What features improve the accuracy of clinical diagnosis in Parkinson's disease:

A clinicopathologic study

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Article abstract—Many authorities have drawn attention to the difficulties in clinically distinguishing Parkinson's disease (PD) from other parkinsonian syndromes. We assessed the clinical features of 100 patients diagnosed prospectively by a group of consultant neurologists as having idiopathic PD according to their pathologic findings. Seventy-six percent of these cases were confirmed to have PD. By using selected criteria (asymmetrical onset, no atypical features, and no possible etiology for another parkinsonian syndrome) the proportion of true PD cases identified was increased to 93%, but 32% of pathologically confirmed cases were rejected on this basis. These observations suggest that studies based on consultant diagnosis of PD, using standard diagnostic criteria, will include cases other than PD, thus distorting results from clinical trials and epidemiologic studies. The strict use of additional criteria can reduce misdiagnosis but at the cost of excluding genuine PD cases.

NEUROLOGY 1992;42:1142-1146

Although in life the majority of patients with Lewy body Parkinson's disease (PD) are correctly diagnosed, misdiagnoses do occur despite the application of stringent diagnostic criteria.[1] Some patients thought clinically to have PD turn out to have alternative pathologies,[2-4] while in others with atypical clinical pictures the diagnosis of PD is established only after death.[5,6] Recent clinicopathologic studies have shown a false-positive rate of around 20%,[7] and estimates of the false-negative rate vary, depending on patient selection, from 5 to 10%.[6,7]

The conventional criteria for diagnosis of PD are the presence of at least two of the following cardinal features: akinesia, rigidity, and resting tremor, in the absence of any exclusion criteria.[1] Some insist on the presence of bradykinesia as an essential cardinal feature, thereby eliminating cases of essential tremor with cogwheeling which would satisfy the less strict definition.[1]

The Parkinson's Disease Society (PDS) brain bank in London receives donor tissue from parkinsonian patients, most of whom have been prospectively examined annually by neurologists associated with the bank. As a follow-up to a recent study assessing the accuracy of clinical diagnosis,[7] we have reviewed the clinical features of 100 patients diagnosed clinically as having PD to ascertain the specificity, sensitivity, and predictive accuracy of a number of clinical criteria commonly thought to be helpful in the diagnosis of PD.

Methods. One hundred consecutive cases with clinically diagnosed PD were studied. The brains were collected over a 3-year period between June 1987 and August 1990 from all over the United Kingdom. Seventy percent of cases were registered brain bank donors and had been prospectively assessed annually by neurologists associated with the PDS brain bank using a standard pro forma assessment sheet. The remainder had been seen by consultant neurologists or geriatricians. Hospital and consultant case notes were reviewed to confirm the clinical diagnosis of PD, and in all cases adequate clinical information was available. All cases had been specifically considered during life to have PD rather than a less well defined parkinsonian disorder. Cases were excluded if the diagnosis of PD was changed prior to death.

Clinical features collated included symmetry of onset, tremor at onset, initial response to levodopa, presence of the three cardinal features of parkinsonism, a classifica-

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Dr. Hughes and Dr. Daniel are funded by the Parkinson's Disease Society, UK. Dr. Ben-Shlomo is a Wellcome research fellow in Clinical Epidemiology.

Received August 9, 1991. Accepted for publication in final form November 5, 1991.

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Table 1. Clinical features, means, and ranges, in 100 patients with clinically diagnosed Parkinson's disease, and divided according to pathologic diagnosis

	All cases (n = 100)	PD (n = 76)	Non-PD (n = 24)
Sex (males)	59 (59%)	47 (62%)	12 (50%)
Age at onset (years)	64.5 (31-85)	63.6 (31-84)	67.6 (34-85)
Duration of disease (years)*	11.9 (2-35)	12.8 (2-30)	8.8 (2-35)
Hoehn & Yahr score at death	4.3 (3-5)	4.3 (3-5)	4.4 (3-5)
Age at death (years)	76.5 (50-91)	76.4 (50-91)	76.6 (62-90)
Marked initial levodopa response†	73 (73%)	57 (75%)	16 (67%)

* Only significant difference between groups with PD and non-PD.
† Marked response defined as greater than 50% motor improvement. See text.

tion of overall disease pattern, symmetry of signs during disease, and the development of drug-induced motor fluctuations and dyskinesias. Atypical features possibly relating to a parkinsonian disorder other than PD, such as early marked autonomic disturbance, early severe dementia, corticospinal tract dysfunction, and supranuclear gaze palsy, as well as the presence of a possible cause for the development of another parkinsonian disorder, such as the use of neuroleptic medication, a history of several cerebrovascular events, or an episode of encephalitis around the time of development of symptoms, were also recorded. The initial response to levodopa was classified as marked if a greater than 50% improvement had occurred, as judged by either the patient or assessing neurologist, on the introduction of levodopa. Disease pattern was classified as tremor-dominant, mixed, or akinetic/rigid depending on the predominant clinical features, and both end of dose "wearing-off" and random "on-off" oscillations were included as motor fluctuations for analysis.

Half-brains fixed in 10% neutral formalin were examined using standard neuropathologic methods as described elsewhere.[7] The diagnosis of PD was based on finding a clear depletion of nigral pigmented neurons with Lewy bodies in some of the remaining nerve cells.[8] In all cases where Lewy bodies were difficult to find, at least three hematoxylin-eosin 7-μm sections of midbrain were examined. In cases lacking the pathologic changes of PD, diagnoses were established using accepted neuropathologic criteria.[2,4,9,10]

The case histories of all patients were reviewed by two of us (A.J.L., A.J.H.) and the clinical diagnosis reevaluated according to the recommended PDS brain bank clinical criteria.[1]

Analysis of data. The proportion of cases with each clinical feature were compared for cases with pathologically proven PD and non-PD using the chi-square test for proportions for a two-by-two contingency table. If an expected cell value was less than five, Fisher's exact test was used.[11] Differences for continuous variables were tested by use of Student's *t* test. For each clinical feature, the sensitivity, specificity, and positive and negative predictive values were calculated[12] (see appendix for more details). To determine the best combination of predictor variables, all the variables were included in a logistic regression model. Sensitivity and positive predictive values were recalculated for the combinations of variables determined by the model. Analyses were carried out using the SAS/PC software.

Analysis of the clinical features for predictive accuracy was performed separately for the group as a whole and then repeated only for those cases that retrospectively satisfied the PDS brain bank clinical criteria.[1]

Results. The mean age at disease onset was 64.5 years (range, 31 to 85) and the mean duration of disease was 11.9 years (range, 2 to 35); 59 patients were men and 41 were women (table 1). The clinicopathologic findings have been described in detail elsewhere.[7] Seventy-six cases fulfilled the pathological criteria for PD, while 24 patients were clinically misdiagnosed. The retrospective application of the recommended diagnostic criteria[1] improved the diagnostic accuracy to 82% (73/89). The principal findings in the 24 cases without Lewy bodies were as follows: progressive supranuclear palsy (6), Alzheimer's disease-type pathology (6), multiple system atrophy (5), vascular disease (3), isolated nigral atrophy with no Lewy bodies (2), postencephalitic parkinsonism (1), and in one case there were no abnormal findings. There was no significant difference between the two groups for sex, age at onset, age at death, or terminal disease severity, although the duration of disease was significantly longer in cases with PD ($p = 0.006$) (table 1).

Table 2 shows the different proportions of true PD and non-PD cases with each of the different features either alone or combined. Only six of the features alone differed significantly between the two groups. When this was repeated, having excluded the 11 cases not satisfying the PDS brain bank clinical criteria,[1] only asymmetrical onset and the absence of any atypical features remained significantly different between the groups. The repeat analyses based on only these 89 cases resulted in a slight increase in the positive predictive values of most of the features (data not shown).

Atypical features possibly indicative of another parkinsonian disorder were present in 11 cases and included an extensor plantar response (4), early severe dementia (2), early marked autonomic disturbance (2), supranuclear gaze palsy (1), upper limb dyspraxia (1), and bulbar palsy (1). A possible cause for a parkinsonian syndrome other than PD was found in 12 cases. These were cerebrovascular events near the onset or early in the course of parkinsonism (5), possible encephalitis (4), neuroleptic medication (2), and repeated head trauma (1).

The logistic regression model selected the following features as the three best predictors: no atypical features for PD, an asymmetrical onset, and no suggestion of a cause for another parkinsonian syndrome. This did not change when the subgroup of 89 cases satisfying the recommended diagnostic criteria[1] was analyzed. Only the first two variables reached conventional levels of significance, but because of the likelihood of a type 2 error (rejecting

Table 2. Diagnostic value of clinical features in 100 patients clinically diagnosed with Parkinson's disease, divided according to pathologic diagnosis

Criteria	PD % (n = 76)	Others % (n = 24)	*χ^2 p value	Sensitivity	Specificity	Pos. pred. value	Neg. pred. value
Initial symptom							
Tremor	72	54	0.11	.72	.46	.80	.34
Asymmetrical	77	42	0.001	.77	.58	.85	.45
Clinical features							
Tremor as a feature of disease	76	50	0.016	.76	.50	.83	.40
Definite asymmetry of signs	59	33	0.03	.59	.67	.85	.34
Marked response to levodopa	79	67	0.56	.79	.33	.78	.35
No atypical features for PD	97	63	<0.001	.97	.38	.83	.82
No etiology for another parkinsonian disorder	91	79	0.16	.91	.21	.78	.42
Presence of fluctuations or dyskinesia	66	48	0.12	.66	.52	.83	.31
Tremor-dominant disease	14	4	0.28	.14	.96	.91	.27
Mixed pattern of disease	63	42	0.07	.63	.58	.82	.34
Akinetic/rigid disease	24	54	0.005	.24	.46	.57	.17
Multiple criteria							
Conventional criteria (2 of T, R, B)	99	92	0.15	.99	.08	.77	.67
All 3 cardinal features (T, R, B)	65	29	0.002	.65	.71	.88	.40
Asymmetrical onset and atypical features	75	25	<0.001	.75	.75	.90	.49
As above and no etiology for another disorder	68	17	<0.001	.68	.83	.93	.45

* χ^2 test comparing the proportion of cases with PD and non-PD having the clinical feature.
T Tremor.
R Rigidity.
B Bradykinesia.

a truly predictive variable because it fails to reach conventional levels of significance), other variables were still considered for their possible effect on predicting true cases. The effect of using an increasing number of criteria for the diagnosis of PD is illustrated by plotting the sensitivity of each combination against positive predictive value for the best stepwise combination of variables as selected by the logistic model (figure).

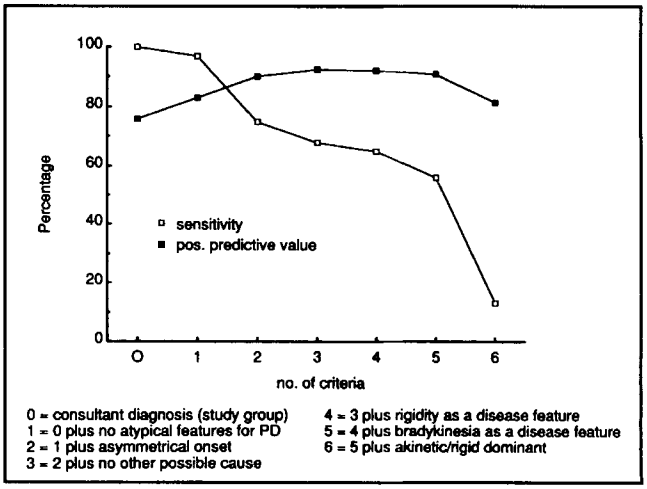

Figure. The effect of including different criteria on the sensitivity and positive predictive value of PD.

Discussion. There are few postmortem studies addressing the predictive accuracy of different clinical features for PD. In the present study, 76% of PD cases diagnosed by a group of neurologists and geriatricians satisfied the established neuropathologic criteria for PD. Any clinical feature with a positive predictive value greater than 0.76 may therefore be useful in discriminating between PD and non-PD cases. The best single criterion for correctly predicting PD was the presence of a tremor-dominant pattern of disease. However, this uncommon feature was only found in a small number of cases and may have occurred by chance. Most of the other variables performed equally well and predicted approximately 80% of all true cases. Almost all cases had at least two conventional features of PD, demonstrating the use of similar broad criteria by all clinicians despite differences in opinion regarding the definition of parkinsonian disorders.[13] The positive predictive value of these criteria was not remarkable and the specificity low, as other conditions that clinically mimicked PD also shared these features. Retrospective application of the brain bank criteria[1] improved diagnostic accuracy to 82%, suggesting that criteria for diagnosis employed by individual neurologists differed somewhat. If only cases with all three features of PD are considered, the predictive value is increased to 88%

although 35% of true PD cases would be rejected. The use of more criteria increases diagnostic accuracy but at the cost of rejecting more true cases of PD. As there are over 8,000 ways to combine the 13 variables, we used a logistic model to determine the most effective combination of variables. The optimum combination of criteria should obtain a high sensitivity and positive predictive value; however, an increase in positive predictive value is balanced by a decrease in sensitivity (figure). Different circumstances will alter the relative importance of these measures. For example, a high sensitivity is more appropriate in a clinical setting where it is preferable to overdiagnose and therefore offer initial treatment with levodopa to some non-PD cases rather than deprive some true PD cases of useful therapeutic intervention. For a drug trial, however, the effect of misclassifying other conditions as PD will result in underestimating the possible beneficial therapeutic effect, assuming non-PD cases are not affected by the drug. Analytical epidemiologic studies will also be compromised by misclassification, distorting the estimated risk associated with an exposure, as will genetic studies. Under these circumstances, a high predictive value is more important than a high sensitivity, although it will be more difficult and time consuming to find eligible cases. The inclusion of an asymmetrical onset and no evidence of another disorder or possible etiology appear the best compromise, resulting in only 7% of non-PD cases being included while excluding 32% of true cases. This selection is superior to using the presence of all three features of PD (table 2). Similar results were obtained when the cases not satisfying the PDS brain bank criteria had been excluded. The implications of using different criteria can be demonstrated by a hypothetical example. If 100 cases of PD are to be recruited for a trial, 122 and 143 possible cases would have to be assessed using the brain bank or our model-selected criteria to enlist 100 eligible cases. This series would contain 82 true PD cases, using the brain bank criteria, and 93 using the model-selected criteria.

Our results are similar to those of Ward and Gibb[14] based on a published pathologic series[15] and an earlier PDS brain bank series. This study had a smaller number of cases and limited data on other features such as levodopa response and asymmetry. Our results should not be compared with studies that have used screening questionnaires to diagnose PD in the community.[16] The latter are used to suggest a possible diagnosis of PD and are usually confirmed by a consultant neurologist. In this study, we are trying to determine which features help distinguish true PD from clinically diagnosed PD, and therefore the usefulness of each feature is totally different. For example, a response to a trial of levodopa is generally regarded as indicative of PD. In a series of pathologically proven PD, 94% of cases showed a response to levodopa.[17] Our results show that the response to levodopa had little discriminatory power. This apparent contradiction results from the inclusion of non-PD cases which showed an apparent levodopa response, thus negating the value of this feature in this series.

Our group of patients are selected and are unlikely to be representative of parkinsonian patients in the general community or possibly even in general neurology clinics. As the positive predictive value of any test is dependent on the prevalence of the disease in the sample, it will be different for a community sample as compared with a clinic-based series of patients. Because of the difficulty in tissue collection, brain banks probably select for institutionalized patients and so for more severe disability or the presence of dementia. Also, studies of this type may concentrate atypical cases without PD but with clinical features commonly thought to predict PD. The prevalence of other conditions that mimic PD may also vary in different populations. These factors need to be borne in mind before extrapolating our findings to other patient groups. However, comparison with clinic-based descriptive studies[18] shows a similar profile of initial symptomatology and clinical course as in our cohort, suggesting that despite these biases, the group may be representative of patients in neurology clinics with a particular interest in movement disorders.

It is surprising that so many cases were diagnosed as PD but also had atypical features or a possible etiology for another parkinsonian syndrome. One explanation may be that a retrospective review over the whole clinical course of the patient could have revealed features not evident when the diagnosis was initially made, and subsequently the diagnosis had not been altered. Additionally, a "soft" atypical sign may not be regarded as significant if the rest of the clinical picture was typical for PD. The observation that only two of the 11 cases with atypical features did not show a response to levodopa (no data available on two cases) supports the idea that individual neurologists used their judgment to decide on the importance of these features. We felt it artificial and misleading to exclude cases with these features from the analysis as in reality such cases are diagnosed as PD. Studies of PD often fail to report on the definite absence of exclusion criteria. Only three of 61 clinically based papers published during 1990 (Ward, personal communication) had specified diagnostic criteria for PD. Even epidemiologic studies,[19] which usually have explicit exclusion criteria, vary on these criteria and in doubtful cases the opinion of a neurologist is usually sought, replicating the situation in our series.

This study highlights the problem of assuming that PD is a specific morbid entity that can be diagnosed reliably on clinical grounds. Until biologic markers or other techniques are developed, we must accept that diverse neuropathologic disorders may produce clinical syndromes indistinguishable from Lewy body PD. The use of strict exclusion cri-

Appendix.

	True PD	Non-PD
Feature present	a	b
Feature absent	c	d

Sensitivity = (a/a+c), the proportion of PD cases that have the feature.
Specificity = (d/b+d), the proportion of non-PD cases without the feature.
Positive predictive value = (a/a+b), the proportion of cases with the feature that have PD.
Negative predictive value = (d/c+d), the proportion of cases without the feature that do not have PD.

Sensitivity and specificity are a measure of the screening test and are not dependent on the prevalence of disease in the sample. The positive and negative predicitive values are dependent on the prevalence of disease and will therefore differ for community as compared with clinic-based samples.

teria and inclusion of only cases with an asymmetrical onset can help reduce misdiagnosis but will also exclude a proportion of genuine cases.

Acknowledgments

The authors wish to thank Miss Siobhan Blankson and Miss Linda Kilford for the histologic preparations.

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Neurology 1992;42;1142
DOI 10.1212/WNL.42.6.1142