Functional Decline in Parkinson Disease

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Objectives: To determine the overall rate of functional decline and to assess the progression of different signs of Parkinson disease (PD).

Patients and Methods: Patients with clinically diagnosed PD followed up for at least 3 years were included in this study. Demographic and clinical data (including the Unified Parkinson's Disease Rating Scale [UPDRS]) were analyzed by the multivariate unbalanced repeated-measurements design using the mixed-effects model to study the association between different symptoms and various demographic variables. Regression models helped estimate the rates of progression of the disease in relation to the various components of the UPDRS. Patients were categorized as having tremor-dominant or postural instability–gait difficulty–dominant PD and the 2 categories were compared for progression of their total UPDRS scores.

Design: A multivariate mixed-effects model was used to study the relationship between the different symptoms and various demographic variables. Nonparametric statistical tests were used to compare the progression of symptoms in the “on” (good function) state and the “off” (poor function) state groups for 2 age-at-onset categories (<57 and ≥57 years).

Results: Data from 1731 visits on 297 patients (181 men) followed up for an average of 6.36 years (range, 3-17 years) were analyzed. The annual rate of decline in the total UPDRS scores was 1.34 when assessed during the on state and 1.58 when assessed during the off state. Patients with an older age at onset had more rapid progression of PD than those with a younger age at onset. Furthermore, the older-onset group had statistically significantly more progression in mentation, freezing, and parts I (mentation) and II (activities of daily living) UPDRS subscores. Handwriting was the only component of the UPDRS score that did not notably deteriorate during the observation period. Regression analysis of 108 patients whose symptoms were rated during their off state showed a faster rate of cognitive decline as age at onset increased. The slopes (ie, the annual rates of decline) of progression in the UPDRS scores, when adjusted for age at the initial visit, were steeper for the postural instability–gait difficulty–dominant group compared with the tremor-dominant group.

Conclusion: Based on longitudinal follow-up data, our findings provide evidence for a variable course of progression of the different PD symptoms, thus implying different biochemical or degenerative mechanisms for the various clinical features associated with PD.

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PROGRESSIVE decline in motor function is the expected natural course of Parkinson disease (PD). There is, however, little or no information on what demographic or clinical features determine or influence the rate of progression of the disease and of the different symptoms. Although some studies have attempted to address this important issue,1,9 most are based on a cross-sectional design or only a short follow-up. Furthermore, while the clinical heterogeneity of PD is well recognized, to our knowledge the long-term prognosis of the different clinical subtypes has not been studied prospectively.

Besides the clinical variability between patients, the different parkinsonian features manifested by individual patients seem to progress at different rates, suggesting a variable involvement of the dopaminergic system and possibly other pathways. Furthermore, it is well recognized that not all patients with PD or with signs of PD respond the same way to levodopa treatment.2,10 The primary objectives of this study are to determine the overall rate of functional decline and to assess the progression of different signs over time in patients with PD who are receiving treatment.

RESULTS

The 297 patients (181 men) generated a total of 2717 of on- and off-state scores in 1731 visits (mean, 5.80 visits per patient; range, 2-24 visits per patient). The average follow-up was 6.36 years (range, 3-17 years). The average age at onset of symptoms was 55.10 years (range, 16-82 years; median, 57 years) and the average duration of symptoms at the time of the initial visit was 6.50 years (range, 0.05-50 years).

In the multivariate, unbalanced, repeated-measurements design model, no
PATIENTS AND METHODS

DATA COLLECTION

Demographic (ie, sex, age at onset, and current age) and clinical data on 297 consecutive patients diagnosed by 1 of us (J.J.) as having typical PD and who were followed up for at least 3 years at Baylor College of Medicine Parkinson Disease Center, Houston, Tex, between 1985 and 2001 were entered into the database. All patients were examined at their initial and subsequent visits for any evidence of atypical features, such as early onset of cognitive decline, postural instability, autonomic dysfunction, or poor response to levodopa treatment. Their condition was also rated on the Unified Parkinson’s Disease Rating Scale (UPDRS). Only patients in whom the diagnosis of PD was maintained during the follow-up period were included in this study; those with atypical parkinsonism suggestive of progressive supranuclear palsy, multiple system atrophy, or other parkinsonian disorders were excluded. In patients treated with levodopa, we specified whether the UPDRS data were obtained when the patients were examined during the “on” (good function) or “off” (poor function) state. The UPDRS rating was categorized as on state when the patients reported that their improvement after the last dose of levodopa treatment was optimal (even though it may have been accompanied by dyskinesias), whereas the off-state scores reflected their state when the levodopa effects from the previous dose completely or almost completely wore off. For practical and ethical purposes, the patients were not instructed to come to the clinic in their off state after an overnight abstinence from levodopa treatment. During the course of their follow-up, the patients were treated with a variety of antiparkinsonian medications besides levodopa, including selegeline hydrochloride and dopamine agonists. An independent audit was performed on 50% of randomly selected medical records to ensure the accuracy of the entered data, as verified against the original records.

STATISTICAL ANALYSIS

The UPDRS scores for each patient visit were first categorized by the patient’s on- or off-state status. Because the number of patient visits in the 2 groups varied from patient to patient, the usual statistical techniques for analysis of repeated measurements was not applicable to this data set. A multivariate unbalanced repeated-measurements design was used to study the relationship between the different symptoms (bradykinesia, falling, walking, freezing, postural stability, tremor, gait, speech, handwriting, sen- sory, and mentation) and age at onset, sex, duration of symp- toms, years of observation, and handedness in the on- and off-state groups. An SAS statistical program (SAS, Cary, NC) was used for the analysis.

Disease progression was defined as the difference between the baseline and the last score for the various components of the UPDRS scores. Multivariate regression models were developed for both the on and off states to study the association of the progression in the total UPDRS scores for parts I through III (ie, mentation, activities of daily living, and motor function, respectively) and the combined score for all 3 parts after adjusting for years of observation. The mean tremor score was defined as the mean of the sum of the baseline tremor (UPDRS part II) and tremor scores (UPDRS part III) for face, right and left hand, right and left foot, and right and left hand action tremor. The mean postural instability–gait difficulty (PIGD) score was defined as the sum of an individual’s baseline falling, freezing, walking, gait, and postural stability scores divided by 5. Patients were categorized as having tremor-dominant PD if the ratio of the mean tremor score to the mean PIGD score was 1.50 or higher and as PIGD dominant if the ratio was 1.00 or lower, similar to previously published method. Using the 2-sample t test, the 2 PD-dominant groups (tremor and PIGD) were compared for progression of their total UPDRS scores.

Mann-Whitney nonparametric statistical tests were used to compare the progression of symptoms in the on- and the off-state groups for 2 age-at-onset categories (ie, ≤57 and >57 years, based on the median age at onset of 57 years) as well as comparing the progression in mentation when individuals at baseline were categorized as below and above the baseline median mentation score.

Men vs Women?

When on-state patients with young age at onset (≤57 years, n=159 patients) were compared with those whose symp- toms began after 57 years (n=133), the older-onset group had significantly (P<.05) more progression in mentation and freezing, and lower UPDRS part I and II subscores. The projected relationship of the total UPDRS scores for the 2 age-at-onset categories with years of observation are plotted in Figure 2. The progression of total mentation scores in patients with baseline mentation scores above the median (n=126 patients) was significantly greater (P<.05) than in those with baseline mentation scores below the median (n=171 patients). The average projected decline in the mentation score for the 2 groups was 0.647 and 0.102, respectively.

When the tremor-dominant group (n=77 patients) in the on-state data set was compared with the PIGD-dominant group (n=149 patients), the only comparison that was statistically significant was the one between total UPDRS part II subscores; the unadjusted means of the
tremor-dominant and PIGD-dominant groups were 5.38 and 2.76, respectively ($P<.05$), for this set of subscores. However, when the slopes (ie, annual rate of decline) of progression per year of observation after adjustment for age at the initial visit were compared between the 2 groups, it was observed that the PIGD-dominant group had a higher projected slope than the tremor-dominant group in all the cases (UPDRS parts I through III and the total UPDRS scores). Figure 3 shows the progression of total UPDRS on-state scores per year of observation for the 2 groups.

In the multivariate regression models when the progression (in UPDRS parts I through III and the total UPDRS on-state scores, respectively) was analyzed for age at onset, type of PD (tremor dominant or PIGD dominant), and sex, male patients progressed at a significantly ($P<.05$) higher rate than female patients in the UPDRS parts I and II subscores (slopes, 0.962 and 2.65, respectively). It was also observed that the UPDRS part II subscores were significantly associated ($P<.05$) with age at onset and type of PD (the corresponding rates of progression were 0.135 and 2.64, respectively).

**COMMENT**

This study of 297 patients, followed up prospectively for an average of 6.30 years, constitutes the largest longitudinally followed cohort of patients with PD. The purpose of the study is not to determine the natural course of untreated disease, which would be ethically unacceptable, but to define factors that may influence the progression of various symptoms in treated PD. We found the annual rate (slope) of decline in the total UPDRS scores to be 1.34 in the on state and 1.58 in the off state. The corresponding projected annual rates of decline based on the regression model were 1.43 and 2.97, respectively. These results are similar to the 1.5-point annual decline, based on longitudinal assessments using the motor function (part III) portion of the UPDRS reported by Louis et al in a community-based study of 237 patients with PD followed up prospectively for a mean of 3.30 years. Several studies have suggested that the rate of progression may be not linear and that the disease may progress more rapidly initially and the rate of deterioration slows in more advanced stages of the disease. This is supported by our findings in moderately advanced cases of PD requiring levodopa treatment compared with patients in early stages of the disease such as those enrolled in the DATATOP study. In that study of early, previously untreated patients, the rate of annual decline in the total UPDRS score was $14.02 \pm 12.32$ (mean $\pm$ SD) in the placebo-treated group. In contrast, in a group of 238 patients treated with levodopa, bromocriptine mesylate, or both in whom progression was estimated based on a retrospectively determined duration of the symptoms, the annual rate of decline in bradykinesia score was 3.5% during the first year but was estimated to be only 1.5% in the 10th year. Furthermore, Jennings et al found, based on sequential $2\beta$-carboxymethoxy-3-$\beta$-(4-[123I]iodophenyl)tropane and single-photon emission computed tomographic imaging at intervals ranging from 9 to 24 months that annual rate of loss of striatal $2\beta$-carboxymethoxy-3-$\beta$-(4-[123I]iodophenyl)tropane uptake to be 7.14% in subjects having a diagnosis of PD for fewer than 2 years compared with a 3.71% rate in those having a diagnosis of PD for longer than 4.5 years. In a more recent study using fludeoxyglucose F18–fluorodopa F6 positron emission tomography, Nurmi et al showed a 10.3% $\pm$ 4.8% decline in the uptake in the putamen over a 5-year period. Finally, based on clinicopathological correlation, Fearnley and Lees suggested that there is a 30% age-related nigral cell loss at disease onset, again indicating rapid decline in nigral dopaminergic cells in the early stages of the disease.

Besides the variable rate of progression during the natural course of the disease, there is evidence that individual parkinsonian symptoms have a variable rate of progression. Louis et al found that in contrast to bradykinesia, rigidity, and gait and balance, all of which progressed at the same rate, tremor was independent of these cardinal signs. This is also consistent with the results of an earlier and a much smaller study involving only 25 patients, followed up prospectively for at least 10 years after initiation of levodopa treatment. In that study,
At least 2 different forms of PD have been proposed: one characterized by PIGD and another dominated by tremor.5,19 The tremor subtype of PD is associated with preserved mental status, earlier age at onset, and slower progression of the disease compared with the PIGD subtype, which is characterized by more severe bradykinesia, cognitive impairment, and a more rapidly progressive course. Furthermore, the PIGD-dominant type of PD had a higher risk of reaching an end point, the degree of disability necessitating levodopa treatment, in the DATATOP study.7 The association between axial (PIGD) impairment and incident dementia has been demonstrated also by other studies.5,19 Our longitudinal follow-up study provides support for the hypothesis that, based on total UPDRS scores, the PIGD group has a less favorable prognosis, showing a steeper slope of progression than the tremor-dominant group (Figure 3).

The variable rate of progression of different types of PD suggests different pathological and biochemical mechanisms and possibly different causes, supporting the notion of Parkinson diseases rather than a single disease entity. This is supported by pathological and genetic studies indicating different mechanisms for phenotypically similar disorders. In one study of patients having clinically diagnosed PD, only 27% of patients with the PIGD form of idiopathic parkinsonism had Lewy bodies at autopsy.20 Furthermore, even within PD, the variable progression of individual signs suggests different pathological and biochemical mechanisms. For example, Hirsch et al21 have demonstrated that patients with PD and prominent tremor have a degeneration of a subgroup of midbrain (A8) neurons, whereas this area is spared in patients with PD without tremor. Using fludeoxyglucose F 18–fluorodopa F 6 positron emission tomography, Vingerhoets et al22 demonstrated that bradykinesia is the parkinsonian sign that correlates best with nigrostriatal deficiency. In contrast, patients with the tremor-dominant PD have increased metabolic activity in the pons, thalamus, and motor association cortices.23 These findings support the hypothesis that differential damage of subpopulations of neuronal systems is responsible for the diversity of phenotypes seen in PD and other parkinsonian disorders. Further clinicopathological-biochemical, and eventually genetic, studies will be required to clarify the mechanisms underlying the observed clinical heterogeneity and to develop highly predictive diagnostic criteria.24

The course of PD may be influenced not only by the clinical presentation of the disease, but also by age at onset and various external factors such as stress,25 pregnancy,26 and anti-PD therapy.27 Several studies, for example, have demonstrated that patients with young-onset PD progress at a slower rate than the late-onset patients, but the patients with young-onset PD are more likely to develop levodopa-induced dyskinesias early in the course of treatment.28,29 Furthermore, the late-onset subtype is char-
acterized by rapidly progressive motor and cognitive disability.3,32 In this study we confirmed that patients 57 years or older with late onset of symptoms had a more rapid progression of disease than those whose symptoms began before the age of 57 years. We also showed that men and older patients progress at a more rapid rate than female patients and patients with young-onset PD. Furthermore, our and other studies have shown that patients with predominantly axial involvement (such as those with the PIGD-dominant type of PD) are more likely to manifest cognitive decline compared with the more typical form of PD.3 This subset of patients may have additional nondopaminergic degeneration, thus explaining the poor response to treatment with levodopa and dopamine agonists.31 Indeed, our findings challenge the traditional view that the symptoms of PD are solely due to nigrostriatal dopamine deficiency. There is growing evidence that local dendritic deficiency. There is growing evidence that local dendritic influences basal ganglia functions and thus may affect the clinical expression and prognosis.32 Furthermore, norepinephrine, serotonin, and other nondopaminergic systems may play an important role in the development of certain PD symptoms and in the natural course of the disease. Finally, as a result of growing appreciation for genetic and other causes, we no longer view PD as a single disease entity but a group of diseases with different pathogenic mechanisms that may variably influence the natural course of the disease.

The results of our study must be interpreted cautiously because the patients were in different stages of their disease at the time of their initial visit, they were followed up for different periods, and they were treated with levodopa and other antiparkinsonian drugs at different dosages and for a variable time. There is no evidence, however, that any of the currently used drugs are neuroprotective or affect the natural progression of the disease. Although we provide UPDRS data during the on and off states, this was based on clinical judgment at the time of the visit and patients were not necessarily at the peak of optimal response (on state) or in their true off state (at least 12 hours after the last dose of levodopa treatment). Because we were interested in the natural course of treated PD, prolonged withdrawal of levodopa treatment (drug holiday) was not justified nor would it be safe or ethical. Furthermore, as this was not a clinico-pathological study, some of our patients having the clinical diagnosis of PD could have had an alternative diagnosis if examined at autopsy. Despite these limitations, the findings from this longitudinal study provide evidence that the various symptoms associated with PD do not progress at the same rate and that they may be mediated through different pathogenic mechanisms. The findings from this study may be useful in designing future clinical trials of therapeutic interventions affecting the natural course of the disease.

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**References**


