The Evolution of Diagnosis in Early Parkinson Disease

Joseph Jankovic, MD; Ali H. Rajput, MD; Michael P. McDermott, PhD; Daniel P. Perl, MD; for the Parkinson Study Group

Context: Since there is no diagnostic biological marker for Parkinson disease (PD), the diagnosis is based on the results of clinical assessment. The accuracy of diagnosis improves with time and repeated assessments. Studies that require only inclusion of early cases of PD present a diagnostic challenge. Previous studies concluded that initial diagnoses of PD made by general neurologists were incorrect in 24% to 35% of the cases when patients were examined at autopsy. Experts in movement disorders are expected to have greater accuracy of initial diagnosis of PD.

Objective: To determine the evolution of clinical diagnosis in patients with early PD made initially by experts in PD.

Design: Eight hundred patients with mild parkinsonian symptoms (Hoehn and Yahr stage 1 or 2) who received a diagnosis of PD less than 5 years before the beginning of the study were included in the original Deprenyl and Tocopherol Antioxidative Therapy for Parkinson’s Disease study. These patients were followed up prospectively with repeated clinical assessments. The following clinical criteria were used to reassess the initial diagnosis: investigator’s confidence in the diagnosis of PD, presence of atypical clinical features, findings of imaging studies, response to levodopa, and results of autopsy examinations.

Results: The mean ± SD duration of illness in the 800 cases at enrollment was 2.2 ± 1.3 years, and the mean ± SD Hoehn and Yahr stage was 1.6 ± 0.5. The mean ± SD follow-up was 6.0 ± 1.4 years (range, 0.2-7.6 years). In 5 cases, PD was not confirmed at autopsy, and in 15 patients, the results of imaging studies indicated the presence of other pathological conditions. Of the 550 cases treated with levodopa, 49 (8.9%) had little or no improvement; 6 of these cases overlap with either autopsy or imaging study exclusion criteria. Two other cases had at least 4 of the 6 atypical clinical features arguing against the diagnosis of PD. Thus, of the 800 patients, 65 (8.1%) did not have PD according to the study criteria. Compared with those patients with the final diagnosis of PD, in the diagnoses of 60 patients without autopsy, the duration of symptoms (mean ± SD, 7.2 ± 2.0 years vs 8.3 ± 1.9 years; P<.001) and the duration of follow-up (5.3 ± 1.6 years vs 6.1 ± 1.3 years; P<.001) were shorter.

Conclusions: We found that 65 (8.1%) of patients initially diagnosed as having PD were later found to have an alternate diagnosis based on multifactorial clinical diagnostic criteria. This alternate diagnosis indicated that experts in PD changed their diagnoses infrequently during the 7.6-year follow-up.

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IN THE ABSENCE of a reliable diagnostic marker, the clinical diagnosis of idiopathic Parkinson disease (PD) is based on the presence of characteristic features. Various clinical diagnostic criteria have been proposed, but none have been conclusively validated.1 Rajput et al2 made the clinical diagnosis of PD when at least 2 of the 3 cardinal signs (bradykinesia, rigidity, and resting tremor) were present, there was no identifiable cause of the disease, and there was no clinical evidence of widespread lesions of the central nervous system. The diagnosis was confirmed after a mean follow-up of 12 years in 31 (76%) of 41 cases. Using the clinical diagnostic criteria of the Parkinson’s Disease Society Brain Bank, London, England, Hughes et al3 reported the same (76%) autopsy-confirmed diagnostic accuracy in 100 brains of patients with parkinsonism. By modifying the criteria to include asymmetric onset, no atypical features, and no possible cause for another parkinsonian syndrome, the diagnostic accuracy was increased to 93% (true-positive cases), but 32% of pathologically proven cases of PD were not identified by these criteria (false-negative cases). Thus, an increase in positive predictive value was associated with a decrease in sensitivity.

Good response to levodopa is often used to support the diagnosis of PD. Of 100 pathologically proven cases from the United Kingdom, Hughes et al4 reported that 77 (77%) had good or excellent ini-
METHODS

The Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP) was a double-blind study designed by the Parkinson Study Group to evaluate the effects of selegiline hydrochloride, vitamin E, both drugs in combination, and placebo on the progression of the disease. The patients were randomized into one of the treatment groups and followed up at regular intervals. Subsequent modifications to the trial allowed for the systematic follow-up of patients for 7.6 years. The methods and the results have been described in previous articles. Briefly, 800 patients with early PD (Hoehn and Yahr stages 1 and 2) were enrolled in 28 US and Canadian centers. The 34 investigators at the 28 centers were selected to participate in the study because they had a major interest in movement disorders and considerable experience in treating patients with PD. Of the 800 patients, 328 (66%) were men and 272 (34%) were women. The follow-up evaluations in the DATATOP study included making clinical assessments using the Unified Parkinson's Disease Rating Scale, completing standard case report forms designed to track the latest clinical diagnosis, and documenting the reasons for any change in diagnosis. The first patient was enrolled on April 1, 1987, and the data on verification of diagnosis included information to September 1996.

PATIENTS

While the diagnostic criteria of PD were not specified, only those patients who the investigators believed had had idiopathic PD, mild disability, and symptoms for 5 years or less and were between the ages of 30 and 79 years were considered candidates for the study. The patients were not undergoing symptomatic antiparkinsonian therapy. Individuals with dementia (22 on the Mini-Mental State Examination), depression (16 on the Hamilton Psychiatric Rating Scale), or resting tremor (≥3 on the Unified Parkinson's Disease Rating Scale) were excluded from the study. Furthermore, patients who in the opinion of the enrolling investigator had clinical evidence of secondary parkinsonism, including those treated with dopamine receptor-blocking drugs, or those who had parkinsonism due to causes other than idiopathic PD were excluded.

The Clinical Correlates Committee of the Parkinson Study Group concerned with diagnostic accuracy formulated the following clinical criteria as evidence of a non-PD diagnosis: diagnosis is not confirmed at autopsy, neuroimaging study results suggest other cause(s) of parkinsonism, little or no response to levodopa, and any 4 of the following criteria based on the standard case report forms completed at annual follow-up examinations: (1) the investigator is less than 40% confident of the diagnosis of PD; (2) PD is not listed by the investigator as 1 of 3 most likely diagnoses; (3) features or course of the illness considered by the investigator as not typical for PD; (4) there is significant autonomic dysfunction with a background of akinetic-rigid syndrome; (5) there are oculomotor, eyelid, or other neurological abnormalities; and (6) dementia emerges within 5 years of randomization.

STATISTICAL ANALYSIS

Characteristics of patients at the DATATOP baseline visit were compared with patients considered to have (735) and not have (65) idiopathic PD using 2-tailed t tests and χ² tests. Composite scores for tremor, rigidity, bradykinesia, and postural instability and gait difficulty (PIGD) were derived from the Unified Parkinson’s Disease Rating Scale as previously described.

To address the possibility of bias due to differential length of follow-up, the 60 patients who were regarded to have an incorrect diagnosis of idiopathic PD according to clinical criteria (ie, not by autopsy) were compared with the 735 patients with PD with regard to duration of symptoms and length of follow-up using 2-tailed t tests.

The Cox proportional hazards model was used to compare the 2 groups with regard to the time it took to reach the DATATOP end point (level of disability sufficient to require levodopa therapy, in the judgment of the enrolling investigator). Treatment with selegeline at randomization was included as a covariate, and the enrolling investigator was included as a stratification factor in this model. Only data from the original DATATOP trial, that is, before patients were all switched to selegeline treatment, were included in the time-to-event analyses.

RESULTS

The mean ± SD age at randomization in the 800 cases was 61.1 ± 9.5 years and duration of symptoms was 2.1 ± 1.4 years, and the mean ± SD Hoehn and Yahr stage at randomization was 1.6 ± 0.5 years (404 patients at Hoehn and Yahr stage 1 and 396 patients at Hoehn and Yahr stage 2). The mean ± SD follow-up was 6.0 ± 1.4 years (range, 0.2–7.6 years).

Of the 800 patients, the diagnosis of PD was changed in 65 (8.1%) according to the study criteria. In 43 cases, little or no response to levodopa suggested most frequently that the diagnosis of PD was in error; of those cases, an additional 6 cases had features overlapping with

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those in other categories. The other major feature indicative of a diagnosis other than PD was an atypical result of neuroimaging studies in 15 cases. In addition, in 5 cases the diagnosis was not confirmed at autopsy. Of the 65 cases, 2 met 4 of the 6 study criteria. The additional cases (with features overlapping with those in other categories) met the following criteria: the investigator was less than 40% confident of the diagnosis of PD (33); PD was not listed by the investigator as 1 of the 3 most likely diagnoses (19); the investigator considered features or course of the illness not typical for PD (11); there was significant autonomic dysfunction (11); there were oculomotor, eyelid, or other neurological abnormalities (54); and dementia developed within 5 years of randomization (21). Results of neuropathological examination were available for 13 of the 18 patients who had an autopsy. Histopathological slides of the brain from 9 of the 13 patients were examined by one of the authors (D.P.P.) and 5 showed atypical pathological features suggestive of a diagnosis other than PD. Of the 3 cases, the results of the autopsies led to the following diagnoses: multiple system atrophy and nigral degeneration with severe gliosis without the presence of Lewy bodies or neurofibrillary tangles (1), PD and Alzheimer disease (1), progressive supranuclear palsy (2), and chronic cerebral infection (possible rickettsial infection and neurosyphilis), and no PD (1). The additional 4 patients not examined by one of the authors were diagnosed as having striatongrial degeneration (2), dementia with the presence of Lewy bodies (1), and “thickened vessels” in the basal ganglia (1).

The 65 patients who did not have PD according to the study criteria had higher mean scores for bradykinesia (P = .03), PIGD (P = .01), and Hoehn and Yahr stage (P = .006) and a lower mean tremor score (P = .03) compared with the 735 patients with PD (Table). Also, the patients without PD were less likely to report tremor at onset of the disease (P = .003) and more likely to report postural instability (P = .005) and gait difficulties (P = .006) as initial symptoms. The 2 groups were not significantly different with respect to duration of symptoms (P = .19), age at symptom onset (P = .16), rigidity score (P = .61), and the likelihood of reporting rigidity (P = .80) and bradykinesia (P = .83) as initial symptoms. The risk of reaching the DATATOP end point per unit of time was 1.3 times higher in the non-PD group than in the PD group, but this hazard ratio was not statistically significant (P = .13).

Compared with the 735 patients with PD as a final diagnosis, in the 60 patients who were clinically regarded to have received an incorrect diagnosis of PD, the mean ± SD time from the onset of symptoms to last follow-up (7.2 ± 2.0 vs 8.3 ± 1.9 years; P < .001) and length of follow-up (5.3 ± 1.6 vs 6.1 ± 1.3 years; P < .001) were less.

### Baseline Characteristics of 800 Patients With and Without a Final Diagnosis of Idiopathic Parkinson Disease (PD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>PD (n = 735)</th>
<th>Non-PD (n = 65)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since symptom onset, y</td>
<td>2.2 (1.3)</td>
<td>1.9 (1.3)</td>
<td>.19</td>
</tr>
<tr>
<td>Age at symptom onset, y</td>
<td>59.3 (9.6)</td>
<td>61.3 (10.2)</td>
<td>.16</td>
</tr>
<tr>
<td>Hoehn and Yahr' stage</td>
<td>1.6 (0.5)</td>
<td>1.8 (0.5)</td>
<td>.006</td>
</tr>
<tr>
<td>Tremor score</td>
<td>4.7 (3.0)</td>
<td>3.9 (2.7)</td>
<td>.03</td>
</tr>
<tr>
<td>Rigidity score</td>
<td>3.8 (3.0)</td>
<td>4.0 (2.9)</td>
<td>.61</td>
</tr>
<tr>
<td>Bradykinesia score</td>
<td>6.6 (4.3)</td>
<td>7.9 (4.4)</td>
<td>.03</td>
</tr>
<tr>
<td>Postural instability score</td>
<td>1.5 (1.2)</td>
<td>2.0 (1.4)</td>
<td>.01</td>
</tr>
</tbody>
</table>

In this study of 800 cases prospectively followed up by experts in PD since the early stages of the disease, the diagnosis of PD changed in only 65 (8.1%) of patients after a mean ± SD follow-up of 6.0 ± 1.4 years. The diagnostic error was based on a set of admittedly arbitrary, but reasonable, clinical criteria, rather than on autopsy data. However, for the patients to be enrolled in the DATATOP study, they had to have received a diagnosis of PD by an experienced expert in PD. Because of the expertise in parkinsonism, this study differs from the study of Hughes et al., in which patients whose brains were collected by the Parkinson’s Disease Society Bank were previously diagnosed and followed up by general neurologists or other clinicians. In another clinico-pathologic study, long-term (mean, 11.7 years) follow-up by the same expert in PD improved the diagnostic accuracy from 65% after the initial evaluation to 76% at death. The diagnostic accuracy could be improved to 85% if all diseases with pathological findings of substantia nigra parkinsonism that were clinically indistinguishable from PD were included. In the study of Litvan et al., the median sensitivity for the diagnosis of PD increased from 73% at the first visit to 80% at the last visit, and the median positive predictive value increased from 46% to 64% after a mean follow-up of 9 years.

Our study differs from the clinico-pathologic studies mentioned herein in several respects. The most important difference is that the diagnoses in all cases in the studies mentioned herein were verified at autopsy, whereas our study relied chiefly on clinical criteria. The 5 cases of non-PD may not be representative of the entire group since patients in whom autopsies were performed were more likely not to have PD. In these cases, the diagnosis was more likely to be questioned, and therefore they were more likely to be considered for an autopsy. Another difference is that in our study the investigators may have been biased against second-guessing their own initial diagnosis. The mean ± SD duration of symptoms in our patients prior to enrollment was only 2.2 ± 1.3 years, and therefore the evolution of evidence of atypical clinical features or abnormal neuroimaging results would not likely be fully appreciated after such a short period. The 60 patients who were clini-
cally regarded to have received an incorrect diagnosis of PD had a shorter mean duration of symptoms to last follow-up and a shorter mean length of follow-up compared with the 735 patients with PD as the final diagnosis. The mean duration of follow-up was not longer for the cases of non-PD than for the cases of PD, and therefore there was no evidence of ascertainment bias (diagnosis was more likely to change with longer follow-up). It would be expected that patients with atypical parkinsonism, such as progressive supranuclear palsy, multiple system atrophy, or corticobasal degeneration, would have a shorter duration of symptoms before the correct diagnosis because unusual results of clinical or neuroimaging studies indicating atypical parkinsonism would “declare” relatively early since such disorders tend to progress more rapidly than typical cases of PD. Even within PD, different subtypes progress at varying rates. For example, in patients with the tremor-dominant form of PD, the disease seems to progress at a slower rate than in those with the PIGD form of PD. The PIGD form may be more likely to be considered a non-PD disorder, and it is often caused by pathological conditions other than the typical disease caused by Lewy bodies. This observation is consistent with our findings that the 65 patients who did not have PD by our criteria had significantly higher mean scores for PIGD and a lower mean tremor score compared with the 735 patients with PD. Furthermore, in the patients with early-onset PD, the disease seemed to progress at a slower rate than in patients with late-onset PD, but patients with early-onset PD were more likely to develop levodopa-induced complications. The late-onset subtype is characterized by rapidly progressive motor and cognitive disability. Highly predictive diagnostic criteria are essential to select an appropriate patient population for genetic studies and clinical trials.

In conclusion, PD is the most common pathologically confirmed variant of parkinsonism, but the predictive value of clinical diagnostic criteria largely depends on the clinical observation and hence on the skills of the individual physician. Given the caveats mentioned herein, the finding that after a mean 6-year follow-up the initial clinical diagnosis was still considered, based on our study criteria, to be the correct diagnosis in 92% of the patients in the DATATOP study suggests a high diagnostic accuracy by the Parkinson Study Group investigators.

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Reprints: Joseph Jankovic, MD, Department of Neurology, Parkinson’s Disease Center and Movement Disorders Clinic, Baylor College of Medicine, 6550 Fannin, Suite 1801, Houston, TX 77030 (e-mail: josephj@bcm.tmc.edu).

REFERENCES