Is fatigue an independent and persistent symptom in patients with Parkinson disease?

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Abstract—*Objective:* To evaluate if mental fatigue is a symptom that appears independently from other clinical features in patients with Parkinson disease (PD), and to study if fatigue is persistent over time in these patients. *Methods:* In 1993, 233 patients with PD were included in a community-based study of fatigue and followed prospectively over 8 years. Fatigue was measured by a combination of a seven-point scale and parts of the Nottingham Health Profile (NHP) at baseline and after 4 and 8 years. In addition, the Fatigue Severity Scale (FSS) was used to evaluate fatigue in 2001. Population-averaged logistic regression models for correlated data were performed to study the relationship between fatigue and various demographic and clinical variables. *Results:* In patients who were followed throughout the 8-year study period, fatigue increased from 35.7% in 1993 to 42.9% in 1997 and 55.7% in 2001. Fatigue was related to disease progression, depression, and excessive daytime sleepiness (EDS). However, the prevalence of fatigue in patients without depression and EDS remained high and increased from 32.1% to 38.9% during the study period. For about 44% of the patients with fatigue the presence of this symptom varied during the study period, as it was persistent in 56% of the patients with fatigue. *Conclusions:* The authors confirmed the high prevalence of mental fatigue in patients with Parkinson disease (PD). Fatigue is related to other non-motor features such as depression and excessive daytime sleepiness, but cannot be explained by this comorbidity alone. In more than half of the patients mental fatigue is persistent and seems to be an independent symptom that develops parallel to the progressive neurodegenerative disorder of PD.

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As with other non-motor problems, fatigue has been an under-recognized symptom in patients with Parkinson disease (PD),[1] and the pathogenesis of fatigue in PD is largely unknown. Pathologic cytokines in certain areas of the brain, frontal lobe dysfunction, and dopaminergic dysfunction in limbic structures are thought to be related to fatigue in PD.[2,3]

Fatigue has been found in between 40% and 56% of patients with PD and has negative impact on their quality of life.[1,4-6] Several studies have shown an association between fatigue and depression in PD patients.[4,7] In contrast, cross-sectional studies have not found a direct relationship between disease severity and the presence of fatigue.[1,4,7-8]

The clinical knowledge of fatigue in PD is mainly based on prevalence studies. The cross-sectional design of such studies limits the possibility to describe the course of fatigue over time. As yet, only one study has made the attempt to evaluate longitudinally fatigue in patients with PD. In that retrospective, questionnaire-based study fatigue was a persistent symptom over 9 years in 26 patients with PD.[9]

In the present study of a population-based cohort of patients with PD we examined prospectively the occurrence and development of mental fatigue over an 8-year period. The aims of this study were to answer the following questions: Which demographic and clinical variables are related to mental fatigue? To which extent is mental fatigue a symptom that is independent of other non-motor problems in patients with PD? Is mental fatigue a persistent symptom over time in patients with PD?

Methods. *Study population.* On January 1, 1993, in a prevalence study in the County of Rogaland, Norway, the crude prevalence rate for PD was 110.9 per 100,000 inhabitants.[10] Totally, 245 patients were diagnosed with PD according to published criteria.[11] Complete case ascertainment was based on hospital records and information from all general practitioners, nursing homes, district nurses, and health visitors in the study area. Details on patient recruitment have been published previously.[10]

In 1993, 233 of these 245 patients were included in a study evaluating fatigue in PD. The patients were re-evaluated in 1997 and 2001. During the 8-year follow-up period 103 had died, 4 refused to participate in the follow-up examinations, and 6 patients were re-diagnosed as not having PD. Forty-two patients could not be evaluated for fatigue due to illnesses like severe dementia. A total of 111 patients were available for examinations of fatigue in 1997 and 78 patients in 2001.

Study design and examination program. This was a prospective longitudinal study evaluating fatigue in a representative population of 233 patients with PD. The original patient cohort was derived from a community-based prevalence study in 1993. Patients were re-examined in 1997 and 2001.

All patients were interviewed and evaluated by a neurologist and a psychiatrist or psychiatric nurse from the study group. They were evaluated by the same standardized examinations and questionnaires in 1993, 1997, and 2001. The evaluation of disease

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severity was done by a clinical examination and rating scales of parkinsonism (Unified Parkinson's Disease Rating Scale [UPDRS] ADL and motor scores,[12] Hoehn & Yahr staging,[13] and the Schwab and England scale[14]). Based on the dominance of different motor symptoms the disease type of the individual patient was classified as tremor-dominant (TD), postural-instability gait difficulty (PIGD), and indeterminate subtype as described in previous studies.[15] For assessment of heredity of PD among the patients we asked for detailed information about occurrence of PD in their families. On the basis of reported familial occurrence of PD patients were classified into three groups: no occurrence of PD in family, occurrence of PD in first-degree relatives, and occurrence of PD in others than first-degree family members.[16] Symptoms of depression were measured by the Beck Depression Inventory (BDI) and the Montgomery & Aasberg Depression Rating Scale (MADRS).[17,18] The Mini-Mental State Examination (MMSE) was used to evaluate cognitive impairment.[19] Patients who reported nighttime sleep problems or used sleeping pills were classified as having insomnia. For assessment of daytime sleepiness the frequency and duration of sleeping periods during daytime were evaluated. Patients who slept more than 2 hours during the day or fell asleep three times or more during daytime were deemed to have excessive daytime sleepiness (EDS).[20] In 2001, patients were also examined with the Epworth Sleepiness Scale (ESS) to test the validity of the classification of daytime sleepiness applied in this study. In 2001, there was a difference in mean ESS scores for patients without EDS (7.0 [SD 4.1]) vs patients with EDS (16.4 [SD 5.8]) (Mann-Whitney test, $p < 0.001$).

Information from two different rating scales of patient-perceived energy was used to evaluate mental fatigue in 1993, 1997, and 2001. The Nottingham Health Profile (NHP),[21,22] a health-related quality of life questionnaire, gives information about lack of energy in one of its six subareas. In the NHP, the patients are asked to answer 38 different questions with "yes" or "no." The items that were included in the evaluation of fatigue in this study were "I am tired all the time," "Everything is an effort," and " I soon run out of energy." In addition, all patients gave a statement of feeling energetic or fatigued on a seven-point scale.[4] They were asked if they mostly felt strong and healthy, somewhat strong and healthy, cannot decide, somewhat tired and worn out, tired and worn out, or very tired and worn out. Patients who scored four or more on the seven-point scale and reported lack of energy in at least one of three questions on the NHP were classified as having fatigue.

To evaluate the validity of this classification, fatigue was also assessed by the Fatigue Severity Scale (FSS) in the 2001 examination.[23,24] Mean FSS score for PD patients with fatigue according to the above described classification was 5.3 (SD 1.5) vs FSS score of 3.7 (SD 1.6) for patients without fatigue. There was a difference in mean FSS score between the patient groups with and without fatigue (Mann-Whitney test, $p < 0.001$).

To investigate the relationship between fatigue and various demographic and clinical variables, we analyzed data at all study visits from the whole patient cohort. In contrast, the evaluation of persistency or possible fluctuations of fatigue over time needs several repeated observations. In consequence, only patients who participated in all examinations in the 8-year study period were included in the analysis of whether fatigue was persistent or not over time. Of the 78 patients who participated in the examinations in 2001, the data of 8 patients were incomplete because of poor compliance in the 1997 evaluation. Therefore, data from 70 patients were available for the analysis of persistency of fatigue in patients with PD. Fatigue was classified as persistent when it appeared as a continuous complaint of the patients in at least two consecutive examinations and criteria for fatigue were fulfilled in 2001. This means that patients who had fatigue at all three observations or at the examinations in 1997 and 2001 were considered to have persistent fatigue. Except for patients who were diagnosed with fatigue only in 2001, patients who had fatigue at least at one examination but did not fulfill the above criteria at the next study visit were classified as having non-persistent fatigue.

Statistical analysis. Statistical analyses were performed using the statistical software programs SPSS 11.0 (SPSS Inc., Chicago) and STATA (StataCorp LP, TX). In cross-sectional data, Mann-Whitney tests were used to compare medians for continuous variables. Differences in proportions for categorical variables were analyzed by χ^2 tests.

The relationship between fatigue and demographic and clinical variables was analyzed by population-averaged logistic regression models for correlated data (Stata procedure xtgee) using all observations available. Since there were only three consecutive points of time, unstructured correlations were used. Covariates considered for the multivariate model were age, sex, disease type (PIGD, tremor-dominant, or indeterminate), family history of PD (absent, PD in first-degree relatives, PD in others than first-degree family members), disease duration, UPDRS motor score and ADL score, Hoehn & Yahr staging, Schwab and England score, MADRS score, BDI score, MMSE score, insomnia (present or absent), and EDS (present or absent).

The significant covariates from the final population-averaged logistic regression model were used to identify patients with low levels of these risk factors, and the proportion of fatigue for these patients at each occasion was investigated to judge whether fatigue occurred independently of identified risk factors. For all data two-tailed p values less than 0.05 were considered significant.

Results. At baseline, there were no significant differences in composition of age or sex between the two groups. Mean disease duration in 1993 for patients with fatigue was 10.3 years compared to 7.8 years for patients without fatigue. This difference was statistically significant. At all study visits, there was a higher proportion of patients with PIGD-subtype in the fatigue group than among patients without fatigue. Patients with fatigue had significantly higher scores of depressive symptoms in at least one of two rating scales for depression (BDI, MADRS) in 1993, 1997, and 2001. Throughout the whole study period patients with fatigue had a significantly higher disease severity (measured by UPDRS ADL and motor score, Hoehn & Yahr staging, and Schwab and England score) and cognitive impairment (measured by MMSE) compared with patients without fatigue. The proportion of insomnia and EDS was significantly higher in the fatigue group in 1993, but not later in the study period. There were no significant differences in levodopa dose between the two groups at any of the study visits. Demographic and clinical patient characteristics at baseline are summarized in table 1.

Demographic and clinical covariates for fatigue. In the population-averaged logistic regression model, fatigue was related to MADRS ($p < 0.001$, OR 1.13, 95% CI 1.07 to 1.19), BDI ($p < 0.01$, OR 1.07, 95% CI 1.02 to 1.12), and EDS ($p < 0.05$, OR 2.36, 95% CI 1.02 to 5.47). In addition, there was a relationship between fatigue and Hoehn and Yahr staging ($p < 0.05$, OR 0.94, 95% CI 0.88 to 1.00).

Independence of fatigue. Since the overlap in symptomatology of fatigue and other non-motor features could have caused the positive relationship between fatigue and depression and EDS, we excluded all patients who showed depressive symptoms (MADRS > 19, BDI > 18) and EDS in the study period. In this selected patient group the prevalence rate of fatigue was still high and increased from 32.1% in 1993 (95% CI 23% to 41%) to 38.9% in 2001 (95% CI 14% to 64%).

Persistence of fatigue. To explore if fatigue was a persistent symptom in patients with PD, we included the patients who had participated in all three examinations during the study period. Among this group of 70 patients the prevalence rate of fatigue increased from 35.7% in 1993 to 42.9% in 1997 and 55.7% in 2001. We found that 74.3% had fatigue at least at one study visit, while 25.7% of the patients did not have fatigue at any time. Of the 52 patients with fatigue at at least one study visit, 23.1% had fatigue throughout the whole study period. A total of 19.2% of the patients were diagnosed with fatigue both in

Table 1 *Demographic and clinical data for patients with and without fatigue at baseline*

	With fatigue	Without fatigue	*p* Values
Number (%)	103 (44.2)	130 (55.8)	—
Mean age, y (SD)	74.2 (7.9)	72.6 (8.8)	0.216
Sex, % female (SD)	48.5 (50.2)	52.3 (50.1)	0.568
Mean duration of disease, y (SD)	10.3 (6.4)	7.8 (4.8)	0.003
Mean levodopa dose, mg/d (SD)	550 (266)	463 (206)	0.080
Mean UPDRS ADL score (SD)	16.9 (9.4)	11.9 (7.1)	0.000
Mean UPDRS motor score (SD)	31.8 (15.7)	24.2 (13.1)	0.000
Mean Hoehn and Yahr stage (SD)	3.1 (1.1)	2.6 (1.0)	0.001
Mean Schwab and England score (SD)	61.7 (23.8)	75.1 (18.7)	0.000
PD type, % PIGD (SD)	82.8 (76.0)	69.4 (92.6)	0.032
Mean MADRS score (SD)	11.6 (7.0)	5.3 (4.0)	0.000
Mean BDI score (SD)	15.7 (8.4)	10.4 (7.4)	0.000
Mean MMSE score (SD)	22.8 (7.4)	26.4 (4.8)	0.000
Insomnia, % (SD)	69.9 (46.1)	51.5 (50.2)	0.005
EDS, % (SD)	26.4 (44.3)	8.4 (27.9)	0.001

Chi-square test for frequency results, Mann-Whitney test for continuous variables. All *p* values are two-tailed. All available observations are included in the results.

UPDRS = Unified Parkinson's Disease Rating Scale; ADL = Activities of Daily Living; PD = Parkinson disease; PIGD = postural-instability gait difficulty; MADRS = Montgomery + Aasberg Depression Rating Scale; BDI = Beck Depression Inventory; MMSE = Mini-Mental State Examination; EDS = excessive daytime sleepiness.

1997 and 2001, but not in 1993. A total of 25.0% were diagnosed with fatigue in 2001 but did not have this symptom in 1993 or 1997. A total of 32.7% of the patients showed fatigue as a non-persistent symptom (table 2). Therefore, among the 39 patients with classifiable (persistent or non-persistent) fatigue, 22 patients (56.4%, 95% CI 40% to 71%) had persistent and the remaining 17 (43.6%) had non-persistent fatigue.

Discussion. In this prospective longitudinal study of 233 patients with PD we assessed the course of fatigue and its relationship to other clinical features over an 8-year period. Our findings confirm the high prevalence of fatigue in PD shown in cross-sectional studies.[4-6,8,25] Among the patients evaluated at all study visits, the proportion of patients with fatigue increased from 35.7% to 55.7% during follow-up. We found persistent fatigue in slightly more than half of the patients and that fatigue was a non-persistent symptom in about 44% of the patients. In the regression model, fatigue was related to depression, EDS, and disease progression (measured by Hoehn and Yahr staging). However, in patients without depressive symptoms and daytime somnolence the prevalence of fatigue remained as high as 32.1% in 1993 and increased to 38.9% in 2001. This indicates that fatigue is present also in the absence of other non-motor problems with possible overlapping symptomatology.

Table 2 *Occurrence and development of fatigue from 1993 until 2001 in 70 patients with Parkinson disease*

	No. %	1993	1997	2001
Never fatigue	18 (25.7)	0	0	0
Nonpersistent fatigue	5 (7.1)	X	0	0
	4 (5.7)	X	0	X
	4 (5.7)	0	X	0
	4 (5.7)	X	X	0
Persistent fatigue	10 (14.3)	0	X	X
	12 (17.1)	X	X	X
Unclassified*	13 (18.6)	0	0	X

* Unclassified = first appearance of fatigue in 2001 and therefore without follow-up information.

0 = no fatigue; X = diagnosed with fatigue.

The strengths of this study are its prospective nature and a rather large population of PD patients that represents an unselected cohort from a restricted geographic area.[10] Explicit diagnostic criteria[11] and generally acknowledged evaluation instruments have been used.[12-14,17-19] Robust statistical analyses of longitudinal data were performed using population-averaged multivariate logistic regression analysis for correlated data.[26]

Fatigue was assessed by a combination of a seven-point scale and parts of the NHP.[4,21,22] The validity of this evaluation of fatigue was confirmed by the results from the FSS in 2001, which showed highly significant differences between the patients with and without fatigue. However, general problems in assessing fatigue are its subjective nature and in PD the high prevalence of other non-motor symptoms that may overlap with the symptomatology of fatigue. Furthermore, both sedative medications and alerting agents may have effects on patients' perception of fatigue. The overlap between fatigue and other non-motor features may lead to an overestimate of fatigue due to low specificity of relevant evaluation instruments. In our study, fatigue was related to depression and daytime somnolence in the regression model. To elucidate this relationship further, we analyzed the prevalence of fatigue in patients without depressive symptoms or EDS in 1993, 1997, and 2001. Among these patients without depression and EDS the prevalence rate of fatigue was still as high as 32.1% in 1993 and 38.9% in 2001, indicating that fatigue to a large extent appears independently from other non-motor features. The correlation between fatigue and depression and EDS, shown in the regression model, may be caused by comorbidity of or overlap between symptoms of these three non-motor features. The problems induced by a low specificity

of current evaluation instruments are difficult to solve because of the close symptomatology of fatigue and the other non-motor features. On the other hand, the high frequency of fatigue also among the patients without depression and somnolence shows that fatigue is still important as an independent symptom in patients with PD.

The comorbidity of fatigue and other non-motor symptoms such as depression, dementia, and sleep problems in our patient cohort is noticeable and in line with previous observations.[1,4,5] In addition, there is a higher prevalence of fatigue among patients with the PIGD-subtype throughout the whole study period. All these features have in common that they usually do not respond to dopaminergic treatment and are more common in patients with advanced disease. Based on results from cross-sectional studies fatigue has been understood as a symptom which is independent from disease severity and progression.[4,8,25] Our finding that the prevalence rate of fatigue increased steadily during the 8 years of follow-up is therefore new and important. The regression model showed a significant relationship between fatigue and the Hoehn and Yahr staging, and it excluded age and disease duration as other potential explanatory factors for this observation. Therefore, we suggest that fatigue is developing parallel to the progressive neurodegenerative disorder of PD and may be the consequence of a more widespread disease.

In a retrospective longitudinal follow-up study of 26 patients with PD fatigue occurred as a persistent feature when measured twice, at baseline and 9 years later, indicating that fatigue is a symptom that becomes permanent when first experienced by a patient.[9] These results could not be confirmed in our study. We found that fatigue occurred as a persistent symptom in about 56% and as non-persistent fatigue in 44%. Although this observation is new and may have implications for the understanding of the nature of this important complaint of patients with PD, the overlap in symptoms between fatigue and other non-motor problems may again complicate the interpretation of this finding. If fatigue was a persistent symptom this would support a clear relationship between fatigue and cerebral lesions. The results from our study are therefore not conclusive about possible underlying causes of fatigue. To further approach the etiology of fatigue in patients with PD, studies combining clinical information and markers of neurobiological changes seem to be necessary.

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