Progression of Parkinsonian Signs in Parkinson Disease

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Background: Current knowledge about the rate of progression of extrapyramidal signs (EPSs) in Parkinson disease (PD) is derived largely from cross-sectional studies comparing subjects at various stages of illness rather than longitudinal studies in which the subjects were followed up over time.

Objective: To longitudinally study the progression of EPSs in PD by quantifying the rate of change of EPSs and by examining each EPS (rigidity, bradykinesia, tremor, and postural instability) separately.

Methods: A community-based cohort of 237 patients with PD living in Washington Heights–Inwood in Manhattan, NY, was evaluated at baseline and at yearly intervals. The EPSs were rated using the motor portion of the Unified Parkinson’s Disease Rating Scale Motor Examination. Analyses of longitudinal data were performed by applying generalized estimating equations to regression analyses.

Results: The total EPS score increased at an annual rate of 1.5 points (1.5%), but, among those who died, the total EPS score increased at an annual rate of 3.6 points (3.6%). Bradykinesia, rigidity, and gait and balance subscores worsened at similar annual rates of 2.0% to 3.1%, whereas the tremor subscore did not clearly worsen with time. Patients with a shorter disease duration (≤3 years) may have progressed more rapidly than patients with longer disease duration (annual rate of change, 1.9% vs 1.4%, respectively), although this did not reach statistical significance. A high total EPS score was independently associated with dementia, low Activities of Daily Living score, and long disease duration at baseline.

Conclusions: In this cohort, the progression of EPSs in PD occurred at a rate of 1.5% per year and at twice that rate among those who died. Bradykinesia, rigidity, and gait and balance impairment worsened at similar rates, whereas tremor did not, suggesting that tremor may be relatively independent of these other cardinal manifestations of PD.

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Clinicians have long appreciated the progressive nature of Parkinson disease (PD), and it is generally accepted that extrapyramidal signs (EPSs), particularly parkinsonian signs, increase in severity over time. Current knowledge about the rate of progression of EPSs in PD is largely inferred from cross-sectional studies comparing subjects with different disease durations at one point. There are few longitudinal studies in which the subjects are followed up over time, and the emphasis of these studies has been on treatment issues rather than the rate of progression of EPSs. Little is known about the specific factors that influence the rate of progression of EPSs in PD.

In a previous longitudinal study of this cohort, it was shown that severe EPSs and dementia at baseline are independent predictors of mortality. In this study, we examined the progression of EPSs more closely by quantifying the rate of change of EPSs and by examining each EPS (rigidity, bradykinesia, tremor, and postural instability) individually.

A large community-based cohort of individuals with PD were evaluated annually for as long as 8 years (mean, 3.3 years after baseline assessment). The goals of the present study were as follows: (1) to estimate the overall annual rate of increase of EPSs in PD, (2) to examine the rate of progression of each EPS in PD, and (3) to examine specific factors that influence the rate of progression of EPSs in PD. Because this was an observational study, no attempt was made to systematically alter dosages of antiparkinsonian medications prescribed by the patients’ personal physicians.
SUBJECTS AND METHODS

SUBJECTS AND SETTING

A community-based registry of patients with idiopathic PD has been in existence since 1988 in Washington Heights-Inwood in northern Manhattan, NY. Diagnoses were based on a standardized neurological evaluation. Idiopathic PD, defined by clinical and research criteria, did not include Parkinson plus syndromes.

BASELINE AND YEARLY ASSESSMENTS

Patients with idiopathic PD were evaluated at baseline and annually by a neurologist using the motor portion of the Unified Parkinson’s Disease Rating Scale Motor Examination. These ratings have been shown to be reliable.

Information on age, sex, ethnic group, education, and medications, including levodopa, was collected at each visit. For ethnic group classification, we used the format suggested by the US Census Bureau for the 1990 population census. Assessment of performance of activities of daily living (ADL) was rated by the physician using the Schwab and England ADL Rating Scale. All patients underwent a standardized battery of neuropsychological tests and were considered demented if they met established criteria (of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition) and if functional difficulties could be attributed to cognitive, rather than physical, disability.

STATISTICAL ANALYSIS

Analyses of the longitudinal data were performed by applying generalized estimating equations to regression analyses with repeated measures. Generalized estimating equations account for multiple visits per subject and that the characteristics of a single subject over time are likely to correlate with one another. Generalized estimating equations allowed us to quantify the average annual rate of increase of the total EPS score or a particular EPS subscore (eg, the bradykinesia subscore) and determine whether any baseline factors (eg, dementia or low ADL score) were significant predictors of a higher total EPS score at each of the annual visits. Generalized estimating equations quantified the difference in the total EPS score at any annual visit between patients who had a factor (eg, dementia) at baseline and patients who did not have this factor at baseline.

Using the motor portion of the Unified Parkinson’s Disease Rating Scale Motor Examination, 25 items were rated on a scale of 0 to 10 (where 0 indicates the normal performance of this item; 4, extreme difficulty performing this item). The total EPS score, with a range from 0 to 100, could also be expressed as a percentage. For several of the generalized estimating equation analyses, the EPS total score was divided into different subscores and each subscore was considered as a separate outcome. Subscores included a tremor subscore (5 items; range, 0-20), a bradykinesia subscore (7 items; range, 0-28), a rigidity subscore (5 items; range, 0-16), and a gait and balance subscore (4 items; range, 0-16).

Age at onset of PD was stratified into 2 groups (young and old) using 2 age cut points. First, 66 years (the median age of onset of PD in this cohort) was used; then, 50 years was chosen to obtain a relatively younger “young onset” group.

Disease duration at baseline also was stratified into 2 groups using 2 cut points. First, groups of subjects with short disease duration (<6.8 years) and long disease duration (>6.8 years) were made based on the mean disease duration in our cohort. Second, to obtain a group of subjects with an even shorter disease duration, we stratified the cohort again into 2 groups with short disease duration, defined as 3 years or less, and long disease duration, defined as more than 3 years. Two groups were established based on the median Schwab and England ADL score of 70% at baseline (low ADL score, ≤70%; high ADL score, >70%). A score of 70% indicated that the patient was not completely independent and required 3 to 4 times as long to perform some chores.

Each generalized estimating equation model incorporated the following variables: age at entry into the study, sex, ethnic group, number of years of education, age at onset of PD (stratified 2 ways into 2 groups: ≤50 years or >50 years; ≤66 years or >66 years), disease duration at baseline (stratified into 2 groups: short disease duration, ≤6.8 years; long disease duration, >6.8 years), levodopa therapy at baseline (taking levodopa or not taking levodopa), dementia at baseline (present or absent), Schwab and England ADL score at baseline (stratified into 2 groups: low, ≤70%; high, >70%), time since baseline visit (years), mortality status (died during follow-up period or did not die during follow-up period), and the interaction between time and each of these covariates.

RESULTS

There were 237 patients with PD who had 1 baseline visit and at least 1 year of follow-up (Table 1). The annual rate of increase in the total EPS score was 1.5 points (1.5%). However, among those who died during the follow-up period (n = 70), the total EPS score increased at an annual rate of 3.6 points (3.6%) (Figure).

We stratified the sample into those with short disease duration (<3 years) and those with longer disease duration (>3 years). The annual rate of progression of the total EPS score was greater in those with short disease duration (1.9 points) than those with longer disease duration (1.4 points); however, the difference was not significant (z = 1.0, P = .3).

Because different components of the total EPS score may progress at different rates, in the subsequent generalized estimating equation models the total EPS score was subdivided as follows: tremor subscore, bradykinesia subscore, rigidity subscore, and gait and balance subscore. The tremor subscore did not increase at a significant annual rate (z = 0.061, P = .31). However, the other EPS scores did. The annual rate of increase of the bradykinesia subscore was 0.6 points (2.1%) of 28 possible points; the annual rate of increase of the rigidity subscore was 0.4 points (2.0%) of 20 points; and the annual rate of increase of the gait and balance subscore was 0.5 points (3.1%) of 16 points.

Several baseline factors were predictors of a higher total EPS score at each annual visit. These baseline factors included dementia, low ADL score, and long disease duration (Table 2). For example, on average, patients with dementia had a higher EPS score at each annual visit than those who did not have dementia.

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baseline dementia had total EPS scores at each annual visit that were 7.9 points higher than those without baseline dementia (Table 2). Baseline factors that were not predictors of higher total EPS score were age at entry into the study, sex, ethnic group, education, age at onset of PD, and levodopa therapy.

**COMMENT**

Few studies have followed the same cohort of individuals over time in an attempt to precisely quantify the rate of progression of their parkinsonian signs. Two previous longitudinal studies included data for a short length of follow-up (eg, 14 months), emphasized early stages of the disease, ascertained cases from specialty clinics (with the resultant possibility that case selection was affected by the degree of mobility and disease severity), and examined the initial timing of levodopa therapy rather than the rate of progression of EPSs. We prospectively examined the rate of progression of EPSs in a large cohort of patients with PD. We demonstrated that EPSs progress more rapidly in the subgroup of patients who died during the follow-up interval; we also demonstrated that all EPSs did not behave similarly, because a progressive annual increase in severity was a feature of bradykinesia, rigidity, and postural instability rather than tremor.

The annual rate of increase in the total EPS score was 1.5 points (1.5%). One prior longitudinal study of PD demonstrated that the motor score of the Unified Parkinson’s Disease Rating Scale Motor Examination worsened at a rate of 0.6% to 4.1% during a 14-month period. We demonstrated that in those who died during the follow-up period, the total EPS score increased at a faster annual rate (3.6%) than in those who survived the follow-up period. It has been previously demonstrated that a high total EPS score was a predictor of mortality, but the magnitude of the annual increase in EPS among those who died was not quantified. While it is conceivable that the association between mortality and high total EPS score could be a result of the confounding effects of dementia, an association between mortality and high EPS score that was not confounded by the effects of dementia has been previously demonstrated.

Our data suggest that all EPSs do not behave similarly. While bradykinesia, rigidity, and gait and balance subscores worsened at similar annual rates of 2.0% to 3.1%, the tremor subscore did not clearly worsen with time. Factor analysis of EPSs in PD has shown that tremor is rela-
tively independent of the other cardinal signs of PD, perhaps representing a different underlying pathophysiological process. The slower rate of progression of tremor in PD is supported by the observation in the literature that tremor-predominant forms of PD are considered to be less rapidly progressive than forms characterized by akinetic rigidity or severe postural and gait instability.

Several baseline factors, including dementia, were predictors of high total EPS score at each annual visit. Baseline dementia is a predictor of a high EPS score and, as previously shown, high EPS score is a predictor of the development of dementia, suggesting that dopamine deficiency might underlie both the motor and cognitive manifestations of PD. A low baseline ADL score was also an independent predictor of a high total EPS score. Similarly, others have reported a relationship between the extent of functional disability and the severity of motor manifestations of PD (especially the rigidity, bradykinesia, and postural instability).

Patients with a shorter disease duration progressed more rapidly than patients with a longer disease duration; however, the difference was not significant. A faster rate of progression was also reported. These data suggest that the rate of progression of EPSs in PD may be nonlinear, although, as an analytical tool, generalized estimating equations cannot test this hypothesis.

This study had limitations. First, most patients were being treated with levodopa at baseline and yearly assessment of their EPSs may have been affected by alterations in their medical regimen and by their “on-off” state at the time of the visit. This was not a study of the natural progression of untreated PD. Rather, this observational longitudinal study documented the rate of progression of EPSs in a more true-to-life group of levodopa-treated patients as they typically exist in a community. In addition, one would expect that the variability in EPSs caused by on-off states would be random rather than nonrandom. Second, our cohort was relatively old. This limits the applicability of these results to younger cohorts and makes it difficult to evaluate whether cases of PD with young ages of onset progress more slowly than those with older ages of onset, as has been suggested in the literature. Finally, our cohort consisted of many patients with advanced disease. At the baseline visit, the mean disease duration was 6.8 years. Hence, these findings may not apply to cohorts consisting of patients with predominantly early PD.

These data provide a basis upon which to understand the progression of EPSs in PD. Those who died during the follow-up period exhibited a more rapid progression of EPSs. Unlike bradykinesia, rigidity, and gait and balance difficulty, which each increased steadily over time, tremor remained constant. This suggests that tremor is relatively independent of disease progression. Precise quantitative data on the rate of progression of EPSs in PD form the basis for prognostic counseling. In addition, the identification of subgroups of patients with PD who demonstrate different rates of progression of motor signs has public health implications for appropriate allocation of clinical resources and important implications for longitudinal therapeutic trials where subgroups of patients may progress at different rates independent of the effect of therapeutic interventions.

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REFERENCES