ORIGINAL CONTRIBUTION

# Accuracy of the Clinical Diagnoses of Lewy Body Disease, Parkinson Disease, and Dementia With Lewy Bodies

## *A Clinicopathologic Study*

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**Background:** Whether Parkinson disease (PD) and dementia with Lewy bodies (DLB) represent 2 distinct nosologic entities or are diverse phenotypes of Lewy body disease is subject to debate.

**Objectives:** To determine the accuracy of the diagnoses of Lewy body disease, PD, and DLB by validating the clinical diagnoses of 6 neurologists with the neuropathologic findings and to identify early predictors of the diagnoses.

**Methods:** Six raters who were unaware of the neuropathologic diagnoses analyzed 105 clinical vignettes corresponding to 29 cases of Lewy body disease (post hoc analysis of 15 patients with PD and 14 with DLB) and 76 patients without PD or DLB whose cases were confirmed through autopsy findings.

**Main Outcome Measures:** Sensitivity and positive predictive value (PPV) were chosen as validity measures and the κ statistic as a reliability measure.

**Results:** Interrater reliability for the diagnoses of Lewy body disease and PD was moderate for the first visit and substantial for the last, whereas agreement for diagnosis of DLB was fair for the first visit and slight for the last. Median sensitivity for diagnosis of Lewy body disease was 56.9% for the first visit and 67.2% for the last; median PPV was 60.0% and 77.4%, respectively. Median sensitivity for the diagnosis of PD was 73.3% for the first visit and 80.0% for the last; median PPV was 45.9% and 64.1%, respectively. Median sensitivity for the diagnosis of DLB was 17.8% for the first visit and 28.6% for the last; median PPV was 75.0% for the first visit and 55.8% for the last. The raters' results were similar to those of the primary neurologists. Several features differentiated PD from DLB, predicted each disorder, and could be used as clinical pointers.

**Conclusions:** The low PPV with relatively high sensitivity for the diagnosis of PD suggests overdiagnosis. Conversely, the extremely low sensitivity for the diagnosis of DLB suggests underdiagnosis. Although the case mix included in the study may not reflect the frequency of these disorders in practice, limiting the clinical applicability of the validity measures, the raters' results were similar to those of the primary neurologists who were not exposed to such limitations. Overall, our study confirms features suggested to predict these disorders, except for the early presence of postural imbalance, which is not indicative of either disorder.

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CONTROVERSY exists as to whether Parkinson disease (PD) and dementia with Lewy bodies (DLB), including diffuse Lewy body disease and a Lewy body variant of Alzheimer disease (AD),[1] represent 2 distinct nosologic entities or whether they exist along the spectrum of a single disorder, Lewy body disease.[2-7] Such debate is the logical consequence of the considerable overlap of clinical and neuropathologic features in disorders associated with Lewy bodies. For example, extrapyramidal features may be found in many patients with severe AD[8,9] and dementia in many patients with PD.[10,11] As yet, there are no clinical markers for these neurodegenerative diseases, thus necessitating neuropathologic examination for their definitive diagnosis. Pathologically, PD was originally defined by the presence of Lewy bodies, first in the substantia innominata and dorsal motor nucleus of the vagus nerve[12] and later in the substantia nigra.[13] Not all neurologists agree that Lewy bodies are essential for a diagnosis of PD[14] because Lewy bodies are found in healthy elderly individuals,[15-21] in patients with dementia but no evidence of parkinsonism,[22] in cases of dementia in which parkinsonian syndrome becomes evident in later stages, and in other neurologic disorders.[23] Nevertheless, Lewy bodies are more numerous in the brains of patients with PD than in healthy elderly subjects



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## METHODS

### SAMPLE AND DATA COLLECTION

Neuropathologists from 7 medical centers selected 105 cases confirmed via autopsy findings from their research and clinical files. The diagnoses were based on the National Institute of Neurological Disorders and Stroke neuropathologic criteria for the diagnosis of PSP and related disorders[40] and on Kosaka's[3] proposed neuropathologic criteria for the diagnosis of Lewy body disease. Diseases were chosen for study because of their similarities with PD and DLB. There were 29 cases of Lewy body disease (PD and DLB) and 76 cases of non-PD and non-DLB. The demographics of the sample are shown in **Table 1**. The raters were provided with the operational diagnosis of dementia given in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV).[41] They considered that at the first visit 45 patients of 91 non-DLB cases exhibited dementia of either the frontal or cortical type. The same data set was used to evaluate the accuracy of the diagnosis of PSP, corticobasal degeneration, Pick disease, and MSA.[42-44]

The case records were abstracted and each summarized into clinical vignettes as described previously.[42] Six neurologists (3 senior movement disorder experts, C.G.G., J.J., and Y.A., and 3 junior neurologists, G.K.W., J.P.B., and E.C.L.) who were unaware of the study design sequentially reviewed the vignettes of the first and last visits and offered an initial and a final diagnosis. Each neurologist completed a standardized form that required them to specify the main features of each case. The initial diagnosis was based on the clinical judgment of the raters without any laboratory and neuroimaging data. The final diagnosis was made after all available information up to and including the last visit was evaluated (Table 1).

### STATISTICAL ANALYSIS

#### Reliability Measures

Generalized κ statistics were used as an outcome measure of group agreement beyond chance.[45] As with correlation coefficients, κ varies from −1.0 (complete disagreement) to 0 (chance agreement) to +1.0 (perfect agreement). Strength of agreement was designed as poor ($\kappa<0$); slight ($\kappa = 0$-0.20); fair ($\kappa = 0.21$-0.40); moderate ($\kappa = 0.41$-0.60); substantial ($\kappa = 0.61$-0.80); and near-perfect to perfect ($\kappa = 0.81$-1.0), as suggested.[46] The pooled test determined the significance between values.[45]

#### Validity Measures

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were ascertained by comparing the neurologists' diagnoses with the neuropathologic diagnoses.[47] Because of concern that specificity might be artificially high because of the large relative frequency of non-PD and non-DLB cases, we chose sensitivity and PPV as outcome measures. Briefly, sensitivity refers to the probability of having a clinical diagnosis of a disease given the neuropathologic presence of the disease. Positive predictive value refers to the probability of having the disease given the clinical diagnosis of having the disease. Thus, sensitivity is relevant for the development of diagnostic criteria or the recruitment of patients for a research study. (Among all the patients who have the disease, what is the proportion of patients clinically diagnosed by the study neurologist as having the disease?) Positive predictive value, while relevant for the assurance of a homogeneous population, is also the most relevant event for the individual patient. (Does a clinical diagnosis of a disease mean that the patient has the disease?) Specificity refers to the probability of not having a clinical diagnosis of a disease given the neuropathologic absence of the disease. Negative predictive value refers to the probability of not having the disease given the clinical diagnosis of not having it.

#### Best Predictive Diagnostic Variables

Logistic regression analysis was used to identify early clinical features (at first visit) that would best predict neuropathologically confirmed cases of Lewy body disease, PD, and DLB and to differentiate PD from DLB.[48] The features the neurologists recorded on the standardized forms were used as variables in the analysis. Variables that might best predict the diseases were analyzed for statistical significance independently and in models of varying combinations of variables. There was a separate analysis for each rater. Significance was defined as $P<.05$.

To avoid data splitting and to reduce bias, we also used the jackknife dispersion test or leave-one-out method to validate the variables identified in the logistic regression analysis.[49] With the jackknife dispersion test, each case was individually classified into a diagnostic category (eg, cases of PD vs non-PD confirmed through autopsy findings) using the predictors identified by the logistic regression analysis on the remaining cases. We calculated the estimates of the jackknife dispersion test and the PPVs and NPVs of each rater's model.

and patients with other neurologic disorders. Pathologic investigation of patients with various presentations of dementia and parkinsonism showed a higher concentration[24] and wider distribution of Lewy bodies, extending into the cerebral cortex, subcortical nuclei, and brainstem nuclei.[25] Such diverse presentations have been described variously as senile dementia of Lewy body type,[26] dementia associated with cortical Lewy bodies,[27] Lewy body variant of AD,[28] AD with PD changes,[29] and diffuse Lewy body disease.[3,25,30] All of these terms were recently classified as DLB.[1] Despite the presence of Lewy bodies in PD and DLB, the relationship between these disorders remains debatable. Differences in the composition of cortical and nigral Lewy bodies for PD and DLB may lead to an artificial nomenclature based on histological features and not pathogenesis,[5,7] and the nonspecificity of Lewy bodies in PD[31] may suggest an inappropriate classification of PD as a single disease entity.[2,10] These issues, together with the absence of disease markers and clinical overlap with other diseases, including multiple system atrophy (MSA) and progressive supranuclear palsy (PSP), challenge clinicians to make an early and accurate clinical diagnosis in patients with parkinsonian symptoms.



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**Table 1. Demographics of the Study Sample***

| Disease | No. | Sex: Male | Sex: Female | Mean (±SD) Age at Onset, y |
|---|---|---|---|---|
| PD and DLB cases | 29 | 24 | 5 | |
| PD | 15 | 14 | 1 | 52.53 ± 2.71 |
| DLB (10 pure form and 4 common form) | 14 | 10 | 4 | 67.77 ± 3.35 |
| Non-PD and non-DLB cases | 76 | 39 | 37 | |
| Progressive supranuclear palsy | 24 | 14 | 10 | 62.08 ± 1.38 |
| Corticobasal degeneration | 10 | 6 | 4 | 62.40 ± 2.57 |
| Multiple system atrophy | 16 | 9 | 7 | 55.44 ± 2.44 |
| Postencephalitic parkinsonism | 7 | 1 | 6 | 42.00 ± 3.65 |
| Pick disease | 7 | 3 | 4 | 64.29 ± 4.26 |
| Alzheimer disease with extrapyramidal features | 4 | 2 | 2 | 80.67 ± 4.06 |
| Creutzfeldt-Jakob disease | 4 | 2 | 2 | 62.25 ± 2.66 |
| Vascular parkinsonism | 3 | 1 | 2 | 71.00 ± 4.93 |
| Whipple disease | 1 | 1 | 0 | 52 |

*PD indicates Parkinson disease; DLB, dementia with Lewy bodies. Data presented as number of cases, with the exception of age at onset.

Only a few studies have compared the clinical diagnosis of PD or DLB with the neuropathologic findings. The accuracy of a clinical diagnosis of PD has been estimated in studies of cases confirmed through autopsy findings,[32-35] but most of these studies did not distinguish between cases that satisfy the pathologic diagnosis of PD and those with DLB (regardless of whether such a distinction is warranted). In addition, they did not estimate false-negative diagnoses (cases of PD confirmed through autopsy findings with a clinical misdiagnosis of other disorders). In contrast, other studies differentiated DLB from AD and multiinfarct dementia[36-38] and from AD alone,[39] yet did not include sample cases of PD confirmed via autopsy findings. Moreover, the generalizability of these studies may be limited because, in practice, clinicians are usually confronted with more than just these diagnostic possibilities.

In our study, we considered PD and DLB as aspects of a single Lewy body disease (post hoc analysis) and as 2 distinct nosologic entities. We addressed 4 main questions: (1) What is the accuracy of the clinical diagnosis of Lewy body disease? (2) Is Lewy body disease separable from non–Lewy body disease and, if so, are PD and DLB distinguishable from one another? (3) What is the accuracy of the clinical diagnosis when PD and DLB are considered as single nosologic entities? (4) What are the characteristics of these 2 disorders when individually compared with all the other disorders (PD vs all other disorders including DLB, and DLB vs all other disorders including PD)?

Accuracy was determined by measuring (*a*) the reliability of 6 neurologists in making the diagnoses, and (*b*) the validity of the clinical diagnoses of both the raters and the primary neurologists (who treated patients during their life) compared with the neuropathologic diagnoses. In addition, logistic regression analysis was used in a search for early predictors (at the first visit) of the diagnosis and to determine the features that could differentiate PD from DLB.

## RESULTS

### LEWY BODY DISEASE (POST HOC ANALYSIS)

#### Reliability and Validity

The interrater reliability of all 6 neurologists for the diagnosis of Lewy body disease was moderate at the first visit ($\kappa = 0.53$; median duration since symptom onset, 36 months; range, 3-240 months) and substantial at the last visit ($\kappa = 0.63$; median interval between visits, 45 months; range, 4-264 months). Seniority of raters and differences between visits were not significant ($P > .05$).

The sensitivity for the diagnosis of Lewy body disease changed from the first visit (median, 56.9%; range, 51.7%-68.9%) to the last visit (median, 67.2%; range, 51.7%-75.8%). The PPV increased from the first visit (median, 60.0%; range, 52.6%-82.6%) to the last visit (median, 77.4%; range, 60.6%-86.9%). The NPV changed minimally from the first visit (median, 84.5%; range, 82.5%-87.8%) to the last visit (median, 87.5%; range, 83.7%-91.0%). The specificity also improved from the first visit (median, 86.8%; range, 76.3%-94.7%) to the last visit (median, 92.7%; range, 82.9%-96.0%).

For the primary neurologists, the sensitivity for diagnosis of Lewy body disease was 65.5% at both visits, whereas the specificity was 78.9% at the first visit and 89.5% at the last visit, and the PPV was 54.3% at the first visit and 70.3% at the last visit.

Of the 29 possible cases of Lewy body disease, there was a median of 12 false-negative diagnoses (range, 8-13; with Lewy body disease diagnosed as other disorders) at the first visit, most of which were classified as AD, MSA, or unknown. At the last visit, there were 10 false-negative diagnoses (range, 8-14) of AD and PSP. False-positive diagnoses (other disorders diagnosed as Lewy body disease) decreased from the first to last visit, with PSP, MSA, and AD representing most cases of misdiagnoses.

#### Best Predictive Diagnostic Variables

The most notable feature for distinction of Lewy body disease from non–Lewy body disease at the first visit was the absence of ocular abnormalities (raters A, C, D, E, and F) (**Table 2**). Excellent response to levodopa (raters D, E, and F), levodopa-induced dyskinesias (raters A and B), and absence of balance disturbances (raters B and D) were also prominent. Additional significant features were unilateral tremor at onset and absence of pyramidal symptoms. Alternative models (not presented) identified hallucinations as a significant but less powerful predictor. With the jackknife dispersion test, the best yet imperfect models for prediction of Lewy body disease were the presence at onset of an excellent levodopa response, absence of balance disturbances, and absence of oculomotor or



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**Table 2. Best Diagnostic Predictive Variables for Lewy Body Disease, PD, and DLB***

| Rater | Predictors | Individual Variable, $\chi^2$ | Odds Ratio | Overall Model, $\chi^2$ | PPV, % | NPV, % |
|---|---|---|---|---|---|---|
| | | **Lewy Body Disease** | | | | |
| A | No oculomotor signs | 8 ($P<.004$) | 30 (5-752) | 36 ($P<.001$) | 41 | 97 |
| | Levodopa-induced dyskinesias | 7 ($P<.009$) | 38 (4-1305) | | | |
| B | No balance disturbances | 15 ($P<.001$) | 8 (3-26) | 23 ($P<.001$) | 22 | 74 |
| | Levodopa-induced dyskinesias | 7 ($P<.007$) | 26 (3-565) | | | |
| C | Unilateral tremor at onset | 5 ($P<.04$) | 4 (1.1-12) | 15 ($P<.008$) | 60 | 79 |
| | No oculomotor signs | 5 ($P<.03$) | 6 (1.5-39) | | | |
| D | Excellent levodopa response | 6 ($P<.02$) | 31 (3-1164) | 30 ($P<.001$) | 83 | 78 |
| | No balance disturbances | 6 ($P<.01$) | 4 (1.4-13) | | | |
| | No oculomotor signs | 4 ($P<.04$) | 12 (1.8-291) | | | |
| E | No oculomotor signs | 8 ($P<.004$) | 6 (2-23) | 24 ($P<.001$) | 86 | 77 |
| | Excellent levodopa response | 7 ($P<.01$) | 20 (3-401) | | | |
| F | Excellent levodopa response | 6 ($P<.01$) | 17 (3-368) | 26 ($P<.001$) | 86 | 77 |
| | No oculomotor signs | 5 ($P<.03$) | 4 (1.2-14) | | | |
| | No pyramidal signs | 4 ($P<.05$) | 6 (1.3-46) | | | |
| | | **PD** | | | | |
| A | Levodopa-induced dyskinesias | 10 ($P<.002$) | 22 (3.5-196) | 27 ($P<.001$) | 86 | 89.6 |
| | Asymmetrical limb rigidity | 9 ($P<.003$) | 8 (2.1-37.5) | | | |
| B | Unilateral tremor at onset | 13 ($P<.004$) | 12 (3.1-50.2) | 19 ($P<.001$) | 88 | 87 |
| | Excellent levodopa response | 7 ($P<.01$) | 10 (1.7-57) | | | |
| C | Unilateral tremor at onset | 10 ($P<.002$) | 8 (2.2-30.8) | 15 ($P<.001$) | 88 | 86 |
| | Levodopa-induced dyskinesias | 4 ($P<.05$) | 16 (1.1-401) | | | |
| D | Rest tremor | 7 ($P<.007$) | 8 (1.9-41.8) | 21 ($P<.001$) | 88 | 90.7 |
| | No pyramidal signs | 3 ($P<.07$) | 13 (1.4-545) | | | |
| | Excellent levodopa response | 8 ($P<.005$) | 39 (3.7-965) | | | |
| E | Asymmetrical limb rigidity | 10 ($P<.002$) | 9 (2.3-38.1) | 21 ($P<.001$) | 81 | 91 |
| | Rest tremor | 5 ($P<.02$) | 5 (1.3-21.2) | | | |
| F | Asymmetrical limb rigidity | 7 ($P<.008$) | 7 (1.7-30.2) | 27 ($P<.001$) | 86 | 88.6 |
| | No oculomotor signs | 4 ($P<.05$) | 10 (1.5-204) | | | |
| | Moderate to excellent levodopa response | 8 ($P<.006$) | 8 (1.8-38.9) | | | |
| | | **DLB** | | | | |
| A | No bradykinesia | 9 ($P<.003$) | 8 (2-32) | 15 ($P<.001$) | 50 | 85 |
| | Family history | 6 ($P<.02$) | 9 (1.6-48) | | | |
| B | Hallucinations | 13 ($P<.004$) | 22 (4-136) | 22 ($P<.001$) | 50 | 91 |
| | No gait disorder | 6 ($P<.01$) | 7 (1.6-36.6) | | | |
| C | Hallucinations | 14 ($P<.001$) | 27 (5-224) | 20 ($P<.001$) | 50 | 91 |
| | No gait disorder | 5 ($P<.02$) | 4 (1.3-53) | | | |
| D | No balance disturbances | 7 ($P<.01$) | 24 (3-633) | 22 ($P<.001$) | 33 | 92 |
| | Early cortical dementia, including frontal deficits | 6 ($P<.02$) | 9 (1.5-65) | | | |
| | Hallucinations | 5 ($P<.02$) | 25 (2-673) | | | |
| E | Hallucinations | 12 ($P<.001$) | 59 (8-1222) | 26 ($P<.001$) | 83 | 93 |
| | No oculomotor signs | 4 ($P<.05$) | 18 (2-654) | | | |
| F | Hallucinations | 11 ($P<.001$) | 50 (7-1053) | 27 ($P<.001$) | 100 | 92 |
| | No balance disturbances | 7 ($P<.01$) | 19 (3-384) | | | |

*PD indicates Parkinson disease; DLB, dementia with Lewy bodies; odds ratios, lower and upper 95%; PPV, positive predictive value using jackknife dispersion test; and NPV, negative predictive value with jackknife dispersion test.

pyramidal symptoms (raters D, E, and F) (PPV, 83.33%-85.71%; NPV, 76.53%-77.90%).

### PD vs DLB

The most notable independent features differentiating PD from DLB at the first visit were the presence of asymmetrical bradykinesia (raters A-F) and asymmetrical limb rigidity (raters A, B, C, E, and F) (data not presented). Additional significant features were absence of cognitive disturbances (raters D, E, and F), unilateral tremor (raters A and B), and levodopa-induced dyskinesias (rater A). The most significant features differentiating DLB from PD at the first visit were the presence of hallucinations (raters B, E, and F; trend for significance for rater C, $P<.06$), absence of tremor (raters A, B, C, D, and E), absence of bradykinesia (raters A, B, C, and E), and absence of dystonia (rater A).

## PARKINSON DISEASE

### Reliability and Validity

Group interrater reliability for the diagnosis of PD was moderate at the first visit ($\kappa = 0.54$; median duration since onset of symptoms, 36 months; range, 3-240 months) and substantial at the last visit ($\kappa = 0.64$; median interval between visits, 106 months; range, 9-228 months). Differences in the seniority of raters were not significant ($P>.05$).



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Median sensitivity for the diagnosis of PD was 73.3% (range, 53.3%-80.0%) at the first visit and 80.0% (range, 60.0%-86.6%) at the last visit. Median PPV, while remaining low, increased from 45.9% (range, 34.2%-61.5%) at the first visit to 64.0% (range, 42.8%-75.0%) at the last visit. The NPV changed minimally from the first visit (95.0%, 91.4%-95.7%) to the last visit (96.3%, 93.5%-97.6%). Median specificity increased from 85.6% (74.4%-94.4%) at the first visit to 92.2% (82.2%-96.7%) at the last visit.

For the primary neurologists, the sensitivity for the diagnosis of PD at both visits was high (93.3%) but the specificity (first visit, 76.7% and last visit, 87.8%) and PPV (first visit, 40% and last visit, 56%) was low.

At both visits, false-negative diagnoses were uncommon. Closer examination of the PD cases misdiagnosed by at least 3 raters at the first visit revealed that these were complicated cases. False-positive misdiagnoses were more numerous, occurring in a median of 13 cases at the first visit and involving primarily DLB, MSA, and PSP. False-positive misdiagnoses at the last visit decreased and still primarily involved DLB.

### Best Predictive Diagnostic Variables

At the first visit, logistic regression analysis identified 2 or 3 features for each of the 6 raters that would best distinguish cases of PD from non-PD confirmed through autopsy findings (Table 2). Asymmetrical parkinsonism (tremor or rigidity) was a predictor for all raters, and levodopa response (moderate to excellent response or levodopa-induced dyskinesias) for 5 raters. Other significant predictors were rest tremor and no pyramidal or oculomotor (ie, supranuclear gaze palsy) signs. All models identified achieved a high PPV and NPV when the jackknife dispersion test was used, but rater D secured the best combination (Table 2). Alternative models (not presented) identified symptom duration longer than 16 years, late onset of gait problems, and absence of balance disturbances at onset as important but less significant predictors.

## DEMENTIA WITH LEWY BODIES

### Reliability and Validity

The interrater reliability for the diagnosis of DLB was fair at the first visit ($\kappa = 0.38$; median duration since symptom onset, 24 months; range, 10-120 months) and slight at the last visit ($\kappa = 0.19$; median interval between visits, 36.5 months; range, 4-264 months). Differences in the seniority of raters were not significant.

The sensitivity for the clinical diagnosis of DLB was extremely low for both the first visit (median, 17.9%; range, 7.1%-42.8%) and the last visit (median, 28.6%; range, 0%-42.9%). The PPV decreased from the first visit (median, 75%; range, 50%-100%) to the last visit (median, 55.8%; range, 0%-80%), and the NPV remained stable (median, 88.7%; range, 87.3%-91.7% [first visit]; median, 89.8%; range, 86.7%-91.5% [last visit]). Median specificity changed minimally between visits (median, 98.9%; range, 97.8%-100% [first visit]; median, 96.7%; range, 94.5%-100% [last visit]).

For the primary neurologists, the sensitivity for diagnosis of DLB was very low (first visit, 0%, and last visit, 14.2%). Although specificity was high for both visits (100%), PPV was 0% at the first visit and 100% at the last visit.

At both the first and last visits, false-negative misdiagnoses were numerous and primarily involved AD and PD. False-positive misdiagnoses at both visits were few, mainly occurring with PD.

### Best Predictive Diagnostic Variables

Features identified most often as distinguishing cases of DLB from non-DLB were the presence of hallucinations (raters B, C, D, E, and F) and the absence of gait or balance disorder (raters B, C, D, and F) (Table 2). Hallucinations significantly correlated with the raters' clinical diagnosis of DLB at the first visit (raters: A, $r = 0.40$; B, $r = 0.61$; C, $r = 0.30$; and E, $r = 0.45$; $P < .001$; raters: D, $r = 0.20$ and F, $r = 0.18$; $P < .05$) and with diagnosis of DLB confirmed through autopsy findings (raters: A, $r = 0.46$; B, $r = 0.49$; C, $r = 0.54$; E, $r = 0.56$; and F, $r = 0.55$; $P < .001$; rater: D, $r = 0.18$; $P < .05$). Additional features included a family history of neurologic disorders, absence of bradykinesia, early cortical dementia, including frontal lobe features, and no oculomotor symptoms. The presence of delusions and excellent response to levodopa, in addition to the other features, were significant independent predictors of DLB for some raters. The jackknife dispersion test identified the model of rater F (presence of hallucinations and absence of balance disturbances) as the best for predicting DLB (PPV, 100%; NPV, 92.41%).

## COMMENT

Our study is the first to evaluate the clinical diagnostic accuracy of PD and DLB as distinct nosologic entities and as phenotypes of a single entity (Lewy body disease). While other studies have focused on accuracy in differentiating DLB from the other dementias observed in dementia clinics,[36-39] we, in an effort to parallel what clinicians are confronted with in movement disorder clinics, focused on differentiating DLB and PD from each other and from other parkinsonian disorders. We also measured the clinical diagnostic accuracy at both early and late stages of the illness and determined whether the clinicians' seniority affected the diagnostic accuracy. All neuropathologic diagnoses were made by experienced neuropathologists using established criteria.[40] However, our population sample was derived from autopsy studies of potentially more atypical cases than those generally seen in medical practice. Nonetheless, the demographics of our sample are similar to those of other PD and DLB studies, except that most of our patients with PD were male.[50-51]

For operational and budgetary reasons, our 6 raters could not efficiently evaluate more than 105 clinical vignettes, and fewer cases of Lewy body disease and AD were included in our sample than are found in the general population[52-53] or in clinical practice[54] because of the need for a varied sample. Furthermore, PSP was overrepresented for other diagnostic reasons.[55] Thus, the applicability of our analysis may be limited. Nonetheless,



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except for the relative frequency of these disorders, our case mix is comparable to what neurologists are confronted with in movement disorder clinics.[32,54] Moreover, even though the primary neurologists were not exposed to these limitations, they also overdiagnosed PD and underdiagnosed DLB, as did our raters. Furthermore, the PPV for the diagnosis of PD in our study is similar to that achieved in 2 other studies.[32,33]

Inclusion criteria were stringent, yet complete information could not always be obtained. For instance, data on levodopa efficacy were missing in many cases at the first visit; in some cases therapy had not yet been introduced because it was the patient's first visit to a clinical center, the referring physician had not initiated treatment, or the parkinsonian symptoms were not severe enough to warrant therapy, as also identified in another study.[56] In addition, hallucinations and other diagnostically relevant features were not systematically recorded in the medical records (missing responses for all raters: mean, 22.2%; range, 6.7%-33.3% for PD; mean, 22.6%; range, 14.3%-28.6% for DLB). Only a well-designed prospective study can overcome the limitations inherent in a retrospective study.

## LEWY BODY DISEASE

Raters' agreement for the clinical diagnosis of Lewy body disease improved from moderate at the first visit to substantial at the last visit. The sensitivity and PPV for the diagnosis were not optimal. Lewy body disease was mostly misdiagnosed as AD and MSA. The diagnostic problems in this disorder were the same as those described later for PD and DLB. Two other studies that evaluated PD without determining if it was associated with DLB[32,33] found similar false-positive cases, including MSA, PSP, AD, and a lacunar state.

Excellent levodopa response, levodopa-induced dyskinesias, the absence of balance disturbances, oculomotor signs, or pyramidal signs were the features present in the best models for predicting Lewy body disease. However, these identified features are the same as those that predict PD and are part of several sets of criteria for PD[33,57,58] but not for DLB. Not surprisingly, these predictors hardly identified cases of DLB confirmed through autopsy findings. Because the identified features distinguishing Lewy body disease from non–Lewy body disease mainly seemed to distinguish PD, we specifically examined the question of whether PD and DLB could be discerned.

## PD VS DLB

We found several features that could distinguish PD from DLB at an early stage. Parkinson disease could be predicted by asymmetrical bradykinesia, asymmetrical limb rigidity, unilateral tremor, levodopa-induced dyskinesias, and absence of cognitive disturbances, and DLB by the presence of hallucinations and the absence of tremor, bradykinesia, and dystonia. Louis et al[56] found that rest tremor is more common in PD (85%) than DLB (55%), whereas myoclonus is more common in DLB (18.5%) than in PD (0%), but they did not find any other differences in extrapyramidal features. They found that myoclonus, absence of rest tremor, no response to levodopa, or no perceived need for treatment with levodopa were 10 times as frequent in DLB as in PD. Differences in findings may be explained by different stages of the disease examined: while Louis et al[56] searched before death for differences between groups, we looked for early predictors of the disease. Perhaps patients' response to levodopa may yield longer-term benefits in patients with PD than in those with DLB, and those with myoclonus may present at later stages with DLB.[56] Different stages of the disease may also explain why hallucinations, a good predictor of DLB in our study and others,[39] were not a good predictor in the same group of patients.[59]

## Parkinson Disease

Our results support 5 main conclusions on the diagnosis of PD: (1) raters achieved moderate to substantial agreement for the clinical diagnosis of PD; (2) PD was overdiagnosed; (3) DLB, MSA, and PSP were the main diseases clinically confused with PD; (4) the best early features for separating PD from other disorders were asymmetrical onset of parkinsonism (bradykinesia, rigidity, and tremor, particularly rest tremor), levodopa response (moderate to excellent benefit and levodopa-induced dyskinesias), and absence of pyramidal and oculomotor symptoms; and (5) early onset of memory disturbances, confusional episodes, hallucinations not attributable to therapy, or postural instability should suggest diagnoses other than PD.

As expected, agreement among raters for the clinical diagnosis of PD improved at the last visit. Because all raters received the same information, differences in interpretation may explain the less-than-perfect agreement. Additionally, while several sets of diagnostic criteria for the diagnosis of PD have been proposed,[33,57,58,60-63] raters were not given any specific one because there is no universally accepted standardized definition of PD. Unfortunately, none of the proposed criteria for PD have been subjected to reliability studies, and only a set from England[16] has been subjected to validity studies.[64]

Our raters' sensitivity for the diagnosis of PD was relatively high, yet not as high as that of the primary neurologists. However, the PPV for diagnosing PD was higher for the raters (first visit median, 46% and last visit, 64%) than for the primary neurologists (first visit, 40% and last visit, 56%). These PPVs were lower than those reported by others at the first visit (65.12%)[32] and the last visit (75.63% and 76%).[32,33] The reasonable sensitivity but low PPV for the diagnosis of PD in our study suggest that PD was overdiagnosed. Moreover, similar results obtained by the primary neurologists offer further evidence for the overdiagnosis of PD in clinical practice.

False-negative diagnoses were infrequent in our study. Some PD cases misdiagnosed as other disorders were complicated cases. For example, one case misdiagnosed as PSP involved a patient who had severe bronchopneumonia, a 2-year history of progressive gait disturbances, and levodopa-responsive asymmetrical parkinsonism without tremor. More importantly, this patient had been erroneously described as having down-



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ward gaze limitation. Exclusion of this case from our analysis did not seriously alter our results. The main problems in the remaining difficult cases, which were mostly confused with MSA, were dysautonomia and anterocollis, which suggest MSA. On the other hand, a few patients had a long history of minimal to moderate parkinsonism, which is unlikely to occur in MSA.[65]

More troublesome were the numerous cases misdiagnosed as PD (false-positive diagnoses). We closely examined 13 cases misdiagnosed by half of the raters. One of the patients with PSP presented with unusual symptoms. The patient had an 11-year history of mild tremors in the left hand progressing to the left foot in 3 years. Postural instability and gait disturbances developed at later stages of the disease but supranuclear ophthalmoplegia was absent. Not surprisingly, this case was misdiagnosed by all raters as PD. It is rare that progressive supranuclear gaze palsy is not observed in PSP, but it is even more unusual for a patient with PSP to present with asymmetrical onset of tremor and late postural instability.[66,67] A second patient with PSP who was misdiagnosed as having PD presented with typical PSP signs (2-year history of severe postural instability, parkinsonism with moderate and transient levodopa response, and frontal lobe-type features), except for normal extraocular movements. Postural instability at the onset strongly suggests an atypical parkinsonian disorder.

None of the patients with olivopontocerebellar-type MSA were misdiagnosed as having PD, since they had cerebellar features that are not present in PD. The striatonigral-type MSA cases misdiagnosed as PD at the first visit were characterized by the absence of autonomic features. However, 2 patients developed unusual signs for PD, one with hypometric horizontal saccades and abnormal horizontal optokinetic nystagmus, and the other with postural instability at onset and bilateral Babinski signs. Pyramidal signs are not part of PD and suggest a combined disorder (eg, spinal cord injury) or an alternative diagnosis (atypical parkinsonism).[68] In fact, pyramidal signs develop in approximately half of patients with MSA, half of those with corticobasal degeneration, and a third of those with PSP.[69-72]

Several DLB cases misdiagnosed as PD had unusual features for PD, such as memory disturbances at the onset of symptoms, confusional episodes, and hallucinations or delusions in the absence of levodopa therapy. Although dementia may develop in 10% to 30% of patients with PD after a long duration of disease,[10,73-76] and patients with PD may have frontal lobe–type dysfunction, none of those features were present at onset in our PD cases confirmed through autopsy findings. Conversely, memory disturbances, confusional episodes, and hallucinations or delusions in the absence of levodopa therapy are characteristic features of DLB and are among the criteria proposed for its diagnosis.[1,27,36,39,59] Not unexpectedly, some patients with DLB presenting at the first visit with normal cognition and absence of hallucinations but with parkinsonian features were misdiagnosed as having PD. Thus, because PD shares several overlapping features with other disorders, our results suggest that physicians should pay attention not only to the presence of a symptom but also to symptom chronology to secure an early and correct diagnosis.

We identified onset of asymmetrical bradykinesia, rigidity or tremor (particularly rest tremor), moderate to excellent levodopa response, levodopa-induced dyskinesias, and absence of pyramidal and oculomotor symptoms as the best features for distinguishing PD from non-PD. Each of these features is identified in other studies on diagnostic criteria for PD (asymmetrical parkinsonism,[10,57,58,61,77] levodopa responsiveness,[10,57,58,61,77] rest tremor,[10,57,60,63,76] and absence of ocular or pyramidal symptoms[10,57,60,63]). The combinations of features allow for an early diagnosis and achieved a high PPV and NPV, offering high diagnostic accuracy since diagnostic distinction is provided by the presence of these features. In fact, asymmetrical parkinsonism at disease onset and absence of atypical features (ie, pyramidal, oculomotor, and cerebellar symptoms) were suggested as the optimum criteria for clinical diagnosis of PD.[64]

Details were not available to allow our raters to classify rest tremor as the classic "pill-rolling, Hz rest tremor."[4-6] While the classic tremor has been reported in 11% of patients with MSA,[78] this symptom has not been described in any other atypical parkinsonian disorder confirmed through autopsy findings. Although rest tremor was identified as a predictor in our study, not all patients with PD have classic rest tremor, and this predictor does not include all patients with PD. In this regard, the models of raters A and F consisting of asymmetrical rigidity, levodopa responsiveness, and absence of oculomotor symptoms would include patients with PD with rigidity and akinesia. These models also distinguish patients with PD with rigidity and akinesia from those with PSP and corticobasal degeneration, but less so from those with MSA. Patients with MSA are likely to exhibit asymmetrical features, and one third may initially respond to levodopa, although the benefit is not long-lasting.[69]

Symptom duration lasting more than 16 years was also identified as a significant predictor. However, this feature does not allow for an early diagnosis and was present in only 4 of the 15 patients with PD prior to their first visit to an academic medical center. Although mandatory features in proposed clinical criteria for the diagnosis of PD vary,[33,57,58,60-62] postural instability is often included.[57,60,61] Yet, as observed in our study and others,[79] postural instability is a late feature of PD but an early feature of PSP and MSA.[77] Thus, the inclusion of postural instability as a criterion most likely decreases the specificity of the diagnosis of PD and favors overdiagnosis. Moreover, because of its late development in PD, the inclusion of postural instability as a requirement for the diagnosis of PD potentially excludes patients with early symptoms of PD in community studies.[62]

### Dementia With Lewy Bodies

The results of our study support 5 main conclusions regarding the diagnosis of DLB: (1) raters achieved a fair to slight agreement for the clinical diagnosis of DLB; (2) DLB was underdiagnosed; (3) DLB was mostly misdiagnosed as AD and PD; (4) the best early predictors for the diagnosis of DLB were hallucinations unrelated to therapy



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and absence of balance disorder at onset; and (5) the validity of the criteria proposed by the Consortium on Dementia with Lewy Bodies[1] was suboptimal at early presentation (first visit).

THE RELIABILITY of our raters for the diagnosis of DLB differs with the results of a study[37] that found, on average, substantial agreement. The disagreement among our raters may be explained by the heterogeneous presentation of DLB, the composition of the sample, and the absence of specific diagnostic criteria, since consensus guidelines were unavailable at the time of the study. Incidentally, failure to provide diagnostic guidelines does not seem to be relevant for the diagnosis of PD or other disorders.[42] Our raters were required to diagnose 10 different and sometimes infrequently occurring parkinsonian disorders, whereas in the study of McKeith et al[36] raters were presented with 3 common dementia disorders (AD, DLB, and multi-infarct). The frequency of the DLB cases in the 2 studies also differed (40% in their study, 13.3% in ours), and a low frequency of cases may influence reliability measures. However, our raters achieved perfect agreement on whether patients had hallucinations ($\kappa = 0.84$), despite the fact that few patients exhibited this symptom (12/105 [11%]).

Our validity results suggest that DLB was severely underdiagnosed, as indicated by the low median sensitivity for its clinical diagnosis during both visits. The primary neurologists also underdiagnosed DLB, which suggests that, in practice, the disorder is also underdiagnosed. However, when they suspected it they were always correct. Difficulty in diagnosing DLB may be explained by the similar biological features of some neurodegenerative disorders, unawareness of diagnostic criteria for DLB, or retrospectively collected data. Our results clearly contrast with those of McKeith et al[37] where, on average, two thirds of the DLB cases were identified. Aside from the differences in methodology discussed earlier, it may be more difficult to differentiate DLB from parkinsonian disorders than from dementia disorders. Additionally, our raters were unaware that they would be evaluating DLB cases, whereas it was the focus of the study by McKeith et al.[36]

False-negative diagnoses of DLB were numerous and most were misdiagnosed as AD. Some of the DLB cases misdiagnosed had classic features of DLB. While parkinsonism was absent at the first visit in a few DLB cases misdiagnosed as AD, early fluctuating cognitive disturbances or early delusions and hallucinations were present. These features are suggestive of DLB when present at disease onset and were, in fact, recently included in the criteria proposed by the Consortium on Dementia with Lewy Bodies.[1] Occasionally, patients with DLB presenting with parkinsonism and dementia were misdiagnosed as having PD or MSA. However, dementia is infrequent in the early stages of PD and is uncommon in MSA.[80,81] In fact, dementia may be an exclusionary criterion for the diagnosis of MSA.[82,83] Other DLB cases were difficult to diagnose. For example, some patients with DLB without cognitive disturbances at presentation were misdiagnosed as having PD and PSP, whereas a patient with DLB with solely cognitive disturbances at presentation was misdiagnosed as having AD. Although DLB cases confirmed through autopsy findings showed features of dementia and supranuclear gaze palsy,[84,85] these were not early features in most of our DLB cases (absence of oculomotor symptoms, 92.9%).

On other hand, study raters made very few false-positive diagnoses, which mostly included AD and PD misdiagnosed as DLB, but none of these cases were misdiagnosed by more than 2 raters at the first visit.

The best models (highest PPV and NPV) for the diagnosis of DLB included as predictors early hallucinations unrelated to therapy and absence of oculomotor or balance disorder. We found that hallucinations significantly correlated with the raters' clinical diagnosis of DLB at the first visit and with the DLB diagnosis confirmed through autopsy findings, which supports the notion that the presence of hallucinations helps to diagnose this disorder. The fact that Lewy bodies are predominantly located in limbic areas suggests the relevance of this symptom.[86] Although absence of bradykinesia at onset and positive family history predicted 50% of cases of DLB, this combination will not predict DLB in a population study, even if family history is reported in a subset of DLB.[87] Yet, this combination of features was relatively useful because most of our patients without DLB had parkinsonism, with the combination occurring sporadically.

Our study identified a few of the cardinal clinical features of DLB.[39,88] Similar to the findings of Mega et al,[39] we found that hallucinations but not delusions or depression are relevant for the diagnosis of DLB and that raters rarely agreed on the presence of fluctuating cognitive function ($\kappa = 0.06$). However, absence of gait and balance disturbances, in contrast to what has been reported by some[36,89] but not others,[56] was a good predictor of DLB. In addition, we found that patients with DLB, in comparison with those who had other parkinsonian disorders, had minimal or no bradykinesia at the onset.[1,85,87-89] Although excellent levodopa response was occasionally a predictor for DLB, this feature was present in only 14.2% of DLB cases.

Using the data recorded at the first visit, we retrospectively tested the validity of the criteria recently proposed by the Consortium on Dementia with Lewy Bodies for the diagnosis of DLB.[1] For this set of criteria, probable diagnosis of DLB requires progressive cognitive decline and the presence of 2 of the following features: fluctuating cognition, recurrent visual hallucinations, or parkinsonism, while suspicion of DLB requires the presence of only 1 of these features.[1] Both the possible DLB criteria (median sensitivity, 35.7%, range, 14.3%-42.9%; PPV, median, 13.7%, range, 8.7%-14.3%); and the probable DLB criteria (sensitivity, 17.9%, range, 0%-28.6%; PPV, median, 50%, range, 0%-50%) were suboptimal (very low sensitivity and PPV). To test this set of criteria, we used frontal lobe–type cognitive impairment as the essential feature representing cognitive impairment. The validity of the criteria hardly improved when early cortical and frontal lobe–type cognitive impairment were included (possible DLB: median, 39.3%; range, 21.4%-42.9%, and PPV, median, 13.1%; range, 10.7%-15.0%; probable DLB: sensitivity, 21.4%; range, 0%-28.6%, and PPV, median, 50%; range, 0%-



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60%). The accuracy of this set of criteria might have improved if our cases were specifically presented or analyzed using this information. However, a previous validity study of 2 similar criteria for DLB[38] achieved low sensitivity (15%-17%), which supports our results. While our study supports the inclusion of hallucinations and the absence of gait or balance disturbances for the diagnosis of DLB, further work is needed to determine which combination of features will improve the diagnostic accuracy in clinical practice.

## CONCLUSIONS

There is an important overlap of clinical features in the various presentations of disorders characterized by the presence of Lewy bodies. Although our study was designed to evaluate the accuracy of the diagnosis of these disorders and not to determine whether PD and DLB are distinct nosologic entities or phenotypic variants of Lewy body disease, our results suggest that there is no benefit from considering them as a single group. When these disorders were classified post hoc as a single nosologic entity, problems associated with their identification emerged, and the overall diagnostic accuracy did not improve. Furthermore, we identified features that separated PD and DLB, which may be used as clinical pointers. Thus, despite the overlap, the clinical differentiation of PD from DLB may be possible and important. Furthermore, while patients with PD benefit from levodopa therapy, patients with DLB who have cognitive impairment may specifically respond to cholinergic therapy,[90] which worsens motor symptoms in PD. In addition, the natural history of PD and DLB is different (eg, pattern of incontinence and duration of symptoms).[91] Grouping the Lewy body disorders into a single nosologic entity at present may be premature and may compromise epidemiological and therapeutic research on these disorders.[59]

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