)	8 (8)
H&Y (on)	3 (1)
H&Y II/III/IV (on)[a]	71/64/18
Clinical data	
Early intervention group[a]	76
Late intervention group[a]	77
UPDRS-total (on)	54 (17)
UPDRS I (on)	3 (2)
UPDRS II (on)	16 (8)
UPDRS III (on)	32 (14)
UPDRS IV (on)	2 (4)
Dynamic activity (% time)	10 (11)
Static activity (% time)	90 (12)
MFI-total	64 (25)
MFI general fatigue	14 (6)
MFI physical fatigue	14 (7)
MFI reduced activity	14 (8)
MFI mental fatigue	11 (8)
MFI reduced motivation	11 (6)
HADS anxiety	6 (6)
HADS depression	7 (5)
Brixton R	21 (12)
Brixton S	4 (4)
MMSE	29 (3)
Levodopa (mg)	400 (350)
Dopamine agonist[a]	105
Selegeline[a]	22
Levodopa + Entacapone[a]	37
Medication other[*]	46

[a]*Expressed as number of patients*

level of fatigue was 64 (IQR = 25) and the median level of dynamic activity was 10% (IQR = 11) of the total time measured. One patient was dropped out 3 weeks after randomization because of a necessary change of drug treatment. In total, 556 of the 612 MFI-total scores were available for random coefficient analysis. All dependent outcomes expressed as percentages were normally distributed by visual plot.

Bivariate random coefficient analysis between dynamic activity and determinants

Table 3.2 shows that most dimensions of fatigue, that is, MFI-total (β = -0.099, SE = 0.032, p = 0.002), MFI physical fatigue (β = -0.277, SE = 0.118, p = 0.019), MFI reduced

Table 3.2 Bivariate association between dynamic activity and candidate determinants (N = 153)

Determinant	β Value of determinant	Standardized β value of determinant
Demography		
Sex	-0.141 (1.755)	-0.006
Age	-0.287 (0.114)[a]	-0.180
Social support	1.436 (2.229)	0.048
PD characteristics		
Disease duration	0.713 (0.161)[a]	0.302
H&Y (on)	-0.700 (1.551)	-0.033
Clinical data		
Treatment allocation	-0.746 (1.733)	-0.031
UPDRS III (on)	-0.189 (0.050)[a]	-0.178
MFI-total	-0.099 (0.032)[a]	-0.144
MFI general fatigue	-0.226 (0.117)	-0.079
MFI physical fatigue	-0.277 (0.118)[a]	-0.102
MFI reduced activity	-0.279 (0.110)[a]	-0.111
MFI mental fatigue	-0.248 (0.115)[a]	-0.087
MFI reduced motivation	-0.261 (0.119)[a]	-0.091
HADS anxiety	0.037 (0.137)	0.012
HADS depression	-0.053 (0.152)	-0.018
Brixton R	0.105 (0.085)	0.089
Brixton S	-0.399 (0.360)	-0.074
MMSE	0.215 (0.476)	0.033
Levodopa	0.003 (0.003)	0.085
Dopamine agonist	-5.931 (1.815)[a]	-0.229
Selegeline	-1.829 (2.457)	-0.054
Levodopa + Entacapone	-5.930 (1.986)[a]	-0.213
Medication other	-4.516 (1.864)[a]	-0.174

[a] *$p < 0.05$; The figures in parentheses represent SE*

activity (β = -0.279, SE = 0.110, p = 0.011), MFI mental fatigue (β = -0.248, SE = 0.115, p = 0.031) and MFI reduced motivation (β = -0.261, SE = 0.119, p = 0.029) were significantly associated with dynamic activity, whereas the dimension general fatigue of MFI approached significance (β = -0.226, SE = 0.117, p = 0.054).

Confounding factors MFI

Table 3.3 presents the adjusted regression coefficient between dynamic activity and MFI-total after correcting for the candidate confounders. The adjusted regression coefficient, corrected for treatment allocation between dynamic activity and MFI-total, did not differ from the bivariate association (i.e. β = -0.099, SE = 0.032, p = 0.002). Adding depression (HADS) to the model resulted in a proportional increase of 22.2% in the regression coefficient of MFI-total. After controlling for depression, a significant association between MFI-total and dynamic activity was still found (β = -0.121, SE = 0.036, p = 0.000). Controlling for motor impairment (UPDRS III) reduced proportionally 14.1% of the found regression coefficient of MFI-total (β = -0.085, SE =

Table 3.3 Multilevel regression model to test the effect of confounders on the predictive value of fatigue for dynamic activity adjusted for treatment allocation[a] (N = 153)

Variables in the model	β Value of candidate confounder	β Value of MFI-total	Standardized β value of MFI-total	Proportional change in the coefficient of MFI-total
MFI-total		-0.099 (0.032)[b]	-0.144	
HADS depression	0.220 (0.169)	-0.121 (0.036)[b]	-0.176	22.2%
UPDRS III (on)	-0.167 (0.051)[b]	-0.085 (0.032)[b]	-0.123	14.1%
HADS anxiety	0.167 (0.144)	-0.110 (0.033)[b]	-0.160	11.1%
Age	-0.236 (0.112)[b]	-0.089 (0.032)[b]	-0.129	10.1%
Dopamine agonist	-5.407 (1.778)[b]	-0.089 (0.032)[b]	-0.129	10.1%
Levodopa + Entacapone	-6.383 (1.925)[b]	-0.108 (0.031)[b]	-0.157	9.1%
Levodopa	0.004 (0.002)[b]	-0.104 (0.032)[b]	-0.151	5.1%
Brixton S	-0.472 (0.382)	-0.094 (0.032)[b]	-0.137	5.1%
Brixton R	0.124 (0.083)	-0.095 (0.032)[b]	-0.138	4.0%
Medication other	-4.149 (1.824)[b]	-0.095 (0.032)[b]	-0.138	4.0%
Selegeline	-0.915 (2.413)	-0.096 (0.032)[b]	-0.139	3.0%
Disease duration	0.699 (0.156)[b]	-0.097 (0.031)[b]	-0.141	2.0%
H&Y (on)	0.230 (1.529)	-0.100 (0.032)[b]	-0.145	1.0%
Social support	1.037 (2.162)	-0.098 (0.032)[b]	-0.142	1.0%

[a]Treatment allocation did not change the bivariate regression coefficient between dynamic activity and fatigue (β = -0.099, SE = 0.032, p = 0.002); [b]p < 0.05; The figures in parentheses represent SE

0.032, p = 0.008). We found no significant confounding for treatment allocation, age, gender, disease duration, disease severity, cognition, anxiety, medication intake and social support. In a multivariate model, which included all candidate confounders, the association between dynamic activity and MFI-total remained significant (β = -0.092, SE = 0.037, p = 0.013, r^2 = 2.0%).

Discussion

This prospective cohort study shows that, over a period of 12 weeks longitudinally, fatigue is significantly associated with dynamic activity in patients with PD. The association found between fatigue and dynamic activity was only significantly distorted by depression. Although depression appears to contribute more to dynamic activity in the multivariate model than fatigue, this contribution was not significant. After controlling for depression, fatigue remained significantly associated with dynamic activity. These findings confirm our hypothesis that the impact of fatigue is independently associated with physical activity in patients with PD. The inverse relationship found between fatigue and dynamic activity further suggests that those patients who experience higher levels of fatigue are less physically active in their daily life and vice versa. However, the total explained variance of dynamic activity by fatigue was small (r^2 = 2.0%), suggesting that fatigue is only a minor factor in the complex of behavioral aspects that determine the amount of daily physical activity in patients with PD.

The aforementioned results are in line with a cross-sectional study by Garber and colleagues [6]. In contrast, two other studies [7, 8] found no clear association between fatigue and physical activity, probably because of small sample sizes and cross-sectional analysis used in both studies.

Depressive disorders are common in patients with PD [29]. Since fatigue is one of the criterion symptoms for a major depressive disorder according to the DSM-IV [30], it is likely that depression is a confounder in the relation between fatigue and physical activity. However, both depression and fatigue have also been observed as symptoms that were independently present in patients with PD [4].

Moreover, Chaudhuri and Behan postulated that fatigue in neurological disorders may be caused by an interruption in the connection between the prefrontal cortex and thalamus, and that lesions in the basal ganglia can also disturb limbic integration for cortically driven voluntary activities [31]. It can be postulated that the collinearity found between depression and fatigue could have been caused by the existing

overlap between the two assessment scales. However, we deliberately used the HADS depression subscale, to prevent overlap in both measurements.

Motor impairment as assessed by the UPDRS III motor score was significantly associated with both fatigue ($\beta = 0.224$, SE = 0.064, $p = 0.000$) and amount of dynamic activity ($\beta = -0.189$, SE = 0.050, $p = 0.000$). These associations are likely, since performing physical activities may require more effort in more severely impaired patients than in those with minor motor impairments. However, motor impairment did not affect the association between fatigue and dynamic activity significantly.

Interestingly, motor impairment reduced the found regression coefficient between the MFI dimension physical fatigue and dynamic activity significantly (22.2%). After controlling for motor impairment the regression coefficient between the MFI dimension mental fatigue and dynamic activity showed a proportional increase of 7.6%. These findings suggest that motor impairment affects mainly the physical domain of fatigue, and further confirm results from a cross-sectional study by Lou and colleagues that physical fatigue and mental fatigue are two independent symptoms in PD [11].

Disturbances in the balance between brain neurotransmitters (i.e. serotonin-dopamine ratio) may influence the level of central activation, which determines the capacity to sustain an activity [32, 33]. The medical management of this sample was aimed at optimizing dopamine levels to maintain smooth motor output during the day. In the present study, medication intake did not significantly confound the association between fatigue and dynamic activity. However, medication intake was measured categorically, making it difficult to draw valid conclusions about the effect of doses of medication on fatigue.

Thus far, fatigue is often believed not to be associated with severity of underlying disease [31]. In contrast, the association we found between fatigue and disease severity (H&Y) remained significant in the multivariate model ($\beta = 4.409$, SE = 1.884, $p = 0.019$). This result is in line with two other more recent studies [4, 34]. However, disease severity did not significantly confound the association between fatigue and dynamic activity.

There are some study limitations that should be acknowledged. First, fatigue has been defined and assessed in different ways [6-8], making direct comparisons between studies difficult. Second, we used an AM to measure physical activity. Activity monitoring might have caused reactivity effects: patients may limit or increase their activities because of the presence of the recorder. However, explicit care was taken to keep patients naive about the specific function of the AM. In addition we did not

measure patients for 24 hours a day, but only during day time waking hours. This restricted period of measurement might have influenced the validity of activity monitoring, although 3-week test-retest reliability was good. Third, in our study we did not control for sleep disorders and apathy. As sleepiness and fatigue are two terms often used interchangeably, it is conceivable that sleep disorders could have distorted the association between fatigue and physical activity. However, Havlikova and colleagues concluded that fatigue was not cross-sectionally related to daytime sleepiness and night-time sleep dysfunction [35]. Apathy might have affected patients' activity level and could have distorted the association between fatigue and physical activity. However, Weintraub and colleagues found no significant association between apathy and activities of daily living [36]. Finally, the present study was part of a randomized clinical trial in which patients received cueing therapy. However, we found no significant distortion of the type of intervention on the amount of physical activity and perceived levels of fatigue.

The amount of physical activity in patients with PD depends on a number of aspects and its determinants are not yet fully understood. Fatigue and motor impairment may lead to a decreased effort capacity, whereas depression and alterations in neurotransmitter balance may result in an increased level of perceived effort [32]. A well-balanced medication regime targeting motor performance and mood disturbances, combined with a multidisciplinary rehabilitation program may reduce symptoms of fatigue, and thus increase levels of physical activity in patients with PD.

Previous studies have focused on the cross-sectional association between fatigue and physical activity. However, the existing relationship between time-dependent symptoms such as fatigue and the amount of physical activity may be more accurately reflected using longitudinal regression analysis. Explorative studies are needed to investigate the clinical and physiological aspects of fatigue in PD. In addition, randomized clinical trials studying the effect of medication management and rehabilitation programs on fatigue in patients with PD are needed.

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