

Fatigue in patients with Parkinson's disease: Motor and Non-motor Clinical Associations

Parkinsonlu Hastalarda Yorgunluk: Motor ve Non-motor Klinik Birliktelikler

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Objective: Fatigue is one of the common non-motor symptoms of Parkinson's disease (PD). In this study, we aimed to investigate the prevalence of fatigue in PD patients and to determine the fatigue-related demographic, motor and non-motor disease characteristics.

Materials and Methods: One hundred seventy-eight idiopathic PD patients were enrolled in the study (mean age 64.8±10.8 years). Demographic data and disease-related motor and non-motor clinical characteristics were recorded and total daily levodopa equivalent dose (LED) was calculated. Modified Hoehn and Yahr Staging (mHY), 'Unified Parkinson's Disease Rating Scale' (UPDRS) part II and III, Parkinson Fatigue Scale (PFS), Mini-Mental State Examination and semi-structured non-motor symptom questionnaire were used to assess the patients. Patients were divided into two groups according to the score of PFS<3.3 as PD without fatigue, PFS≥3.3 as PD with fatigue. Then we compared the disease characteristics between the two groups. Bivariate associations were analyzed using the chi-square and the independent samples t-test.

Results: The fatigue prevalence was 48.9% in all PD patients. There was no significant difference between groups regarding age and the duration of disease, but the mean LED in PD patients with fatigue was significantly higher than without fatigue ($p=0.011$). Parkinson's disease stage, activities of daily living and disease severity were not different between two groups. Orthostatic hypotension and sleep disturbances such as restless legs syndrome (RLS) and REM sleep behavior disorder (RBD) were significantly frequent in PD group with fatigue ($p=0.02$, $p=0.004$, $p=0.005$ respectively).

Conclusion: Fatigue affects about 50% of PD patients. Association of fatigue and non-motor symptoms may reflect the dopaminergic and non-dopaminergic underlying pathologic mechanisms.

Key Words: *Parkinson's disease, Fatigue, Motor symptoms, Non-motor Symptoms*

Amaç: Yorgunluk, Parkinson hastalığının (PH) en sık görülen non-motor semptomlarından biridir. Bu çalışmada Parkinson hastalarında yorgunluk prevalansını araştırmayı ve hastalığın yorgunluk ile ilişkili olabilecek demografik, motor ve non-motor özelliklerini belirlemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya 178 idiyopatik Parkinson hastası alındı (ortalama yaş 64.8±10.8 yıl). Demografik veriler, hastalık ile ilişkili motor ve non-motor klinik özellikler kaydedildi ve günlük kullanılan levodopa eşdeğer dozlar (LED) hesaplandı. Hastaları değerlendirmede modifiye Hoehn Yahr evreleme (mHY), Birleşik Parkinson Hastalığı Değerleme Ölçeği (BPHDÖ) bölüm II ve III, Parkinson yorgunluk ölçeği (PYÖ), mini mental durum muayenesi ve yarı yapılandırılmış non-motor semptom anketi uygulandı. Hastalar PYÖ puanlarına göre PYÖ<3.3 yorgunluğu olmayan, PYÖ≥3.3 yorgunluğu olan olmak üzere iki gruba ayrıldı. Gruplar arası farklılıklar ki-kare ve bağımsız örneklem t-testi ile analiz edildi.

Bulgular: Parkinsonlu hastalarda yorgunluk prevalansı %48.9'du. Gruplar arasında yaş ve hastalık süresi açısından anlamlı fark yoktu, ancak ortalama LED yorgunluğu olan Parkinson hastalarında olmayanlara göre anlamlı yüksekti ($p=0.011$). Gruplar arasında PH evresi, günlük yaşam aktiviteleri ve hastalık şiddeti açısından fark yoktu. Ortostatik hipotansiyon, huzursuz bacak sendromu ve REM uyku davranış bozukluğu gibi uyku bozuklukları yorgunluğu olan PH grubunda anlamlı ölçüde sıklığı (sırasıyla $p=0.02$, $p=0.004$, $p=0.005$).

Sonuç: Yorgunluk Parkinson hastalarının yaklaşık yarısını etkiler. Parkinson hastalığında yorgunluk ile bazı non-motor semptomların birlikteliği altında yatan dopaminergik ve nondopaminergik patolojik mekanizmayı yansıtır olabilir.

Anahtar Sözcükler: *Parkinson hastalığı, yorgunluk, Motor semptomlar, Non-motor semptomlar*

Received: Dec. 18, 2017, 2017 • Accepted: Dec. 26, 2017

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Fatigue is one of the most common non-motor symptoms of Parkinson's disease (PD). The importance of fatigue arises because symptom may cause disability and reduce the quality of life (1). Fatigue has been defined as an overwhelming sense of tiredness

(2). It is characterized by a subjective feeling of energy to start and maintain a regular activity, without any connection with depression or muscle weakness and consists both mental and physical component (2,3).

The first prevalence study of fatigue in PD patients was published by Friedman *et al.* in 1993 (4). Reported fatigue prevalence changes between 33%-58% in different studies (1). Patients with PD may experience fatigue at the every stage of the disease, sometimes it may be seen as a pre-motor symptom (1,5). To date, underlying fatigue mechanism has not sufficiently understood yet, but some significant evidence supported that the fatigue was an intrinsic symptom related to PD pathology (1). PD-related fatigue primarily arises from PD pathology is a distinct clinical syndrome, therefore all other potential secondary fatigue causes including untreated depression, chronic pain, sleep disorders, medications orthostatic hypotension, systemic and metabolic conditions have to be ruled out (1). Fatigue may be a pre-motor symptom of PD and fatigue complaints may often be seen in the early stages of the disease. Accordingly, there is no correlation between fatigue and motor fatigability (1,6). Likewise, fatigue in PD does not well respond to dopaminergic or surgical therapies (6).

Previous studies could not find a clear relationship between fatigue and motor severity of PD symptoms assessed by UPDRS and HY stage while some other reports have found a relationship between fatigue and severity of disease (7-11). Moreover, fatigue was reported as more severe in patients with postural instability and gait disorders (12). There are also reports suggesting that many of non-motor symptoms of PD are correlated with fatigue in PD patients. Fatigue consistently associated with depression (6), is also inconsistently associated with sleep disorders and sleep quality (1,13). There is a preliminary evidence suggesting that fatigue may be associated with cognitive impairment, particularly frontal executive dysfunction (14).

In this study, we aimed to assess the prevalence of fatigue in PD patients and to determine the potential relationship between fatigue and clinical features including age, sex, disease duration and severity, presence of dyskinesia and motor fluctuations. We also investigated the possible associations between fatigue and motor (tremor, bradykinesia, rigidity, gait/postural instability), and non-motor symptoms of PD.

Patients and Methods

Subjects

Patients were consecutively recruited from the Diskapi Yildirim Beyazıt Training and Research Hospital, Movement Disorders Outpatient Clinic, Ankara, between January 2015 and September 2017. This cross-sectional study consisted 178 patients (103 male, 57.9%), selected from patients who were diagnosed with idiopathic PD according to the UK Brain Bank criteria (15). Patients with severe dementia, vascular and secondary parkinsonism and fatigue-related diseases (including severe liver disease, renal failure, and cardiopulmonary disease) were excluded from the study. This study was carried out according to the Helsinki Declaration and was approved by the local ethics committee. All participants provided informed consent.

Demographic data including age, sex, comorbidities and disease characteristics (duration of the disease and treatment regimens) were recorded. A total daily levodopa equivalent dose (LED) was calculated based on previous reports with LED: (regular levodopa dose x 1) + (levodopa controlled release dose x 0.75) + (pramipexole dose x 1) + (ropinirole dose x 20) + (rasagiline dose x 100) + (entacapone dose = levodopa x 0.33) + (amantadine x 1) + (apomorphine x10) (16).

Assessments of Patients

Stage of disease, activities of daily living and the severity of disease were determined by the 'modified Hoehn and Yahr Staging' (mHY), 'Unified Parkinson's Disease Rating Scale' (UPDRS) part II and III, respectively (17,18). All patients were examined during 'on' period. UPDRS subscores obtained from specific items of UPDRS part III were calculated: tremor (items 20, 21), rigidity (item 22), bradykinesia (items 23-26, 31) and gait/postural instability (items 27-30). In addition, the presence of dyskinesia and motor fluctuations were also noted.

Fatigue was assessed using the Parkinson Fatigue Scale (PFS). The Parkinson Fatigue Scale was designed to assess fatigue exclusively associated with PD. This self-report questionnaire consists 16 items. Each item responses range from 1 (strongly disagree) to 5 (strongly agree). The Parkinson Fatigue Scale cut-off score 3.3 was used to indicate the presence of fatigue (19). Patients were divided into two groups according to the PFS < 3.3 as PD without fatigue and PFS ≥ 3.3 as PD with fatigue.

The global cognitive status was evaluated using the standardized 'Mini-Mental State Examination' (MMSE). Non-motor symptoms including orthostatic hypotension, sleep and neuropsychiatric disturbances, gastrointestinal and urinary symptoms, olfactory dysfunction, sweating disturbances and pain were assessed by interviewing and a semi-structured questionnaire.

Statistical Analysis

Statistical analyses were performed using MedCalc for Windows, version 15.2 (MedCalc Software, Ostend, Belgium). Descriptive statistics are presented as the mean ± standard deviation for continuous variables and number (weighted %) for nominal

variables. Normal distribution was tested using the Shapiro-Wilk test. 'Fatigue' was used as dependent variable. Bivariate associations were analyzed using the chi-square test for categorical variables and the independent samples t-test for continuous variables. Results with a value of $p < 0.05$ were considered statistically significant.

Results

Demographic and Clinical Features

Demographic and clinical characteristics of the groups are shown in Table 1.

The fatigue prevalence was 48.9% in all PD patients. Female PD patients presented with fatigue more frequently compared to males, but this difference was not significant. The mean age was 64.8 ± 10.8 years and mean duration of the disease was 7.2 ± 5.9 years. There was no significant difference between the groups regarding age and the duration of disease, but the mean LED in PD patients with fatigue was significantly higher than without fatigue ($p = 0.011$).

Motor Characteristics of the PD with and without Fatigue groups

The stage of disease, activities of daily living and disease severity were not different between two groups according to mHY stages and UPDRS part II/III scores. Additionally, UPDRS motor sub-scores determined by tremor, rigidity, bradykinesia, and gait/postural instability were similar between the PD with and without fatigue groups.

Table 1. Patient Characteristics

Variables	All PD patients (n=178)	PD with fatigue (n=87)	PD without fatigue (n=91)	p
Age (years) [†]	64.8±10.8	63.4±10.4	66.3±10.6	0.067
Female gender [‡]	75 (42.1)	43 (57.3)	32 (42.7)	0.054
Disease duration (years) [†]	7.2±5.9	7.0±5.4	7.3±6.4	0.719
mHY stage [†]	2.0±0.8	2.0±0.8	2.1±0.9	0.836
1 (n)	51	25	26	
1.5 (n)	5	4	1	
2 (n)	44	14	30	
2.5 (n)	50	32	18	
3 (n)	21	11	10	
4 (n)	5	0	5	
5 (n)	2	1	1	
UPDRS II score [†]	12.9±7.8	12.8±7.4	13.0±8.3	0.898
UPDRS III score [†]	18.2±9.9	18.1±9.6	18.3±10.2	0.891
UPDRS tremor sub-score [†]	1.8±1.6	1.9±1.6	1.8±1.6	0.836
UPDRS rigidity sub-score [†]	1.9±0.9	1.9±0.8	2.0±0.9	0.712
UPDRS bradykinesia sub-score [†]	9.1±4.7	9.2±4.5	9.0±4.8	0.768
UPDRS gait/postural instability sub-score [†]	3.4±3.9	3.4±3.5	3.4±4.2	0.994
Motor fluctuations [‡]	96 (53.9)	46 (52.9)	50 (54.9)	0.782
Dyskinesia [‡]	55 (30.9)	29 (33.3)	26 (28.6)	0.492
LED (mg/day) [†]	754.6±447.9	841.1±451.7	671.9±305.8	0.011*
MMSE score [†]	25.2±4.2	25.6±3.6	24.8±4.7	0.194
Orthostatic hypotension [‡]	53 (28.3)	33 (37.9)	20 (22.0)	0.020*
Sleep disturbances				
Fragmentation of sleep [†]	101 (56.7)	51 (58.6)	50 (54.9)	0.621
Excessive daytime sleepiness [†]	63 (35.4)	36 (41.4)	27 (29.7)	0.102
RLS [‡]	69 (38.8)	43 (49.4)	26 (28.6)	0.004*
RBD [‡]	85 (47.8)	51 (58.6)	34 (37.4)	0.005*
Neuropsychiatric disturbances				
Apathy [‡]	37 (20.8)	19 (21.8)	18 (19.8)	0.735
Depression [‡]	79 (44.4)	43 (49.4)	36 (39.6)	0.185
Anxiety [‡]	67 (37.6)	38 (43.7)	29 (31.9)	0.104
Hallucinations [‡]	38 (21.4)	21 (24.1)	17 (18.7)	0.374
Gastrointestinal symptoms				
Constipation [‡]	103 (57.9)	54 (62.1)	49 (53.8)	0.267
Dysphagia [‡]	30 (16.9)	17 (19.5)	13 (14.3)	0.349
Sialorrhea [‡]	73 (41.0)	42 (48.3)	31 (34.1)	0.054
Urinary symptoms				
Nocturia [‡]	104 (58.4)	57 (65.5)	47 (51.6)	0.061
Incontinence [‡]	63 (35.4)	36 (41.4)	27 (29.7)	0.102
Olfactory dysfunction [‡]	63 (35.4)	33 (37.9)	30 (33.0)	0.489
Sweating disturbances [‡]	73 (41.0)	42 (48.3)	31 (34.1)	0.054
Pain [‡]	95 (53.4)	51 (58.6)	44 (48.4)	0.170

* Difference is statistically significant ($p < 0.05$)

† Data reported as mean±standart deviation

‡ Data reported as n, %

Abbreviations: PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; mHY, modified Hoehn and Yahr staging; MMSE, Mini-Mental State Examination; LED, Levodopa equivalent dose; RLS, Restless legs syndrome; RBD, REM sleep behavior disorder

Non-motor Characteristics of the PD with and without Fatigue groups

Orthostatic hypotension and sleep disturbances such as restless legs syndrome (RLS) and REM sleep behavior disorder (RBD) were significantly frequent in PD with fatigue group ($p=0.02$, $p=0.004$, $p=0.005$ respectively). Other non-motor symptoms such as apathy, depression, anxiety, hallucinations, gastrointestinal and urinary symptoms, olfactory dysfunction, sweating disturbances and pain were not different between the two groups. We could not find any significant difference in cognitive functioning assessed by MMSE.

Discussion

Fatigue is one of the most common non-motor symptoms in PD. We found the fatigue prevalence as 48.9% in our study. This result is consistent with previous investigations. The reported fatigue frequency changes between 33%-58% (1).

Our study showed no association between age, sex and the duration of the disease between the groups. While female PD patients presented fatigue more than males, this tendency was not significant. A previous Norwegian study reported that there was a difference between fatigue and gender, however other studies did not support this result (9,10,12). Additionally, Herlofson and Larsen and Martinez Martin *et al* reported no relationship between the severity of fatigue and age, disease duration, which is consistent with the findings of the present study (20,21).

Herlofson and Larsen also reported that fatigue was associated with the stage and the severity of disease as well as increased severity of postural disorders (1). Many other reports did not show a relationship between fatigue and the stage and the severity

of disease and the severity of axial symptoms and UPDRS sub-scores (3,6,11). There was no association between fatigue and motor fluctuations and dyskinesia in the previous studies (3).

Which pathology may cause fatigue in PD has not been clear yet. Chaudhuri and Behan proposed a general model and they hypothesized circuits which connects the basal ganglia and medial frontal areas such as anterior cingulate gyrus being affected may contribute fatigue in PD (22). There have been no neuropathologic studies of PD fatigue, and only three neuroimaging studies (1,23,24). Summary of these studies suggested that prefrontal hypoperfusion on SPECT may associate cognitive deficits, serotonergic dysfunction in striatum an insula using PET (supports non-dopaminergic mechanisms) and limbic dysfunction may contribute fatigue in PD (1).

Earlier studies showed levodopa reduces physical fatigue in PD and suggested dopaminergic treatment can improve some aspects of fatigue (25) It was also reported a relationship between fatigue and the daily dose of levodopa (3,20). We also found a significant difference between fatigue and higher LED, therefore we thought the fatigue in PD may be a dopamine-sensitive symptom. In clinical practice, fatigue is not a levodopa responsive symptom. ELLDOPA trial showed fatigue in 'levodopa-treated patients' progressed slower compared with placebo. It is not clear how this effect occurs with a direct effect of levodopa or secondary to the motor increased activity levels (1). Thus, restoring dopamine levels in the central nervous system by means of dopaminergic medication, such as levodopa, might be an essential strategy for the treatment of fatigue in PD (26). In addition, Pavese *et al.* found reduced serotonin transporter binding in the basal ganglia and limbic circuitry, as well as significant reduction in dopamine uptake in the caudate and insula (23).

Therefore, serotonergic pathway plays a predominant role in fatigue and reduced dopaminergic function also contributes to fatigue (23). Fatigue is closely related to other non-motor symptoms of PD. Studies assessing the association between fatigue and other non-motor symptoms have demonstrated that at least one symptom occurs in 88% of PD patients, two or more occur in 59%, three or more occur in 39%, four or more occur in 23% and more than five occur in 11% (3).

We found a positive association between fatigue and orthostatic hypotension in current study. Autonomic dysfunction may be involved in the pathogenesis of fatigue in PD (2). Increased orthostatic tolerance has been observed in patients with chronic fatigue syndrome (2). Thus, PD patients with orthostatic hypotension may experience fatigue.

Fatigue can appear as a consequence of sleep disorders and is related to apathy, but it seems that fatigue, apathy, depression and excessive daytime sleepiness are independent symptoms occurring in PD (3,27). Although the mechanisms of sleep disturbances and fatigue have not been clarified, increased inflammatory cytokine release has been associated with poor sleep and fatigue (26). Interleukin-1 β and tumor necrosis factor- α promotes non-rapid eye movement sleep. Moreover, reduction of serotonin transporters was found in PD with fatigue patients. Therefore, serotonergic functions may play a role in sleep and fatigue (26). Or may be it's just because PD patients cannot have a good night's sleep, and feel fatigue on the following day.

Comparing the groups of PD with and without fatigue we did not identify any relationship between the presence of fatigue and apathy, depression, anxiety and cognitive functioning. Because we did not use standardized detailed specific tools to assess these symptoms, we couldn't find any

association between fatigue and such non-motor symptoms.

The present study has several limitations. First, it was a single-centered study and there was no control group. Additionally this study is consisted of nearly 80% patients with earlier stages of PD (mHY 1-3) thus we couldn't compare the groups within the PD stages. Also we could not compare the fatigue severity between PD patients and controls. Therefore these results

may not be generalized. Last, further studies needed to determine the possible relationship between the non-motor symptoms and specific dimensions of fatigue (e.g., mental fatigue and physical fatigue) in PD.

Conclusion

Fatigue is a frequent, disabling symptom of PD affecting about 50% of patients. It may be seen at every stage of the disease and may not be

associated with motor disability. Non-motor symptoms including orthostatic hypotension and sleep disorders such as RLS and RBD may be related to fatigue in PD. Many patients with fatigue may respond dopaminergic therapies and need higher doses of levodopa for treatment. Association of fatigue and non-motor symptoms in PD may reflect the underlying dopaminergic and non-dopaminergic pathogenic mechanism.

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