Predicting Motor Decline and Disability in Parkinson Disease

A Systematic Review

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Context: The clinical course of Parkinson disease (PD) varies from patient to patient. A number of studies investigating predictors of prognosis in patients with PD have been performed.

Objective: To summarize evidence on predicting the rate of motor decline and increasing disability in early PD.


Study Selection: Cohort and case-control studies investigating associations between clinical features and subsequent motor impairment or disability were selected.

Data Extraction: Study methods and results were abstracted by a single reviewer.

Data Synthesis: The results of 13 studies were summarized qualitatively. Study methods were highly variable, particularly regarding the choice of outcome measure. Baseline motor impairment and cognitive impairment are probable predictors of more rapid motor decline and disability. A lack of tremor at onset and older age both appear to be predictive of increasing disability, but conflicting results exist for their association with the rate of change of motor impairment. Family history of PD does not appear to be prognostically important. The prognostic value of many other factors studied is uncertain owing to conflicting or unconfirmed results.

Conclusions: Uncertainty remains about the prognostic importance of many baseline clinical features in PD. Greater baseline impairment, early cognitive disturbance, older age, and lack of tremor at onset appear to be adverse prognostic factors.

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The clinical course of Parkinson disease (PD) varies from patient to patient, and this variability has led to a number of studies investigating predictors of prognosis in PD. Predicting the clinical course of PD is important for several reasons. It helps patients recently diagnosed with a progressive disorder make social and occupational decisions that take into account their likely future physical functioning. Understanding the variables associated with disease progression also guides the design and interpretation of clinical trials of neuroprotective and symptomatic therapy. It would be important, for example, to ensure balance between groups on the basis of important prognostic factors.

The heterogeneity of PD has been noted by many authors. For example, in their 1999 report of the Sydney, Australia, multicenter study of PD, Hely et al showed that despite the wide availability of current treatment strategies and excluding patients developing signs and symptoms atypical for PD in follow-up, during 10 years of observation, 9 of 126 patients progressed to confinement to bed or a wheelchair unless aided, whereas 13 patients remained without significant functional restriction. Such variability leaves us with the challenge of predicting the future course of PD in individuals and groups of patients.

We conducted a systematic review to identify predictors of motor decline and disability in patients with PD. We focused on motor impairment and disability because motor impairment is the defining feature of this illness and it affects patients largely through increasing physical disability.

METHODS

DATA SOURCE

Using the MEDLINE database, we searched the English-language and French-language literature published from 1966 through January 31,
2002. The medical subject headings “Parkinson disease” and “prognosis” were combined with either of the text words “progression” or “natural history,” and we limited the search to clinical trials or cohort studies.

### STUDY SELECTION

We reviewed 457 titles and abstracts for reports investigating the association between progression of motor features or disability and patient or disease-related factors (as opposed to the effect of an intervention). These articles and relevant articles from their reference lists were obtained for review. Reports published only in abstract form and reports of predictive factors for dyskinesias or motor fluctuations were excluded.

We included only studies that prospectively documented disease progression, whether this was within the context of the study (prospective cohort studies) or from medical records (retrospective cohort studies and case-control studies). Studies that made a single observation of outcome were considered to be cross-sectional and were excluded.

### DATA EXTRACTION

Study methods and results were abstracted by one of us (C.M.). Studies were assessed for methodologic quality using 5 criteria adapted from the Evidence-Based Medicine Working Group’s Users’ Guide to the Medical Literature criteria for appraising an article about prognosis and from the methodologic and quality scoring instrument developed by Cho and Bero (criterion 5 of our instrument).

1. Patients within 5 years of symptom onset at first observation.
2. Median or mean follow-up of at least 2 years.
3. Greater than 80% of patients followed up.
4. Clearly defined and reproducible outcome measures.
5. Known confounders accounted for in the design or analysis. When examining the prognostic significance of other variables, baseline status on the outcome of interest, disease duration, and treatment allocation (if applicable) should be adjusted for statistically or should be balanced between groups.

### OUTCOME MEASURES

Studies were grouped by category of outcome measure, either disability or motor impairment.

### RESULTS

Of the studies assessed, 41 articles were identified that investigated factors (other than treatment) associated with outcome in PD; 27 of these were excluded from our review: 13 were cross-sectional studies, 10 studies investigated only nonmotor outcomes (cognitive dysfunction, 8 studies; mortality or institutionalization, 2 studies), 1 study investigated factors associated with time to requiring therapy with levodopa, and 3 were review articles. One cohort study was excluded because the source of subjects (inpatients having had a computed tomographic scan of the head) was felt to significantly limit the external validity of the study.

### DATA SYNTHESIS

Variables investigated for their association with increasing disability are presented in Table 2. Presentation without tremor (bradykinesia/rigidity type) was found to be a marker of poor prognosis in 2 studies by Guillard et al and Guillard and Chastang, and a trend toward this result was noted in 2 other studies.

### PREDICTING DISABILITY

Variables investigated for their association with increasing disability are presented in Table 2. Presentation without tremor (bradykinesia/rigidity type) was found to be a marker of poor prognosis in 2 studies by Guillard et al and Guillard and Chastang, and a trend toward this result was noted in 2 other studies.
Guillard and Chastang did not report their results quantitatively. Hoehn and Yahrs reported that at the end of their follow-up period, 19% of patients with tremor at onset were disabled vs 24% of patients without tremor at onset. Goetz et al found an odds ratio of 0.43 for progression to Hoehn and Yahr stage 3 when tremor was the first symptom. In a fifth study investigating the dominant symptom type of PD (postural instability gait disorder vs tremor), Jankovic and Kapadia found that subjects with a tremor-dominant subtype (they did not classify patients by initial symptom) experienced slower worsening of Unified Parkinson’s Disease Rating Scale (UPDRS) activities of daily living (ADL) scores.

Early lack of physical independence, a positive Babinski sign, and cognitive disturbance within the first year of symptoms were found to be poor prognostic factors by Guillard and Chastang, again with a subjectively defined outcome and no quantitative result given. A positive Babinski sign and cognitive disturbance within the first year would be unusual for patients with PD, raising the possibility that these signs are markers of alternative diagnoses with a worse prognosis.

Older patients had a poorer prognosis in 4 of 5 studies. Diamond et al found that older patients had poorer outcomes after 6 years of levodopa therapy. Patients older than 60 years experienced little net change in UCLA (University of California, Los Angeles) scale scores (99 to 92) compared with a net score change of −39 points (92 to 33) in those younger than 50 years (ie, younger patients maintained their improvement with levodopa; higher scores indicate greater disease severity). Goetz et al found that patients who progressed to Hoehn and Yahr stage 3 during 2 years of observation were older (mean age, 65 years) than a group of patients matched for disease duration and initial Hoehn and Yahr stage who did not progress beyond stage 2 (mean age, 52 years). Older age at onset was reported to predict earlier loss of independence by Guillard et al and a more rapid worsening of UPDRS ADL scores by Jankovic and Kapadia. Hoehn and Yahr did not find an association between increasing age and disability.

Three studies generated differing results regarding the prognostic importance of depression in patients with PD. Using a prospective design, Starkstein et al found depression at baseline to predict greater decline in Northwestern University Disability Scale score (2.7 point deterioration in patients with depression vs 0.1 point mean improvement in individuals without depression during 1 year). This contrasts with 2 retrospective studies that did not detect an association between depression and future disability (disability not defined).

A family history of PD had no significant prognostic value in 4 studies. Other variables investigated for their association with increasing disability with conflicting or negative results are presented in Table 2.

### Table 2. Variables Investigated for Association With Increasing Disability in Patients With Parkinson Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Predictive</th>
<th>Not Predictive</th>
</tr>
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<tbody>
<tr>
<td>type (vs tremor at onset or tremor dominant)</td>
<td>Guillard et al,1986</td>
<td>Hoehn and Yahr,1967</td>
</tr>
<tr>
<td>Cognitive disturbance</td>
<td>Guillard and Chastang,1978</td>
<td>Kapadia,1999</td>
</tr>
<tr>
<td>in the first year</td>
<td>Guillard and Chastang,1978</td>
<td>Kapadia,1999</td>
</tr>
<tr>
<td>Initial lack of independence</td>
<td>Guillard and Chastang,1978</td>
<td>Kapadia,1999</td>
</tr>
<tr>
<td>Male sex</td>
<td>Guillard et al,1986</td>
<td>Jankovic and Kapadia,1999</td>
</tr>
</tbody>
</table>

*Includes Hoehn and Yahr stage as an outcome.
†Guillard and Chastang,1978, and Guillard et al,1986, used overlapping samples of patients.
‡There was a trend toward a worse prognosis in patients without tremor at onset.
§Measles prior to age 18 years and chemical, herbicide, or well water exposure were analyzed separately.

Factors investigated for association with motor impairment are shown in Table 3. Dementia at baseline was found to be associated with faster motor decline in 2 studies; however, in only one did this remain significant after adjusting for other baseline factors. Louis et al found that the UPDRS motor scores of patients with dementia were, on average, 7.9 points higher (higher scores represent greater severity) at each annual visit than in those without dementia at baseline. Although there was adjustment for several baseline factors, there was no adjustment made for initial motor score.

The degree of baseline motor impairment was found to be positively correlated with later impairment in 2 studies. Louis et al found that a baseline Schwab and England ADL score of 70 or less (lower scores indicate greater disability) was associated with mean UPDRS motor scores 11.7 points higher at each annual visit over a mean follow-up of 3.3 years compared with those with ADL scores greater than 70.

**PREDICTING MOTOR IMPAIRMENT**

Facts about these studies are presented in Table 2. Factors investigated for association with motor impairment are shown in Table 3. Dementia at baseline was found to be associated with faster motor decline in 2 studies; however, in only one did this remain significant after adjusting for other baseline factors. Louis et al found that the UPDRS motor scores of patients with dementia were, on average, 7.9 points higher (higher scores represent greater severity) at each annual visit than in those without dementia at baseline. Although there was adjustment for several baseline factors, there was no adjustment made for initial motor score.

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Chastang found that the median time to significant motor impairment (not defined) was 6 years in patients with mild akinesia at baseline and 4 years in patients with more severe akinesia. In contrast, Goetz et al found that baseline UPDRS scores showed a negative correlation \((r = -0.25)\) with the change in scores during the subsequent 4 years. The correlation is modest, and this could represent a tendency for outlying observations to regress to the mean.

Older age was associated with more rapid progression of motor impairment in 2 of 4 studies. Hely et al studied a cohort of patients followed prospectively for 10 years. Each increase in age of 10 years was associated with an odds ratio of 2.41 (95% confidence interval, 1.24-4.66) for an increase in Columbia University Rating Scale score by 20 or more points. Diamond et al found a significant effect of age using the UCLA scale, as described previously. They noted that tremor and rigidity changed little and that the most decline occurred in gait, balance, rising from a chair, and rolling over in bed. In contrast, 2 other studies did not find age at onset to be associated with increasing UPDRS scores.

Sex was not found to be related to motor decline in 4 studies. A fifth study by Hely et al found that female sex was predictive of a deterioration in modified Columbia University Rating Scale score of more than 20 points in univariate (odds ratio not given) but not multivariate analysis. Conversely, men did more poorly in 2 studies using disability and increasing UPDRS ADL scores as outcome measures (Table 2).

Two studies investigated the relationship between type of presentation (tremor vs bradykinesia/rigidity type) and progression of motor impairment. In contrast with the studies of disability, this was not found to be an important predictor of motor impairment in either study. Other factors with contradictory or negative results can be seen in Table 3.

### METHODOLOGIC APPRAISAL

Of 13 studies, 9 did not identify their cohort by duration of disease. Two studies followed their cohort for less than 2 years and 2 studies did not achieve greater than 80% follow-up of their cohort. Three studies did not objectively define the outcomes used and 6 studies did not account for potential confounders in their analysis.

### SUMMARY OF RESULTS

Our systematic review identified trends for the prognostic importance of 4 baseline factors. First, those with more severe baseline impairment continue to be more impaired later in the disease course. Second, there is some inconsistent evidence that a presentation without tremor (predominant bradykinesia/rigidity or postural instability) and increasing age may be predictors of more rapidly increasing disability but not of more rapidly increasing motor impairment. Regarding age, this raises the possibility that measures of disability are detecting an association between increasing age and non-PD related disability. Finally, cognitive impairment at baseline also appears to be associated with future disability and motor impairment. Sex does not appear to have prognostic importance for progression of motor impairment; for changes in disability, the evidence is conflicting. Family history of PD was consistently found not to be an important prognostic factor for motor impairment or disability. However, it is important to consider that family history may not be a significant prognostic factor for sporadic PD but rare familial forms may have distinct prognoses. For example, mutations in the parkin gene can cause a recessively inherited parkinsonism clinically indistinguishable from idiopathic PD other than by younger average age at onset and a relatively benign course. Epidemiologic studies may not detect this association because of the rarity of these “types” of PD (especially in older cohorts).

### Table 3. Variables Investigated for Association With Increasing Motor Impairment in Patients With Parkinson Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Predictive</th>
<th>Not Predictive</th>
</tr>
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<tbody>
<tr>
<td>Bradykinesia/rigidity presentation</td>
<td>Jankovic and Kapadia, 2001</td>
<td>Hely et al, 1995†</td>
</tr>
<tr>
<td>Dementia</td>
<td>Hely et al, 1995‡</td>
<td>Louis et al, 1999</td>
</tr>
<tr>
<td>Schwab and England score &lt;70</td>
<td>Louis et al, 1999</td>
<td>Louis et al, 1999</td>
</tr>
<tr>
<td>Greater tremor severity</td>
<td>Hely et al, 1999†</td>
<td>Hely et al, 1999†</td>
</tr>
<tr>
<td>Baseline UPDRS§ score</td>
<td>Goetz et al, 2000</td>
<td>Hely et al, 1999‡</td>
</tr>
<tr>
<td>Early (prestudy) disease progression</td>
<td>Hely et al, 1999†</td>
<td>Hely et al, 1999‡</td>
</tr>
<tr>
<td>Older age</td>
<td>Diamond et al, 1990</td>
<td>Louis et al, 1999</td>
</tr>
<tr>
<td>Older age at onset</td>
<td>Hely et al, 1999†</td>
<td>Jankovic and Kapadia, 2001</td>
</tr>
<tr>
<td>Longer illness duration</td>
<td>Louis et al, 1999</td>
<td>Goetz et al, 2000</td>
</tr>
<tr>
<td>Female sex</td>
<td>Hely et al, 1999†</td>
<td>Hely et al, 1995‡</td>
</tr>
<tr>
<td>Depression</td>
<td>Starkstein et al, 1992§</td>
<td>Starkstein et al, 1992§</td>
</tr>
<tr>
<td>Living in a rural area</td>
<td>Ferraz et al, 1996</td>
<td>Hely et al, 1995†</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>Goetz et al, 2000</td>
<td>Hely et al, 1995†</td>
</tr>
<tr>
<td>Symmetry of disease</td>
<td>Hely et al, 1995‡</td>
<td>Louis et al, 1999</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Louis et al, 1999</td>
<td>Louis et al, 1999</td>
</tr>
<tr>
<td>Level of education</td>
<td>Louis et al, 1999</td>
<td>Louis et al, 1999</td>
</tr>
</tbody>
</table>

*The variable was predictive in univariate but not multivariate analysis. †Hely et al, 1995, and Hely et al, 1999 used the sample of patients at 5 and 10 years of follow-up, respectively. §UPDRS indicates Unified Parkinson’s Disease Rating Scale. ¶Depression predicts a greater change in Hoehn and Yahr stage but not tremor, rigidity, or bradykinesia scores.
in the case of parkin mutations\(^{18}\) and their geographic clustering.

Prognostic factors may also be different depending on the outcome being evaluated. We did not consider other important outcomes such as cognitive deterioration, mortality, institutionalization, or the development of dyskinesias and motor fluctuations. For example, younger age has been shown in several different studies to predispose to the development of drug-induced dyskinesias earlier in the disease course.\(^{19,20}\)

**METHODODOLOGIC VARIABILITY ACROSS STUDIES**

We noted conflicting results on many potential prognostic factors that have been investigated, and this may be due in part to variable methods used by the investigators. For example, defining a cohort by (mild) symptom severity or only by having the disease rather than by duration of disease favors the selection of patients with more slowly progressive PD who live longer and have more mild symptoms for a longer duration. Also, short duration of follow-up limits the ability to detect important prognostic factors in a disease that often lasts more than a decade.

Of 13 studies, 6 did not indicate whether they excluded patients developing atypical symptoms during the follow-up period.\(^{3,7,8,11,12}\) Patients with atypical symptoms may have distinct disorders with distinct prognostic factors, despite early clinical features entirely consistent with PD.

Finally, outcome measures varied markedly across studies. The use of different outcome scales in different studies may further contribute to apparently conflicting results. It would be helpful for future research to make use of previously used outcome measures to build on the results of past studies.

**CONCLUSIONS**

Our review identified baseline severity of motor symptoms and possibly early cognitive impairment as factors influencing the progression of motor symptoms and disability. Increasing age and lack of rest tremor appear to predict more rapid accumulation of disability, but not necessarily motor impairment. Conflicting results were found concerning the prognostic importance of many other factors, and this may result, in part, from methodologic variability across studies.

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**Author contributions:** Study concept and design (Drs Marras and Lang); acquisition of data (Drs Marras); analysis and interpretation of data (Drs Marras, Rochon, and Lang); drafting of the manuscript (Drs Marras and Rochon); critical revision of the manuscript for important intellectual content (Drs Marras and Lang); obtained funding (Dr Marras); administrative, technical, and material support (Dr Lang); study supervision (Drs Rochon and Lang).

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**REFERENCES**