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The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service

Andrew J. Hughes,[1,3] Susan E. Daniel,[1] Yoav Ben-Shlomo[2] and Andrew J. Lees[1]

[1]*The United Kingdom Parkinson's Disease Society Brain Research Centre, Institute of Neurology, London,* [2]*Department of Social Medicine, University of Bristol, Bristol, UK and* [3]*Neurology Department, Austin and Repatriation Medical Centre, Melbourne, Australia*

Correspondence to: Professor Andrew J. Lees MD, FRCP, Reta Lila Weston Institute of Neurological Studies, Windeyer Building, 46 Cleveland Street, London W1T 4JF, UK
E-mail: a.lees@ion.ucl.ac.uk

Summary

We have reviewed the clinical and pathological diagnoses of 143 cases of parkinsonism seen by neurologists associated with the movement disorders service at The National Hospital for Neurology and Neurosurgery in London who came to neuropathological examination at the United Kingdom Parkinson's Disease Society Brain Research Centre, over a 10-year period between 1990 and the end of 1999. Seventy-three (47 male, 26 female) cases were diagnosed as having idiopathic Parkinson's disease (IPD) and 70 (42 male, 28 female) as having another parkinsonian syndrome. The positive predictive value of the clinical diagnosis for the whole group was 85.3%, with 122 cases correctly clinically diagnosed. The positive predictive value of the clinical diagnosis of IPD was extremely high, at 98.6% (72 out of 73), while for the other parkinsonian syndromes it was 71.4% (50 out of 70). The positive predictive values of a clinical diagnosis of multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) were 85.7 (30 out of 35) and 80% (16 out of 20), respectively. The sensitivity for IPD was 91.1%, due to seven false-negative cases, with 72 of the 79 pathologically established cases being diagnosed in life. For MSA, the sensitivity was 88.2% (30 out of 34), and for PSP it was 84.2% (16 out of 19). The diagnostic accuracy for IPD, MSA and PSP was higher than most previous prospective clinicopathological series and studies using the retrospective application of clinical diagnostic criteria. The seven false-negative cases of IPD suggest a broader clinical picture of disease than previously thought acceptable. This study implies that neurologists with particular expertise in the field of movement disorders may be using a method of pattern recognition for diagnosis which goes beyond that inherent in any formal set of diagnostic criteria.

Keywords: Parkinson's disease; parkinsonism; clinicopathological study; diagnostic accuracy

Abbreviations: CBD = corticobasal degeneration; DLB = dementia with Lewy bodies; IPD = idiopathic Parkinson's disease; MSA = multiple system atrophy; NHNN = The National Hospital for Neurology and Neurosurgery, London; PEP = post-encephalitic parkinsonism; PSP = progressive supranuclear palsy; UKPDSBRC = The United Kingdom Parkinson's Disease Society Brain Research Centre

Introduction

Remarkably few detailed clinicopathological studies of patients with parkinsonian disorders have been published (Hughes *et al*., 1993; Wenning *et al*., 1995; Litvan *et al*., 1996*a*) which has made assessment of the accuracy of clinical diagnosis difficult. The largest clinicopathological series of patients with multiple system atrophy (MSA) and progressive supranuclear palsy (PSP), the two disorders most likely to mimic idiopathic Parkinson's disease (IPD), include only 38 and 24 cases, respectively, with the latter comprising cases originating from seven centres in four countries (Litvan *et al*., 1996*a*; Wenning *et al*., 2000).

Two clinicopathological studies published in the early 1990s both found an accuracy of clinical diagnosis of IPD of 76% (Rajput *et al*., 1991; Hughes *et al*., 1992). A recent study in the UK, using ascertainment and methodology comparable with one of the earlier studies, has shown an improvement in this diagnostic accuracy to 90% (Hughes *et al*., 2001). This improvement coincides with increased awareness amongst

neurologists of the pitfalls in the differential diagnosis of parkinsonian syndromes and the publication of consensus operational criteria for the diagnosis of IPD, MSA, PSP and corticobasal degeneration (CBD) (Gibb and Lees, 1988; Litvan *et al*., 1996*b*; Gilman *et al*., 1999; Riley and Lang, 2000). However, there is little information available about the accuracy of diagnosis of other parkinsonian syndromes and whether specialists in movement disorders are superior to general neurologists. Two clinicopathological studies have suggested that approximately one-third of patients with pathologically proven MSA seen by specialists in movement disorders carry the incorrect diagnosis at death (Wenning *et al*., 1995; Litvan *et al*., 1997*a*). This figure may be as high as 50% in patients diagnosed by general neurologists (Litvan *et al*., 1997*a*). In PSP, available clinicopathological correlative data would suggest that between 41 and 88% of patients with pathologically proven PSP are diagnosed correctly in life (Daniel *et al*., 1995; Litvan *et al*., 1996*a*; Verny *et al*., 1996).

To assess further the accuracy of diagnosis of parkinsonian disorders, we have reviewed the clinical and pathological diagnoses of patients seen by neurologists associated with the movement disorders service at The National Hospital for Neurology and Neurosurgery in London (NHNN) who came to neuropathological examination at the United Kingdom Parkinson's Disease Society Brain Research Centre (UKPDSBRC) over a 10-year period.

Cases and methods

We identified 143 cases of parkinsonism seen by neurologists associated with the movement disorders service at the NHNN who came to neuropathological assessment at the UKPDSBRC from the beginning of 1990 until the end of 1999.

Clinical data acquisition

The cases were identified from all cases referred to the UKPDSBRC over the 10-year period, by review of all case records and clinical summaries, completed at the time of neuropathological assessment, and by a search of the clinical database for the names of the treating consultant neurologists and for any record of attendance at the NHNN. The accrual rate of 14–15 brains per year represents ~8% of patients with parkinsonism admitted to the hospital each year and <5% of such patients attending the out-patient clinics each year. In the main, patients coming to autopsy at the UKPDSBRC enrolled in the programme after contact with promotional literature circulated through the Parkinson's Disease Society. They then approached either their neurologist, the UKPDSBRC directly or their GP regarding registering as a prospective donor. A small number of cases of particular interest were approached in the latter stages of their disease while attending the NHNN. Some cases in the present series have been included in previous publications that included cases from the UKPDSBRC (Hughes *et al*., 1993, 2001; Wenning *et al*., 1994, 1995, 2000; Daniel *et al*., 1995; Litvan *et al*., 1996*c*, 1997*a*, *b*, 1998). The clinical features of the 143 cases identified were abstracted by one neurologist (A.J.H.), unblinded to the pathological diagnosis, from clinical records which included hospital, consultant and general practice case notes as well as UKPDSBRC annual assessment data. Clinical features were entered on a database for subsequent analysis. In addition to standard clinical parameters, particular attention was paid to the initial clinical diagnosis, the timing of that diagnosis in relation to the initial onset of symptoms, the time of any change to the clinical diagnosis and the time prior to death of the last clinical assessment. Where more than one possible clinical diagnosis was listed in the clinical files, an attempt was made to ascertain the clinical diagnosis thought most likely. Only in cases where this was unclear, or where a definite 'unclassifiable' label had been used was a final clinical diagnosis of 'parkinsonism undetermined' recorded. For analysis of diagnostic accuracy, cases with a final diagnosis of parkinsonism undetermined were classified as having a parkinsonian syndrome other than IPD and were considered to have an incorrect clinical diagnosis.

The clinical diagnostic label of dementia with Lewy bodies (DLB) was problematic because of the evolution in the clinical understanding of this entity and its clinicopathological definition over the time of the study (McKeith *et al*., 1996, 1999). The classification of patients as having DLB at autopsy was also complicated by occasional cases with moderate numbers of cortical Lewy bodies who either had no cognitive impairment in life or who first developed cognitive dysfunction after a disease course of 10 years or more. As such, cases clinically felt to have IPD and coexistent dementia at the time of death were classified as having a clinical diagnosis of IPD, and all cases satisfying the neuropathological criteria for IPD with or without cortical Lewy body deposition were classified neuropathologically as having IPD.

Neuropathological methods

Half-brains fixed in 10% neutral formalin were examined using standard neuropathological techniques. Tissue for paraffin embedding was taken from the cerebral cortex, striatum, mid-brain, pons, medulla and cerebellum. In the majority of cases, all areas of cortex (frontal, temporal, parietal and occipital) were examined. Sections were stained with haematoxylin–eosin, luxol fast blue–cresyl violet and modified Bielschowsky silver impregnation. On selected regions, immunocytochemistry was performed using the biotin–streptavidin method and antibody to ubiquitin (Dako, polyclonal 1 : 150), α-synuclein (gift from Professor B. Anderton, 1 : 500), tau (Dako, polyclonal 1 : 150) and GFAP (glial fibrillary acidic protein; Dako, polyclonal 1 : 400).

The pathological diagnoses were made using established criteria by one neuropathologist (S.E.D.). The diagnosis of IPD was based on finding a clear depletion of brainstem

pigmented neurones with Lewy bodies in some of the remaining nerve cells and a normal appearance in the striatum (Oppenheimer, 1984). In cases lacking pathological changes in IPD, diagnoses were established by accepted neuropathological criteria. PSP was diagnosed according to NINDS criteria (Hauw *et al*., 1994). Cases of MSA were subdivided into those showing predominantly striatonigral involvement, predominant olivopontocerebellar damage or equal involvement of both systems (Quinn, 1994). Cases of vascular parkinsonism were diagnosed when there was evidence of white matter ischaemic damage in conjunction with ischaemic infarcts within the striatum in the absence of any definable pathology known to be responsible for parkinsonism. Corticobasal degeneration (CBD) was diagnosed according to Revesz and Daniel (1998). A single case of post-encephalitic parkinsonism (PEP) was distinguished by very severe nigral damage with widespread brainstem tangles in a patient with disease onset following an encephalitic-like illness when aged 10 years in 1928 and who died aged 81 years. In four cases, other pathological diagnoses were made according to the neuropathological features (Geddes *et al*., 1993; Jackson and Lowe, 1996; Morris *et al*., 1999; O'Sullivan *et al*., 2000).

Calculation of diagnostic measures and statistical methods

We compared selected clinical features for cases diagnosed as IPD or another parkinsonian syndrome using the *t*-test and χ^2 test for continuous and categorical variables. By cross-tabulating the clinical and neuropathological diagnoses, the four standard diagnostic parameters were calculated: (i) sensitivity: the percentage of cases with a particular pathological diagnosis that had been clinically diagnosed correctly as having that diagnosis prior to death; (ii) specificity: the percentage of cases without a particular pathological diagnosis that had been clinically diagnosed correctly as not having that diagnosis prior to death; (iii) positive predictive value: the percentage of cases which the clinicians had diagnosed correctly with a particular diagnosis which was confirmed at post-mortem; and (iv) negative predictive value: the percentage of cases which the clinicians correctly thought did not have a particular diagnosis, that was confirmed to be correct at post-mortem. As positive and negative predictive values are a function of the prevalence of disease in the population, they will vary for different populations even when sensitivity and specificity remain constant, the latter two being a function of the diagnostic test or, in this case, the clinicians' diagnostic acumen. We therefore calculated the positive and negative predictive values for IPD, MSA and PSP under three scenarios. First, what was observed from the UKPDSBRC sample under study. Secondly, given the unusual nature of this sample and the over-representation of other parkinsonian disorders, we applied prevalence data from a recent population-based prevalence study of parkinsonism (Schrag *et al*., 1999) to a hypothetical sample of 1000 cases. This scenario examines predictive performance in an ideal world where specialists diagnose all parkinsonian cases in the community. Thirdly, using the same population-based prevalence data, we contrived a more realistic scenario where we assumed that all new non-IPD cases, being atypical and diagnostically more complex, would be referred to an expert in movement disorders as well as a minority (20%) of new IPD for diagnostic confirmation. This latter figure is hypothetical, based partially on the experience of NHNN, but is used mainly for illustrative purposes enabling a sensitivity analysis.

Results

Clinical diagnoses

A total of 143 cases (89 male, 54 female) were identified. The clinical diagnoses were made by 11 neurologists, with five dedicated movement disorder specialists seeing 92% (132). The mean age of disease onset was 55.5 (range 5–80) years and the mean disease duration was 13 (range 2–71) years (see Table 1). The mean time from symptom onset to initial clinical diagnosis was 1.6 (range 0–7) years. The clinical diagnosis was later revised in 44 of the 122 cases where full follow-up information was available, after a mean of 3.4 (range 0.5–12) years. The mean duration of disease to final clinical diagnosis in these 44 cases was 5.3 (range 1.5–19) years. The mean time of the last clinical assessment by the treating neurologist prior to death was 2.4 years, with 54% of patients being seen within the last year of life.

Seventy-three (47 male, 26 female) patients had a final clinical diagnosis of IPD and 70 (42 male, 28 female) patients were diagnosed as having another parkinsonian syndrome (see Table 1). IPD cases were more likely to be older at diagnosis, and had a longer disease duration. There was no difference between time from onset of symptoms to initial clinical diagnosis, but as almost two-thirds of those with a final clinical diagnosis of another parkinsonian syndrome had their diagnosis changed, they had longer disease duration at the time of their final clinical diagnosis. The clinical diagnosis had been revised to IPD in only two cases after 3 and 4 years of disease.

The clinical diagnoses in the 70 cases thought to have a parkinsonian syndrome other than IPD (see Table 2) were: MSA (35), PSP (20), CBD (three), vascular parkinsonism (three), parkinsonism undetermined (four), PEP (two) and one case each of pallidopyramidal degeneration (not further classified), dopa-responsive juvenile parkinsonism and focal cerebral atrophy with myoclonus (not further classified).

Pathological diagnoses

The final neuropathological diagnoses in the 143 cases (see Tables 2 and 3) were IPD (79), MSA (34), PSP (19), CBD (four), vascular parkinsonism (two) and one case each of

Table 1 *Simple clinical parameters of 143 cases of parkinsonism divided according to clinical diagnostic groupings*

	All cases (n = 143)	Final clinical diagnosis IPD (n = 73)	Final clinical diagnosis another parkinsonian syndrome (n = 70)
Age at disease onset	55.5 (5–80)	57.1 (29–80)*	53.6 (5–79)
Disease duration (years)	13 (2–71)	16.2 (4–35)*	9.4 (2–71)
Hoehn and Yahr stage at initial diagnosis	1.8 (1–3)	1.5 (1–3)	2.2 (1–3)
Hoehn and Yahr stage at death	4.7 (2–5)	4.5 (2–5)	4.8 (3–5)
Time from initial onset of symptoms to initial clinical diagnosis (years)	1.6 (0–7)	1.3 (0–4)	1.8 (0.5–7)
Disease duration at time of final clinical diagnosis (years)	2.9 (0–19)	1.4 (0–4)*	4.1 (0.5–19)
Cases where clinical diagnosis was revised†	44	2	42
Disease duration at time of final clinical diagnosis in those where the diagnosis was revised (years)	5.3 (1.5–19)	4.3	5.4 (1.5–19)

†Information available on 122 cases regarding the timing of both initial and final clinical diagnoses; *$P < 0.05$, for comparison of cases with a final clinical diagnosis of IPD and another parkinsonian syndrome.

PEP, frontotemporal dementia (without distinctive histology), tauopathy (not otherwise specified), neuronal intranuclear inclusion disease and chronic brainstem meningoencephalitis.

Clinicopathological correlations

Only one case diagnosed clinically as IPD was not confirmed pathologically (see Tables 2 and 3). However, seven cases of pathologically proven IPD had been misdiagnosed as either MSA (four), CBD (one), PEP (one) and 'parkinsonism undetermined' (one). The clinical diagnosis of MSA was also good, but cases of both IPD (four) and PSP (one) were wrongly included. Similarly, four cases of pathologically confirmed MSA had been misdiagnosed as PSP (two) and 'parkinsonism undetermined' (two). Other misdiagnoses for PSP included CBD (one) and one case found to have a tauopathy (not otherwise specified).

Of the three cases clinically diagnosed as CBD, only one had the pathological changes of CBD, while one had IPD and one had frontotemporal dementia (without distinctive histology). Two of the three cases clinically diagnosed as having vascular parkinsonism had this diagnosis at post-mortem, while the other had CBD. Only one of the two cases diagnosed as PEP fulfilled the neuropathological criteria, whilst the other was pathologically confirmed as IPD. One case clinically diagnosed as pallidopyramidal degeneration (not otherwise classified) had a chronic brainstem meningoencephalitis (reported in detail elsewhere; Geddes *et al*., 1993). The case clinically classified as dopa-responsive juvenile parkinsonism had neuronal intranuclear inclusion disease at post-mortem (also reported in detail elsewhere; O'Sullivan *et al*., 2000) and the case classified as having focal cerebral atrophy with myoclonus had CBD. Of the four cases with the final diagnostic label of 'parkinsonism undetermined', two had MSA, one PSP and one IPD.

Of the four cases with pathological CBD, only one was clinically diagnosed as CBD. One was clinically diagnosed as having vascular parkinsonism, one PSP and one clinically labelled as having focal cerebral atrophy with myoclonus (not further classified). Both cases of pathologically established vascular parkinsonism and the one case of PEP had been clinically diagnosed correctly.

Diagnostic parameters for the main clinical diagnoses

Overall, 122 out of 143 cases were clinically diagnosed correctly, giving an overall positive predictive value of 85.3% (see Table 4). Other than vascular parkinsonism, which was based on two cases, the clinical diagnosis of IPD showed the best overall sensitivity (91.1%) and positive predictive value (98.6%), followed by MSA and then PSP. The figures for CBD and vascular parkinsonism are based on very small numbers. The specificity for all the major diagnoses was extremely high (between 95.4 and 98.4%) with little difference for any of the groups, indicating that these neurologists were extremely good at correctly ruling out these specific diagnoses.

Predictive values for clinical diagnoses under different scenarios

Table 5 demonstrates how the positive and negative predictive values for each of the main three diagnoses vary as the prevalence of the specific diagnosis alters. The most dramatic effect is seen for IPD, which had a negative predictive value of 90% in the UKPDSBRC sample. When applied to a normal population sample, where IPD is *a priori* likely to be the most likely diagnosis, this propensity to overdiagnose less common causes of parkinsonism amongst pathologically proven IPD has an important detrimental effect on the negative predictive

Table 2 *Pathological diagnoses in 143 cases of parkinsonism divided according to the clinical diagnosis*

Clinical diagnosis	Pathological diagnoses
Idiopathic Parkinson's disease (73)	Idiopathic Parkinson's disease (72)
	Progressive supranuclear palsy (1)
Multiple system atrophy (35)	Multiple system atrophy (30)
	Idiopathic Parkinson's disease (4)
	Progressive supranuclear palsy (1)
Progressive supranuclear palsy (20)	Progressive supranuclear palsy (16)
	Multiple system atrophy (2)
	Corticobasal degeneration (1)
	Tauopathy—not otherwise specified (1)
Parkinsonism undetermined (4)	Multiple system atrophy (2)
	Progressive supranuclear palsy (1)
	Idiopathic Parkinson's disease (1)
Corticobasal degeneration (3)	Corticobasal degeneration (1)
	Idiopathic Parkinson's disease (1)
	Frontotemporal dementia—without distinctive histology (1)
Vascular parkinsonism (3)	Vascular parkinsonism (2)
	Corticobasal degeneration (1)
Post-encephalitic parkinsonism (2)	Post-encephalitic parkinsonism (1)
	Idiopathic Parkinson's disease (1)
Pallidopyramidal degeneration—not otherwise classified (1)	Chronic brainstem meningoencephalitis* (1)
Dopa-responsive juvenile parkinsonism (1)	Neuronal intranuclear inclusion disease* (1)
Focal cerebral atrophy with myoclonus (1)	Corticobasal degeneration (1)

*Cases described in detail elsewhere (Geddes *et al*., 1993; O'Sullivan *et al*., 2000).

value. In absolute terms, however, this would still only result in 81 false-negative diagnoses in every 1000 cases. The relatively good positive predictive values for both MSA and PSP are markedly attenuated in the community sample, where these disorders are far less common. The clinical predictive value in Table 5, scenario 3, designed to reflect a specialist movement disorder clinic, is much more like that observed from the UKPDSBRC sample.

Discussion

The present study has considerable advantages over most previously published clinicopathological series. These include the detail of clinical documentation and ancillary investigation, the consistency of neuropathological evaluation and the independence and impartiality of data acquisition. The NHNN is a tertiary referral centre, and diagnostic conundrums, atypical presentations and unusual cases are seen more frequently than in general hospitals or even regional neurological centres. This leads to a disproportionate bias in the frequency of atypical parkinsonian syndromes in the clinics. Furthermore, patients who are undiagnosed or more severely affected and die in hospitals or nursing homes are more likely to have an autopsy. That almost 50% of the cases included in this study were clinically thought to have a cause for parkinsonism other than IPD suggests that the cohort is not representative of patients seen in clinics with a particular interest in movement disorders. Approximately one in four patients with parkinsonism attending the movement disorders clinics or admitted to the NHNN over the last 5 years had a clinical diagnosis of a parkinsonian syndrome other than IPD. However, comparison of diagnostic subgroups, for example IPD, with clinic-based descriptive studies (Hoehn and Yahr, 1967) shows a similar profile of initial symptomatology and clinical course, suggesting that despite the biases, the subgroups may be reasonably representative of those seen in movement disorders clinics. The predictive value of these clinical diagnoses was, as expected, highly sensitive to the prevalence of disease and hence the context within which patients are seen. In a community setting, the positive predictive values for the less common diseases were far worse, whilst for IPD there was a deterioration in the negative predictive value. It is likely that a specialist seeing patients in an outreach clinic based in primary care would quickly adjust to the different patient patterns and may subsequently alter their threshold for diagnosing rarer causes of parkinsonism. Primary care patients are also seen much earlier in the natural history of the disease and hence cases of MSA and PSP may not have such well developed atypical features to facilitate accurate diagnosis.

We found a gratifyingly high accuracy for the diagnosis of IPD amongst movement disorder specialists. At 98.6%, the positive predictive value for a diagnosis of IPD is certainly higher than previously published data. The only other single centre clinicopathological study of parkinsonism was published a decade ago and found an accuracy for clinical

Table 3 *Clinical diagnoses in 143 cases of parkinsonism divided according to the pathological diagnosis*

Pathological diagnosis	Clinical diagnoses
Idiopathic Parkinson's disease (79)	Idiopathic Parkinson's disease (72) Multiple system atrophy (4) Corticobasal degeneration (1) Parkinsonism undetermined (1) Post-encephalitic parkinsonism (1)
Multiple system atrophy (34)	Multiple system atrophy (30) Progressive supranuclear palsy (2) Parkinsonism undetermined (2)
Progressive supranuclear palsy (19)	Progressive supranuclear palsy (16) Multiple system atrophy (1) Idiopathic Parkinson's disease (1) Parkinsonism undetermined (1)
Corticobasal degeneration (4)	Corticobasal degeneration (1) Vascular parkinsonism (1) Progressive supranuclear palsy (1) Focal cerebral atrophy with myoclonus (1)
Vascular parkinsonism (2)	Vascular parkinsonism (2)
Post-encephalitic parkinsonism (1)	Post-encephalitic parkinsonism (1)
Neuronal intranuclear inclusion disease (1)	Dopa-responsive juvenile parkinsonism (1)
Chronic brainstem meningoencephalitis (1)	Pallidopyramidal degeneration—not otherwise classified (1)
Frontotemporal dementia—without distinctive histology (1)	Corticobasal degeneration (1)
Tauopathy—not otherwise specified (1)	Progressive supranuclear palsy (1)

diagnosis of IPD of only 76% (Rajput *et al*., 1991). A year later, a clinicopathological series from the UKPDSBRC found an identical diagnostic accuracy in cases collected from all over the UK (Hughes *et al*., 1992). In a subsequent interim series, the diagnostic accuracy had increased to 84% (Ansorge *et al*., 1997), while in a more recent study it reached 90% (Hughes *et al*., 2001). Although the majority of diagnoses in this most recent series were made by neurologists, 14% of cases were diagnosed by general physicians or geriatricians (Hughes *et al*., 2001). That study also evaluated several sets of diagnostic criteria which were unable to improve this diagnostic accuracy significantly. Although this finding suggested that a clinical diagnostic accuracy of 90% may approximate the maximum that can be expected, our findings suggest that specialists in movement disorders may exceed this. However, in the clinicopathological study of Litvan *et al*. (1998), experts in movement disorders correctly diagnosed only 77.4% of cases of Lewy body disease (including both IPD and DLB) when retrospectively reviewing clinical vignettes of cases compiled from information gathered at the last clinical assessment prior to death. In that study, the lack of direct patient contact and the proportion of cases included with parkinsonian syndromes other than IPD may have adversely affected the diagnostic accuracy. The diagnostic accuracy by the primary treating neurologists for the same cases was 70.3%.

Although we found the sensitivity for a clinical diagnosis of IPD to be high at 91.1%, the seven false-negative cases (9%) suggest a broader clinical picture of disease than formerly recognized. Alternatively, there may have been a tendency amongst the clinicians to place too much importance on subtle atypical clinical features for IPD and overdiagnose less common parkinsonian syndromes. This is perhaps not unreasonable when they work in a hospital setting where the probability of such disorders is relatively high. While the false-positive rate for the diagnosis of IPD has fallen over the last decade, there is less information regarding false-negative cases. One clinicopathological series found that 10% of cases with pathologically proven IPD died with an alternative clinical diagnosis (Hughes *et al*., 1993). The retrospective application of accepted clinical diagnostic criteria to that series suggested that 12% had clinical features atypical for the accepted clinical spectrum of IPD. These included early severe dementia, no apparent response to an adequate trial of levodopa, early fluctuating confusional states, myoclonus, apraxia, onset of parkinsonism while taking neuroleptic medication, presence of focal dystonia, early marked autonomic dysfunction, onset following significant head trauma and a stuttering course suggestive of vascular events. Half of those cases had a pathological process in addition to IPD that may have explained the atypical clinical appearance: significant plaque and neurofibrillary tangle deposition, dense cortical Lewy bodies and striatal infarction. This still left 6% of pathologically proven IPD cases without additional contaminating pathology with clinical features outside the prevailing perceptions for the

Table 4 *Summary of the diagnostic accuracy for the major parkinsonian syndromes in 143 cases of parkinsonism that came to neuropathological examination over a 10-year period*

Diagnosis	Positive predictive value (%)	Sensitivity (%)	Specificity (%)
All cases (n = 143)*	85.3		
Idiopathic Parkinson's disease	98.6	91.1	98.4
Multiple system atrophy	85.7	88.2	95.4
Progressive supranuclear palsy	80.0	84.2	96.8
Corticobasal degeneration	33.3	25.0	98.6
Vascular parkinsonism	66.7	100	99.3

See text for definitions of positive predictive value, sensitivity and specificity. Limited conclusions can be drawn from the small number of cases with CBD and vascular parkinsonism. *For the purpose of analysis, a final clinical diagnosis of parkinsonism undetermined was considered an incorrect diagnosis.

Table 5 *Positive and negative predictive values of a diagnosis of IPD, MSA and PSP under various scenarios*

	Scenario 1	Scenario 2	Scenario 3
IPD			
Prevalence (%)	51.0	91.8	69.0
PPV (%)	98.6	99.8	99.2
NPV (%)	90.0	49.9	83.3
MSA			
Prevalence (%)	24.5	2.4	8.9
PPV (%)	85.7	58.4	85.1
NPV (%)	96.3	99.8	99.1
PSP			
Prevalence (%)	14.0	3.5	13.3
PPV (%)	80.0	68.1	90.0
NPV (%)	97.6	99.7	98.6

1 = Sample in the present study, diagnosed by neurologists associated with the movement disorders service at the NHNN and coming to autopsy at the UKPDSBRC over a 10-year period.
2 = Prevalence of conditions in the population sample, assuming movement disorder specialists diagnose all parkinsonian cases in the community.
3 = Assuming all atypical cases of parkinsonism and 20% of IPD cases referred to specialist neurologists associated with a movement disorder service. PPV = positive predictive value; NPV = negative predictive value.

syndrome of IPD. An even higher false-negative rate was seen in another clinicopathological study (Litvan *et al*., 1998) where the sensitivity for the diagnosis of Lewy body disease (including both IPD and DLB) and for IPD alone was 67.2 and 80%, respectively. Of the seven false-negative cases in the present series, no alternative neuropathological cause for the atypical clinical features could be found in six. The seventh case had dense cortical Lewy body deposition but a clinical history somewhat atypical for DLB, with parkinsonism preceding the onset of cognitive impairment by 10 years with associated autonomic impairment, corticospinal tract dysfunction, supranuclear gaze palsy and myoclonus. One of the remaining six cases was diagnosed clinically as probably having PEP, because of a history of an encephalitic illness 6 months prior to the onset of symptoms. Otherwise this case had long duration disease with a clinical course typical for IPD. This leaves five cases (6%) with pathologically proven brainstem Lewy body IPD having clinical features outside the commonly accepted clinical spectrum. The atypical features seen in these cases include poor levodopa response (four), early autonomic impairment (four), early falls (four), disproportionate antecollis (four), denervation on sphincter EMG (one) and prolonged isolated gait freezing before the development of parkinsonism and dementia (one).

The problems associated with the diagnostic label of DLB in this series have already been described. Probably because of referral bias towards patients with a dominant parkinsonian motor syndrome in this movement disorder service, this situation was not common. There were only two cases where early cognitive decline (occurring within 12 months of the onset of parkinsonism) in patients already diagnosed as having IPD, was clinically felt to be due to DLB and who subsequently satisfied the pathological criteria for this entity (McKeith *et al*., 1996, 1999). There were a further 12 cases with moderate numbers of cortical Lewy bodies who either had no cognitive impairment in life or who first developed cognitive dysfunction after a disease course of 10 years or more. Those cases with dementia had a clinical diagnosis of IPD with dementia. As with previous series (Hughes *et al*., 1992), small numbers of cortical Lewy bodies were identified in the vast majority of cases of pathologically confirmed IPD.

Over the last decade, a number of clinical and clinicopathological series have clarified the clinical features of MSA and PSP, the two conditions most commonly misdiagnosed as IPD (de Bruin and Lees, 1994; Litvan *et al*., 1996*a*; Wenning *et al*., 1997, 2000). Increased awareness of these features and their clinical overlap with IPD is likely to be responsible for the improvement in the diagnostic accuracy of IPD and has led to a refinement of the clinical diagnostic criteria for both MSA and PSP (Litvan *et al*., 1996*b*; Gilman *et al*., 1999). Nevertheless, the accuracy of clinical diagnosis of the other common neurodegenerative parkinsonian syndromes was less than with IPD. However, the positive predictive value and sensitivity for a diagnosis of both MSA and PSP in the present

study were higher than most previous prospective clinicopathological series and studies using the retrospective application of clinical diagnostic criteria (Litvan *et al*., 1996*a*, *c*, 1997*a*; Wenning *et al*., 2000).

The situation with MSA is made difficult by the 10–20% of cases who have relatively pure parkinsonism which may be characterized by features previously thought to be more typical of IPD, including asymmetry, levodopa responsiveness and the development of levodopa-induced dyskinesias and motor fluctuations (Wenning *et al*., 1994, 1997, 2000). Two studies comparing the clinical features of pathologically proven MSA and IPD (Litvan *et al*., 1997*a*; Wenning *et al*., 2000) have pointed to preserved cognition and the absence of neuropsychiatric toxicity as previously unrecognized features more suggestive of MSA than IPD. We have found that neurologists specializing in movement disorders were correct in 85.7% of cases clinically diagnosed with MSA, equating to a false-positive rate of 14.3%. The false-positive rate in MSA has received relatively little attention to date, although in one cohort retrospectively analysed by movement disorder specialists it approximated 20% (Litvan *et al*., 1997*a*).

In the present study, we found the sensitivity for a diagnosis of MSA to be 88.2%, with 30 of the 34 cases of pathologically proven MSA being diagnosed correctly. In one of the largest clinicopathological studies of MSA (Wenning *et al*., 1995), a third of 35 pathologically proven cases carried another clinical diagnosis, usually IPD, at the time of death. Subanalysis of those cases suggested that the diagnostic accuracy was far higher amongst cases seen by neurologists specializing in movement disorders (seven of the patients in that series were also included in the present series). Similarly, in another series (Litvan *et al*., 1997*a*), only 50% of cases with pathologically proven MSA had been diagnosed correctly by their primary neurologist, while retrospective analysis by neurologists specializing in movement disorders improved this sensitivity to ~70%. Several studies have compared the clinical features of pathologically proven MSA with IPD and developed scoring systems weighted for different clinical features (Colosimo *et al*., 1995; Wenning *et al*., 2000). These have produced sensitivities of ~90%. The application of these scoring systems in new independent clinical series is likely to be less impressive as they are internally derived and therefore overestimate their true performance.

We found an 80% accuracy for the clinical diagnosis of PSP in the present series. There is little available comparative literature, but there are case reports of patients with pathologically established MSA, DLB, CBD and diffuse subcortical gliosis being clinically diagnosed as having PSP (Fearnley *et al*., 1991; Wenning *et al*., 1998). The clinical heterogeneity of PSP, with cases lacking a supranuclear gaze palsy, presenting as an isolated akinetic–rigid syndrome or as a pure progressive dementing syndrome, has been delineated more clearly over the last decade (Daniel *et al*., 1995; Litvan *et al*., 1996*a*; Verny *et al*., 1996). This difficulty in clinical diagnosis is likely to be responsible for the reduced sensitivity seen in some earlier studies and is reflected in the number of different sets of diagnostic criteria which have been proposed (Litvan *et al*., 1996*c*). In the present study, the sensitivity for the diagnosis of PSP was 84.2%. The most recently proposed clinical diagnostic criteria for PSP have been validated retrospectively in a data set of cases with pathologically established parkinsonian syndromes (Litvan *et al*, 1996*b*). They appear relatively restrictive, with sensitivities of 83 and 50% for a diagnosis of possible and probable PSP, respectively, although they await further validation.

Although the number of cases with CBD was very small in the present study, it is of note that both the positive predictive value and sensitivity were poor. Only one of the three cases clinically diagnosed was confirmed pathologically, and only one of the four cases found at post-mortem was clinically diagnosed in life. The clinical and pathological heterogeneity of CBD is now well recognized (Rinne *et al*., 1994; Wenning *et al*., 1998; Kertesz *et al*., 2000). A proportion of cases with CBD may not be seen by movement disorder specialists at all, coming under the care of psychiatrists, dementia specialists or psycho-geriatricians. Previous larger series have varied considerably in the accuracy of clinical diagnosis of CBD, with between 53 and 94% of clinically diagnosed cases having the disease at post-mortem and ~50% of pathologically established cases being diagnosed correctly in life (Litvan *et al*., 1997*b*; Wenning *et al*., 1998; Boeve *et al*., 1999).

More than 60% of cases with the final clinical diagnosis of a parkinsonian syndrome other than IPD had their diagnosis changed during the course of their illness. Of these, 60% were changed from an initial clinical diagnosis of IPD. This is similar to previous clinicopathological studies where clinical information is available regarding the temporal dynamics of changes in the clinical diagnosis between the first and last clinical assessments (Litvan *et al*., 1996*a*, 1997*a*; Wenning *et al*., 1998). Revision of the clinical diagnosis occurred after a mean of 5.4 years of disease, but in several cases it occurred well into the second decade of ill-health.

The present study has shown a high degree of diagnostic accuracy for IPD, MSA and PSP amongst neurologists specializing in movement disorders. Many previous series assessing diagnostic accuracy have used retrospective methods relying on abstracted clinical information developed into artificial clinical vignettes then assessed by specialists who have had no contact with the patient. This methodology potentially allows certain subtle, but diagnostically valuable, clinical information to be highlighted in the vignette, increasing the chances of an accurate diagnosis, while on the other hand it depends heavily on the reliability and completeness of the supplied clinical picture by the participating neurological centre. We believe our findings reflect the reality of diagnostic accuracy amongst experienced fully trained neurologists specializing in movement disorders. We have not sought to describe in detail the clinical features of the cases nor to apply available consensus diagnostic criteria, merely to report the observed diagnostic accuracy in the light

of the available literature. The cohort of cases studied is clearly a small subgroup of patients with parkinsonism who were seen over the 10-year study period, and has many of the biases of all post-mortem series. However, these limitations do not detract from the conclusion that despite the absence of a biological marker, movement disorder specialists will accurately diagnose five out of six of all patients referred with a neurodegenerative parkinsonian syndrome. It is interesting that the diagnostic accuracy exceeded that claimed for most clinical diagnostic criteria and suggests that neurologists with experience in movement disorders are better at correctly eliciting and interpreting key clinical features. In addition, they may be using a method of pattern recognition for diagnosis that goes beyond any formal set of diagnostic criteria.

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