Resting Tremor in Parkinson Disease

A Negative Predictor of Levodopa-Induced Dyskinesia

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Background: It is unclear whether patients with different clinical subtypes of Parkinson disease (PD) differ in their risk of developing levodopa-induced dyskinesia (LID) and whether resting tremor is negatively correlated with this risk.

Objectives: To determine whether resting tremor as an initial manifestation of PD negatively correlated with subsequent occurrence and severity of LID and to study the correlations between LID and other epidemiological factors (eg, age at onset of PD and duration of PD).

Design: Logistic regression analysis was used to determine predictive factors of LID. Spearman rank correlations between LID and epidemiological factors and motor signs (including tremor) were calculated.

Setting: Institutional tertiary referral center for movement disorders.

Patients: Cohort of 85 patients with PD.

Main Outcome Measure: Occurrence of LID according to the Unified Parkinson Disease Rating Scale part IV.

Results: Resting tremor as an initial manifestation of PD was associated with reduced risk of developing LID independent of other predictors of LID (duration of PD, axial signs, and levodopa dose).

Conclusion: Resting tremor as an initial manifestation of PD predicts lower probability of developing LID under levodopa treatment.

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EVODOPA-INDUCED DYSKINESIA (LID) is a common and disabling long-term complication of dopaminergic therapy for Parkinson disease (PD). For example, the ELLDOPA (Earlier vs Later Levodopa Therapy in Parkinson Disease) study showed that as many as 16.5% of patients experience dyskinesia within 9 months after initiating levodopa treatment.1 Several clinical factors are known to increase the risk of developing LID, such as more advanced Hoehn and Yahr2 stage (H&Y stage), higher cumulative levodopa dose, and longer duration of PD.3-5

However, it is unclear whether patients with different clinical subtypes of PD differ in their risk of developing LID. Patients with PD having so-called benign tremulous parkinsonism were reported to have a benign clinical course with slowly progressive disease.6 Yet, it remains unknown whether resting tremor is negatively correlated with the risk of developing LID.

In this cohort study, we aimed to determine whether resting tremor as an initial manifestation of PD is negatively correlated with subsequent occurrence and severity of LID. Furthermore, the Spearman rank correlations between LID and other epidemiological factors (eg, age at onset of PD and duration of PD) were studied.

Methods

Using the database at our Movement Disorders Center in Berne, Switzerland, we studied 85 consecutively seen patients with PD. For each patient, data were used from 1 single assessment. Inclusion criteria were clinically diagnosed PD according to the United Kingdom Brain Bank guidelines,7 no deep brain stimulation surgery, and a complete medical record with available data on the following: duration of PD, actual treatment regimen, clinical assessment scores (described herein), disease stage (H&Y stage and Schwab and England Disability Scale score [S&E score]), and onset and nature of initial symptoms (according to medical history or predominant symptoms at the initial visit).
Eighty-five patients (57 men and 28 women) had a mean (SD) age of 64.6 (8.4) years. Their mean (SD) age at onset of PD was 55.3 (10.6) years, and they had had PD for a mean (SD) of 9.5 (6.4) years; 48 patients had resting tremor as an initial manifestation of PD. Seventeen patients were examined in the off-medication state (ie, not taking their current dopaminergic therapeutic regimen); all others were examined in the on-medication state (ie, taking their current dopaminergic therapeutic regimen). Patients were assessed using the Unified Parkinson Disease Rating Scale (UPDRS) part III (motor function), Hoehn and Yahr stage, and Schwab and England (S&E) scale. Occurrence and severity of LID were quantified using the UPDRS IV-A, a calculated subscore of the UPDRS IV (anamnestic information on dyskinesia duration, disability, early morning dystonia, and painful dyskinesia during the preceding week). We also used the following motor subscores based on the UPDRS III: rigidity subscore, resting tremor and action tremor subscores, axial subscore (voice, rising from a chair, posture, gait, and postural stability), and bradykinesia subscore (finger tapping, hand movements, hand pronation and supination, and leg agility).

We performed univariate and multivariate logistic regression analyses (separately calculated for anamnestic and clinical variables) to assess the contribution of each of the following variables: duration of PD, age at onset of PD, S&E score, Hoehn and Yahr stage, UPDRS III subscores, and current levodopa-equivalent daily dose (LEDD).

We performed univariate and multivariate logistic regression analyses (separately calculated for anamnestic and clinical predictors) to assess the contribution of each of the following variables to the presence or absence of LID: sex, LEDD, duration of PD, age at onset of PD, UPDRS III subscores, S&E score, Hoehn and Yahr stage, and initial manifestations of PD (tremor or other manifestations). For these analyses, patients were divided into dyskinetic and nondyskinetic groups according to their UPDRS IV-A subscores (patients in the dyskinetic group had a nonzero UPDRS IV-A subscore). A forward stepwise multivariate logistic regression analysis was then performed to identify independent predictors. To avoid potential systematic bias, we excluded 17 patients who were examined in the off-medication state from all analyses correlating the UPDRS III subscores and Hoehn and Yahr stage with the UPDRS IV-A subscores and from the multivariate logistic regression analyses. Therefore, we avoided correlating clinical off-medication signs with the UPDRS IV-A subscores, which reflect the on-medication state during the past week. Nevertheless, small therapeutic differences between groups (tremor or other manifestations) are possible because cumulative LEDD was not recorded. Only small proportions of both groups were receiving amantadine sulfate treatment.

**RESULTS**

Thirty-nine of 85 patients had LID (a nonzero UPDRS IV-A subscore). Correlations between severity of LID and the various clinical variables are given in Table 1.

Univariate logistic regression analysis identified 8 of 12 variables as significant predictors of LID (eTable; available at http://www.archneurol.com). Patients in the dyskinetic group had longer duration of PD, were younger at onset of PD, had a higher UPDRS III axial subscore, and less frequently had resting tremor as an initial manifestation of PD; however, they had higher LEDD, lower S&E score, higher Hoehn and Yahr stage, and lower tremor subscore.

Because patients in the dyskinetic group had significantly longer duration of PD, a multivariate logistic regression analysis (Table 2) was performed among all prognostic variables in the statistical model. Identified as independent predictors of LID were LEDD, duration of PD, UPDRS III axial subscore, and type of initial motor manifestation of PD (tremor or other manifestations). The absence of resting tremor among initial manifestations of PD was a strong predictor of LID (odds ratio, 8.67) independent of the duration of PD.

### Table 1. Spearman Rank Correlation Coefficients Among Patients in the Dyskinetic Group

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Coefficient</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Age at onset of PD</td>
<td>-0.50</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Duration of PD</td>
<td>0.67</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Schwab and England Disability Score</td>
<td>-0.45</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Levodopa-equivalent daily dose</td>
<td>0.55</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hoehn and Yahr stage</td>
<td>0.46</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>UPDRS III subscore</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>0.19</td>
<td>.1</td>
</tr>
<tr>
<td>Resting tremor</td>
<td>-0.26</td>
<td>.04</td>
</tr>
<tr>
<td>Action tremor</td>
<td>-0.15</td>
<td>.21</td>
</tr>
<tr>
<td>Rigidity</td>
<td>0.01</td>
<td>.91</td>
</tr>
<tr>
<td>Axial</td>
<td>0.42</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Abbreviations:** PD, Parkinson disease; UPDRS, Unified Parkinson Disease Rating Scale.

A Spearman rank correlation coefficients are between severity of levodopa-induced dyskinesia in the week before examination (UPDRS IV-A subscore) and the different clinical variables. Patients in the dyskinetic group had a nonzero UPDRS IV-A subscore.

### Table 2. Multivariate Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial manifestations of PD without resting tremor</td>
<td>8.67 (1.38-54.55)</td>
<td>.02</td>
</tr>
<tr>
<td>Duration of PD</td>
<td>1.45 (1.12-1.87)</td>
<td>.004</td>
</tr>
<tr>
<td>Levodopa-equivalent daily dose</td>
<td>1.01 (1.00-1.01)</td>
<td>.008</td>
</tr>
</tbody>
</table>

**Abbreviation:** PD, Parkinson disease.

Includes all prognostic variables found to be significant in the univariate analyses (eTable; available at http://www.archneurol.com). This best set of independent predictors confirmed that resting tremor as an initial manifestation of PD is a negative predictor of levodopa-induced dyskinesia independent of the duration of PD.

**COMMENT**

About 50% of patients with PD have resting tremor as an initial manifestation of the disease. The disease course depends on the PD subtype. Josephs et al described a subgroup of 16 patients with PD having predominant resting tremor whose motor manifestations other than tremor progressed more slowly. Only 2 of these patients developed dyskinesia; however, not all patients in this cohort were treated with levodopa. We observed that the absence of resting tremor at onset of PD is an important independent pre-
predictor of the development of LID during the course of PD. This agrees with the observation of a more benign course of PD in tremor-dominant forms. Moreover, we found a positive correlation between the severity of LID and axial motor signs, which may best be explained by the fact that both reflect advanced disease.

Multivariate logistic regression analyses revealed that LID was independently predicted by LEDD, duration of PD, and the presence or absence of resting tremor as an initial manifestation of PD. Most important, the duration of PD was a weaker predictor than the type of initial manifestation. Therefore, our findings suggest that resting tremor as an initial manifestation of PD is a negative predictor of LID (presence and severity) during the course of PD independent of LEDD and the duration of PD.

However, the pathophysiological mechanisms of resting tremor are not completely understood and cannot be fully explained as the result of a dopaminergic deficit. Functional imaging studies, including positron emission tomography and single-photon emission computed tomography, show poor correlation between resting tremor and dopaminergic deficiency, while bradykinesia and rigidity are highly correlated with the degree of dopaminergic denervation. The relative resistance of resting tremor to levodopa, as well as the effectiveness of nondopaminergic drugs like clozapine or the glutamate antagonist budipine against resting tremor, implies that the pathogenesis of resting tremor may involve nondopaminergic, possibly compensatory, mechanisms. Therefore, the negative association between LID and resting tremor as an initial manifestation of PD might be caused by differing patterns of neurodegeneration in these subgroups of patients. It has also been proposed that resting tremor may be linked with secondary compensatory mechanisms that might prevent LID, despite levodopa treatment.

Aside from the known clinical predictors of LID, occurrence of resting tremor as an initial manifestation of PD may predict not only slower progression of the disease but also lower probability of developing LID. However, selection bias owing to the referral of more severe cases to our tertiary care center cannot be excluded. Nevertheless, it is unlikely that a referral bias falsified our findings because no systematic selection of patients occurred. Prospective studies are desirable to correlate occurrence of LID with cumulative levodopa dose in subgroups of patients with PD.

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REFERENCES