

# Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases

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## Abstract

**Few detailed clinico-pathological correlations of Parkinson's disease have been published. The pathological findings in 100 patients diagnosed prospectively by a group of consultant neurologists as having idiopathic Parkinson's disease are reported. Seventy six had nigral Lewy bodies, and in all of these Lewy bodies were also found in the cerebral cortex. In 24 cases without Lewy bodies, diagnoses included progressive supranuclear palsy, multiple system atrophy, Alzheimer's disease, Alzheimer-type pathology, and basal ganglia vascular disease. The retrospective application of recommended diagnostic criteria improved the diagnostic accuracy to 82%. These observations call into question current concepts of Parkinson's disease as a single distinct morbid entity.**

Necropsy studies of patients with Parkinson's syndrome show that idiopathic Parkinson's disease (IPD) comprises between 60 and 75% of cases.<sup>1,2</sup> In life most of these are correctly diagnosed, but despite the application of stringent diagnostic criteria<sup>3</sup> misdiagnoses do occur, with some patients thought clinically to have IPD turning out to have other illnesses.<sup>1,2,4</sup> Conversely, in other patients with atypical clinical pictures the diagnosis of IPD is established only after death.<sup>5,6</sup>

There are few clinico-pathological studies from which to assess the accuracy of clinical diagnosis but it is estimated at around 80%.<sup>2,7</sup> Multiple system atrophy, progressive supranuclear palsy, Alzheimer's disease, and cerebrovascular pathology are thought to make up most misdiagnoses.<sup>1,2,4</sup>

The Parkinson's Disease Society Brain Bank (PDSBB) in London receives donor tissue from parkinsonian patients, most of whom have been prospectively examined annually by a neurologist. To assess the accuracy of clinical diagnosis we examined the neuropathology in 100 patients who were thought to have IPD. For patients in whom the diagnosis was histologically substantiated the clinical variables were correlated with the pathological findings.

## Materials and methods

We studied 100 consecutive cases with clinically diagnosed IPD. The brains were collected over a three year period between June 1987 and August 1990 from all over the United

Kingdom. Seventy cases were registered donors and had been prospectively assessed annually by neurologists associated with the PDSBB. All other cases had been diagnosed by consultant neurologists or geriatricians as having IPD. Hospital and consultant case notes were reviewed to supplement clinical information. Age at onset of illness, disease duration, initial response to levodopa, and severity of disease at death, as measured by the Hoehn and Yahr score,<sup>8</sup> were correlated with the pathological findings.

Half brains fixed in 10% neutral formalin were available for examination by standard neuropathological methods. Tissue for paraffin embedding was taken from the cerebral cortex, striatum, midbrain, pons, and medulla. In most cases all areas of cortex (frontal, temporal, parietal, occipital) and the cerebellum (hemisphere and vermis) were examined. Sections were stained with haematoxylin-eosin (HE), luxol fast blue cresyl-violet, and modified Bielschowsky silver impregnation. On selected regions, immunocytochemistry was performed with biotin-streptavidin method and antibody to ubiquitin (Dako, polyclonal 1:400).

The diagnosis of IPD was based on finding a clear depletion of brain stem pigmented neurones with Lewy bodies in some of the remaining nerve cells.<sup>9</sup> In all cases where Lewy bodies were difficult to find, at least three HE stained 7 $\mu$  sections of midbrain were examined. In each section there were usually more than 150 pigmented nigral neurones. The cerebral cortex was carefully screened for intraneuronal Lewy bodies with HE stained sections. In most cases the frontal anterior cingulate gyrus was used, however, in a few cases only the parahippocampal gyrus was available. Lewy bodies were considered to be found easily if identified within 5 minutes' inspection.

Sections were stained with anti-ubiquitin if Lewy bodies had not been identified after 10 minutes' observation time. Nerve cell loss in the substantia nigra and the locus coeruleus was assessed by two independent observers with a 4 point (1 = mild, 4 = severe) grading system, which was based on comparison with age-matched controls. The presence of Lewy bodies in the locus coeruleus and dorsal vagal nucleus was recorded for each case.

In cases lacking the pathological changes of IPD, diagnoses were established by accepted neuropathological criteria. The criteria proposed by Khachaturian<sup>10</sup> were used to identify cases in which neocortical senile plaques were numerous. This group was sub-divided into

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Alzheimer's disease and Alzheimer-type pathology. For the diagnosis of Alzheimer's disease the presence of numerous neocortical neurofibrillary tangles and a history of dementia were required. Cases with Alzheimer-type pathology had few or no neocortical tangles and no definite dementia. Progressive supranuclear palsy was classified as histologically typical<sup>11</sup> and atypical; the latter being distinguished by predominant pallido-luysio-nigral degeneration with neurofibrillary tangles, few brain stem tangles, and a normal dentate nucleus. Cases of multiple system atrophy<sup>4</sup> showed striatonigral involvement combined in all the cases with some degree of olivopontocerebellar damage. Arteriolosclerosis with widening of perivascular spaces in the deep grey nuclei was considered a normal accompaniment of ageing. Vascular damage was considered important when there were ischaemic infarcts. A single case of post-encephalitic parkinsonism<sup>1</sup> was distinguished by severe nigral damage with widespread brain stem tangles in a patient with disease onset in 1955, when aged 34, having possibly been exposed to an encephalitic-like illness at the age of eight years.

Clinical variables were correlated with the neuropathological features with Spearman's rank correlation test. The clinical and pathological data from patient subgroups were compared with Student's *t* test. The case histories of all patients were reviewed by two of us (AJL, AJH) and the clinical diagnoses re-evaluated with the PDSBB clinical criteria<sup>3</sup> (box).

## Results

The mean age of disease onset was 64.5 (range 31–85) years, and the mean duration of disease was 11.9 (range 2–35) years; 59 patients were men and 41 were women. Seventy six cases

fulfilled the pathological criteria for IPD, while 24 patients were clinically misdiagnosed. There was no significant difference between the two groups for age at onset, age at death, or terminal disease severity (table 1). The duration of disease was significantly longer in cases with IPD, mean 12.8 (range 2–30) years, compared to those with other diagnoses, mean 8.8 (range 2–35) years ( $p = 0.006$ ). Where information was available, 96% (66/69) of those with pathologically confirmed IPD and 82% (18/22) of those without Lewy body pathology had a definite initial response to levodopa. After retrospective assessment of the clinical features 11 patients were judged not to fulfil the PDSBB clinical criteria for IPD.<sup>3</sup> Nine had exclusion criteria for Parkinson's disease (table 1), including no response to an adequate trial of levodopa (4), early severe dementia (2), early autonomic failure (2), history of stepwise progression related to strokes (1), and supranuclear gaze palsy (1). The two others had inadequate supportive positive criteria (table 1). Eight of the 11 patients had pathological findings other than IPD while three had typical Lewy body pathology.

**Neuropathological findings**—Lewy bodies were found easily in the substantia nigra of most cases with histological IPD. In a few, where there was severe cell loss, it was necessary to examine more than one section before they were identified. Lewy bodies were also present in the locus coeruleus in 76% (54/71) and in the dorsal vagal nucleus in 79% (49/62) of cases where suitable tissue was available for examination. Cortical Lewy bodies were found in all cases with histological IPD, including seven patients in whom the disease duration was 5 years or less. In 58 (76%) they were easily found; nine (12%) required a prolonged search; a further nine (12%) needed ubiquitin staining for identification. A formal study of Lewy body distribution in the different cortical areas was not undertaken. In most cases, however, we found that examination of the anterior cingulate gyrus yielded positive results most quickly. Only one case showed more than five Lewy bodies per field at  $\times 100$  magnification, thereby satisfying the recently proposed criteria for diagnosis of diffuse Lewy body disease.<sup>12</sup> Cell loss in the substantia nigra, relative to age-matched controls, was estimated as mild in eight (11%), mild to moderate in 23 (30%), moderate to severe in 30 (39%), and severe in 15 (20%) of cases.

Co-existing striatal pathology was found in 27 (36%) IPD brains; in most there was vascular damage with multiple lacunar infarcts (table 2). Pathology outside of the nigro-striatal system occurred in 19 (22%) cases; in nine (12%) there was co-existent Alzheimer's disease, seven (9%) had vascular damage, and one case had Alzheimer-type pathology.

The principal findings in the 24 cases without Lewy bodies were progressive supranuclear palsy (six; two classical and four atypical), multiple system atrophy (five), Alzheimer's disease (three), Alzheimer-type

### UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria

#### Step 1 Diagnosis of Parkinsonian syndrome

- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- And at least one of the following:
  - muscular rigidity
  - 4–6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

#### Step 2 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

#### Step 3 Supportive prospective positive criteria for Parkinson's disease

(Three or more required for diagnosis of definite Parkinson's disease)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70–100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

**Table 1** Clinical variables in patients with histologically confirmed Parkinson's disease and in those with other pathological diagnoses<sup>3</sup>

Variable	IPD (n = 76)	Non-IPD (n = 24)
Mean (range) age at onset (years)	63.6 (31–84)	67.6 (34–85)
Mean (range) duration of disease (years)	12.8 (2–30)	8.8 (2–35)
Mean (range) Hoehn and Yahr score at death	4.3 (3–5)	4.4 (3–5)
Mean (range) age at death (years)	76.4 (50–91)	76.6 (62–90)
Initial levodopa response		
unknown	7	2
nil to poor	3	4
moderate	9	2
good	37	12
excellent	20	4

pathology (three), vascular disease (three), isolated nigral atrophy with no Lewy bodies (two), and postencephalitic parkinsonism (one) (table 3). In one case there were no abnormal pathological findings and review of the clinical details raised the possibility of benign essential tremor.

**Clinico-pathological correlations in the cases of IPD**—For the 76 patients with histological IPD there was a positive correlation between the severity of nigral cell loss and both disease duration ( $r = 0.31$ ;  $p = 0.008$ ) and severity at death ( $r = 0.39$ ;  $p = 0.001$ ). There was also a positive correlation between the duration of disease and severity at death ( $r = 0.34$ ;  $p = 0.003$ ) and between cell loss in the substantia nigra and the locus coeruleus ( $r = 0.38$ ;  $p =$

**Table 2** Pathological findings in 76 cases with histologically confirmed Parkinson's disease

Pathological findings	No of cases
IPD with co-existent striatal pathology	27
Vascular	19
lacunar infarction	16
putaminal haemorrhage	2
putaminal AVM	1
Striatal plaques	7
with neocortical involvement	5
isolated to striatum with normal neocortex	2
Caudate atrophy	1
IPD with pathology outside nigro-striatal system	19
Alzheimer's disease	9
Alzheimer-type pathology	1
Vascular events	7
cerebral infarction	5
cerebellar infarction	1
cerebellar haemorrhage	1
Abscess	1
"Diffuse Lewy body disease"	1

See text for definitions of Alzheimer's disease. Alzheimer-type pathology and diffuse Lewy body disease.

**Table 3** Pathological findings in 24 cases clinically mis-diagnosed as Parkinson's disease

Pathological findings	No of cases
Progressive supranuclear palsy	6
atypical	4
classical	2
Multiple system atrophy	5
Alzheimer's disease	3
with striatal involvement	1
without striatal involvement	2
Alzheimer-type pathology	3
with striatal involvement	3
Vascular, lacunar state	3
Nigral atrophy without Lewy bodies	2
Postencephalitic parkinsonism	1
Normal ?essential tremor	1

See text for definitions of Alzheimer's disease. Alzheimer-type pathology, progressive supranuclear palsy, multiple system atrophy, postencephalitic parkinsonism.

0.002). In 54 (71%) patients the cause of death was known. All correlations were greatest for the 46% (26/54) of patients who died from causes clearly unrelated to their IPD (for example, myocardial infarction, stroke, cancer). The  $r$  value for the correlation between nigral cell loss and disease duration in this group increased to 0.52 ( $p = 0.01$ ).

## Discussion

The concept of Parkinson's disease is historically a clinical one stemming from James Parkinson's<sup>13</sup> seminal description which was later embellished by the nineteenth century neurologists Charcot and Gowers. Many authorities have drawn attention to the difficulties in distinguishing Parkinson's disease clinically from other parkinsonian syndromes. Progress in this area has been hampered by the failure to apply rigid clinical criteria and sparse clinical documentation in published pathological series.<sup>14 15</sup> Furthermore, how much disease classification relied on pathological criteria such as severity of nigral cell loss or the presence of Lewy bodies, is unclear.

In our study 76% of cases satisfied the established neuropathological criteria for IPD. Despite the guideline PDSBB criteria for the clinical diagnosis of IPD<sup>3</sup> those used by individual neurologists clearly differed. Nevertheless, each patient included in this study had been specifically considered during life to have IPD rather than a less well-defined parkinsonian syndrome. The retrospective application of the recommended diagnostic criteria<sup>3</sup> improved the diagnostic accuracy to 82% (73/89); 16 of the 24 cases misdiagnosed, however, still fulfilled these criteria and three others with atypical clinical features had typical Lewy body pathology.

The occurrence of cortical Lewy bodies in all cases of IPD has not been previously reported. Our finding suggests the causative agent of IPD produces damage beyond the confines of those nuclei regularly reported as being involved—for example, substantia nigra, substantia innominata, locus coeruleus, dorsal vagal nucleus. We suggest that the widespread distribution of Lewy bodies may reflect a "field change" in certain neuronal types, one of which may be cells synthesising tyrosine hydroxylase, which have recently been identified in the cerebral cortex.<sup>16</sup> Whether Lewy bodies are formed primarily at a specific site—for example, the substantia nigra—with later development elsewhere is not known, but our findings of widespread Lewy bodies in patients with short disease duration suggest concurrent formation may occur.

An unexpected finding was the high incidence of Alzheimer's disease and Alzheimer-type pathology which had been diagnosed clinically as IPD. Extrapyramidal signs in Alzheimer's disease are well reported and have in part been attributed to the severity of cell loss in the substantia nigra.<sup>17 18</sup> In previous reports, however, it has been suggested that these patients are easily distinguishable from those with IPD.<sup>19</sup> Our findings suggest that



such a distinction cannot always be made. Furthermore, we wish to draw attention to those patients with a parkinsonian syndrome and Alzheimer-type pathology, who may represent cases of "preclinical" Alzheimer's disease.<sup>20</sup> In both groups the preponderance of striatal plaques and cell loss in the substantia nigra may together have contributed to the extrapyramidal features.

We have confirmed previous reports correlating nigral cell loss with disease duration and severity<sup>15 21</sup> especially in patients dying of causes unrelated to Parkinson's disease. This group contained more patients at different stages of disease (mean Hoehn and Yahr score at death 3.6 (range 2–5), mean nigral cell loss score 2.4 (range 1–4)) and thus reflected more broadly the natural history of decline of IPD. In comparison, those dying of parkinsonian-related causes had more end stage disease with clear disability and more severe cell loss (mean Hoehn and Yahr score 4.8 (range 4–5), mean nigral cell loss score 3.0 (range 1–4);  $p = 0.005$  and  $0.01$  respectively). If the presence of Lewy bodies in brain stem nuclei is considered an essential prerequisite for the diagnosis of Parkinson's disease, then currently used criteria will lead to an 18% incidence of false positives. Furthermore, although the incidence is unknown, cases with atypical clinical pictures may turn out to have typical Lewy body pathology. This finding throws into question many clinical studies that assume that IPD is a specific morbid entity and may be diagnosed on clinical grounds alone. Although the pathogenesis of Parkinson's disease may prove to be multifactorial further clinico-pathological correlations may help to refine the clinical diagnostic accuracy of Lewy body Parkinson's disease. Until biological markers or more specific neuro-imaging techniques are developed it may have to be accepted that diverse neuropathological disorders including multiple system atrophy and neurofibrillary tangle pathology may produce clinical syndromes indistinguishable from Lewy body Parkinson's disease.

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