

Lewy body cortical involvement may not always predict dementia in Parkinson's disease

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J Neurol Neurosurg Psychiatry 2003;**74**:852–856

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Received
24 January 2003

Accepted
14 February 2003

Clinicians have noted a close association between disturbed cognition and idiopathic Parkinson's disease (PD) for more than a century. Dementia affects up to 20% of all patients with PD and is particularly common in those aged 65 years and over.¹ While selective degeneration of the dopaminergic nigrostriatal neurons with Lewy bodies (LB) found in surviving perikarya is regarded as the primary neuropathological correlate of motor impairment in PD, the neurobiological basis of the dementia of PD is still unclear.^{2–4}

The LB is a distinctive intraneuronal inclusion of complex biochemical composition that is regarded as a diagnostic hallmark of PD.⁵ LB have been also identified in the cerebral cortex by conventional histochemical stains for decades, but unlike classic nigral LB, cortical LB have a less distinct morphology and are poorly visualised by these methods.⁶ In the past few years, the development of newer immunohistochemical techniques for identifying LB throughout the brain has been followed by numerous reports describing demented parkinsonian patients in whom widespread LB were found in the cerebral cortex and brain stem.^{7–8} A dementia syndrome, originally termed diffuse LB disease because of abundant cortical LB,^{9–12} was renamed dementia with LB (DLB) by a consensus conference held in 1996¹³ and updated in 1999,¹⁴ and is now recognised to be the second most common cause of dementia after Alzheimer's disease (AD).

The participants in the consensus conference identified both neuropathological and clinical features of DLB: LB scores on a

Background: The presence of Lewy bodies (LB) in the neocortex and limbic system in patients with Parkinson's disease (PD) is commonly thought to be linked with cognitive impairment. The authors present here a series of patients with diagnosis of PD in life and no significant cognitive impairment who, at necropsy, satisfied the current neuropathological criteria for dementia with Lewy bodies (DLB).

Methods: Two hundred and seventy six brains with PD pathology were examined at the Queen Square Brain Bank in London between 1993 and 1999. The neuropathological diagnosis was PD, but 117 patients also had sufficient LB involvement above the brain stem to satisfy the current neuropathological criteria for DLB (50 patients had a neuropathological picture consistent with the limbic category of DLB and 67 with neocortical DLB). Forty eight cases were excluded who developed early cognitive impairment together with motor features of parkinsonism, 12 cases for lack of detailed clinical history, and 19 cases with coexistent features of advanced Alzheimer's disease changes. Thirty eight patients (13.8% of the total with PD pathology and 32.5 % of the total with DLB pathology) were found where there was no or very late cognitive impairment reported in the clinical records.

Results: Selected cases were 24 men and 14 women, with a mean (SD) age at onset of parkinsonian symptoms of 60.1 (10.1) years and a mean disease duration of 15.3 (5.5) years. At some time during the evolution of the disease 21 patients developed different degrees of cognitive impairment (after a mean disease duration of 12.2 (4.8) years). Clinical diagnosis at death was PD in 10 cases and PD with dementia in 11. In the remaining 17 patients no history of cognitive impairment was ever recorded in life and all of them had a clinical diagnosis of PD at death; in this subgroup, nine patients later revealed a neuropathological picture consistent with limbic (or transitional) category of DLB and eight with neocortical DLB. Interestingly, in all these patients the parkinsonian features including the response to dopaminergic drugs were indistinguishable from classic brain stem PD.

Conclusions: The authors demonstrate that the classic pathology of DLB can commonly be seen outside the generally accepted clinical spectrum for DLB and that important factors other than the absolute number of LB in the neocortex and limbic system influence the development of cognitive impairment in PD. Furthermore, the pathology of PD may be indistinguishable from that reported in DLB, suggesting that the two clinicopathological syndromes may be attributable to the same biological abnormality.

semi-quantitative scale in selected areas were used to distinguish brain stem predominant, limbic (transitional) or neocortical category at neuropathological brain examination. Key cognitive features of DLB include a fluctuating attentional deficit, severe visuo-perceptual impairments, and a relative preservation of episodic memory when compared with AD.^{12–15} Persistent visual hallucinations, autonomic failure, and sensitivity to neuroleptics may also be associated.¹⁶ Parkinsonism may accompany the dementing illness, but motor signs and cognitive decline should occur contemporaneously or within one year of one another.¹³ When patients became clinically demented two or more years after the onset of motor symptoms of parkinsonism the term PD with dementia (PDD) has been proposed. Pathologically, such cases are indistinguishable from those with DLB, suggesting that DLB and PDD are best viewed as syndromes along a continuum of LB disease, rather than as discrete or competing diagnostic categories.¹⁷

Whether or not DLB is a disease entity or a variant of PD is still debated but clinical distinction has relevance because of different therapeutic and prognostic implications. The motor symptoms in DLB have been described as somewhat different

Abbreviations: LB, Lewy bodies; PD, Parkinson's disease; DLB, dementia with Lewy bodies; AD, Alzheimer's disease; PPD, Parkinson's disease with dementia

Table 1 Demography of 38 patients with PD, PD with late dementia, and pathology consistent with DLB

Clinical diagnosis	PD	PD with late dementia
Sample size	17	21
M/F	11/6	13/8
Age at onset, y, mean (range)	60.3 (36–81)	59.8 (40–71)
Mot-Dem, y, mean (range)	–	12.2 (6–26)
Dur-Dem, y, mean (range)	–	3.4 (0–7)
Age at death, mean (range)	75.4 (51–91)	75.3 (57–86)
Disease duration, y, mean (range)	15.1 (5–28)	15.5 (8–27)
Response to levodopa	17/17	21/21
Motor fluctuations	12/17	10/21
Rest tremor	14/17	15/21
Hallucinations	8/17	16/21
LB count, mean (range)	5.9 (3–10)	7.6 (3–10)
Neuropathological category of DLB	9 L / 8 N	7 L / 14 N

Mot-Dem, interval between onset of motor symptoms and onset of dementia; Dur-Dem, duration of dementia; L, limbic; N, neocortical.

from PD (less tremor, more symmetric picture, myoclonus, more falls, and less favourable response to levodopa¹⁸). Despite several reports suggesting that cognitive impairment in PD is attributable to LB number in the cortex,^{10–17,19} we report a clinicopathological case series in which typical clinical features of PD existed for many years before the development of behavioural and cognitive changes. All these patients presented with bradykinesia, rigidity, and often resting tremor, which were highly responsive to levodopa. Serial clinical evaluation revealed no evidence of dementia until late in the disease, and in 17 cases no significant cognitive impairment at all. In all cases postmortem analysis revealed typical PD plus limbic and neocortical LB involvement compatible with the currently accepted neuropathological criteria for DLB.

METHODS

Case selection

Two hundred and seventy six brains with PD pathology were examined at the Queen Square Brain Bank in London, United Kingdom, between 1993 and 1999. This centre, affiliated to the Institute of Neurology of the London University, has been collecting brain tissue of parkinsonians since 1989. The neuropathological diagnosis was PD, but 117 patients also had sufficient LB involvement above the brain stem to satisfy the current neuropathological criteria for DLB (50 patients had a neuropathological picture consistent with the limbic category of DLB and 67 with neocortical DLB). We excluded 48 cases who developed early cognitive impairment together with motor features of parkinsonism, 12 cases for lack of detailed clinical history, and 19 cases with coexistent features of advanced AD changes (Braak stages V–VI).²⁰ Thirty eight patients (13.8% of the total with PD pathology and 32.5% of the total with DLB pathology) were found where there was no or very late cognitive impairment reported in the clinical records. They comprised 24 men and 14 women, with a mean (SD) age at death of 75.4 (8.2) years. All these cases had been examined neurologically during the disease and had detailed information available on the main clinical features of the disease.

Clinical data reviewed for each case were the following: age at onset, symptoms at onset, duration of the disease, type of parkinsonian symptoms, and presence of dementia. Other symptoms relevant to the clinical consensus criteria for DLB such as cognitive fluctuations, visual hallucinations, systematised delusions, and history of orthostatic hypotension, syncope, and unexplained recurrent falls were also recorded. Neurological examination in many cases had been conducted according to a standardised protocol. This consisted in the United Kingdom PD Research Group annual follow up form, including evaluation of main parkinsonian features (bradykinesia, rigidity, and rest tremor), Hoehn and Yahr stage, response to dopaminergic treatment (% of improvement in

motor disability), complications of treatment (such as early morning and nocturnal akinesia, wearing off, and on-off), depressive symptoms, and cognitive status.

A critical factor in this study is that an accurate evaluation of mental status in PD patients is often confounded by severe motor disability, cognitive slowing (bradyphrenia), and the adverse effects of antiparkinsonian drugs, which frequently produce visual hallucinations, delusions, and confusion, even in non-demented people.²¹ For the purpose of this study, the evaluation of cognitive status was conducted through retrospective chart reviews of all cases by two experienced clinicians (CC and AJH): they were aware of the neuropathological diagnoses of the cases, which have been previously formulated for purposes unrelated to this study. Each of them reviewed each chart independently and later a consensus was reached in order to guarantee uniformity of diagnosis of dementia. In most cases, a clinical diagnosis of dementia had already been made by the treating specialist's best global clinical impression, using criteria from the Diagnostic and Statistical Manual of Mental Disorders-IIIIR²² and information supplied by the patient's spouse or closely involved caregiver. Neuropsychological testing (Mini-Mental State Examination,²³ or more extensive test batteries) was performed in unselected patients, usually earlier in the course of the declining mental status. No attempt was made to subclassify the dementias into cortical or subcortical subgroups. In a few patients in whom there was insufficient clinical information in the clinical records, the spouse or nearest relative was interviewed by telephone, using a non-standardised interview, to estimate the patient's final physical and mental status. Because the omission of some of these symptoms in retrospectively reviewed charts may be wrongly interpreted as their absence, we were careful to consider the absence of a certain symptom when it was made explicitly clear either through the clinical history or examination.

Tissue processing

Postmortem examination of the brain followed previously described protocols to identify macroscopic and microscopic evidence of disease. All brains had been fixed in 10% buffered formalin and routinely dissected according to a standardised protocol. Tissue blocks were obtained from 18 areas, embedded in paraffin wax, and sections cut at 7 µm. Sections were stained with haematoxylin and eosin, Luxol fast blue/cresyl fast violet, and modified Bielschowsky method. Sections were also immunostained with polyclonal anti-ubiquitin, τ and α synuclein antibodies. On this basis a pathological diagnosis of DLB had been made where there were classic intracytoplasmic LB within the neurons of pigmented brain stem nuclei and similar eosinophilic inclusion bodies distributed throughout limbic and neocortical regions.

For quantitative neuropathological assessment we studied areas chosen to represent brain stem (substantia nigra at the

Table 2 Clinical and pathological features by subject

Subject number	Sex/age at onset (y)	Duration (y)	Tremor	Asymmetry at onset †	Cognition	Hallucinations	AF	LB score	Category
1	M/66	10	R	L	Normal	V	OH	8	N
2	M/40	21		Rg	Late dementia	V,A	OH	10	N
3	F/71	10	R	L	Normal			4	L
4	M/36	15	R	L	Normal	V		7	N
5	M/56	16	R	Rg	Normal	V		7	N
6	F/70	12	R		Late dementia	V	OH	4	L
7	M/68	12	R	Rg	Late dementia	V		6	L
8	M/55	16	R	L	Late dementia	V		10	N
9	M/71	12	R	Rg	Late dementia	V	OH	6	L
10	M/81	5	R		Normal			10	N
11	M/52	19			Normal	V	OH	8	N
12	F/57	18	R	L	Late dementia	V	OH	5	L
13	F/65	21		Rg	Late dementia			4	L
14	M/51	15	P	Rg	Late dementia	V,A	OH	7	N
15	F/61	12	R	Rg	Late dementia	V	OH	10	N
16	F/50	17	R		Normal	V	OH	4	L
17	F/69	17	R	Rg	Late dementia			10	N
18	M/54	27	R	Rg	Late dementia	V,A		8	N
19	M/47	22	R	Rg	Normal	V		6*	N
20	F/65	16	R	L	Normal			4	L
21	M/59	13		L	Late dementia	V	OH	10	N
22	F/73	8	P		Normal		OH	10	N
23	M/49	8	R		Late dementia	V,A		6*	N
24	M/70	11	R	L	Late dementia	V		10	N
25	M/55	19	P		Late dementia	V		10	N
26	F/52	14	R	L	Late dementia	V		10	N
27	M/70	8	R	L	Normal	V		4	L
28	M/60	14	R	Rg	Normal			3	L
29	F/70	8	R	L	Late dementia	V		3	L
30	F/58	16		Rg	Normal			6	L
31	M/80	11	R	Rg	Normal			4	L
32	M/60	14	R	Rg	Normal	V		3	L
33	M/45	27	R	Rg	Normal			10	N
34	M/55	21	R	Rg	Late dementia			4	L
35	F/55	28	R	L	Normal			3	L
36	M/58	21			Late dementia			10	N
37	F/63	14	R	Rg	Late dementia			8	N
38	M/63	14	R	L	Late dementia	V		8	N

R, rest; P, postural; Rg, right; L, left; †, when no side is reported the symptoms were symmetrical; V, visual hallucinations; A, auditory hallucinations; AF, autonomic failure; OH, orthostatic hypotension; L, limbic; N, neocortical; *these patients had scores higher than 1 in at least one neocortical area.

level of the red nucleus), paralimbic areas (entorhinal cortex, cingulate gyrus, insula, and hippocampus), and neocortex (medial frontal, superior temporal and associative occipital cortex). Cortical LB were quantified using ubiquitin immunohistochemistry¹³ and, from 1997, the monoclonal antibody HC3 against α synuclein, which is recognised as a very specific immunomarker for LB.^{24–28} Twenty cases had few tangles only in hippocampus and perirhinal areas (Braak stages I–IV), consistent with modest AD changes.^{29–30} The current series provides a gradient of neuropathological material ranging from no to little overlap between DLB and AD.³¹ Seven cases also showed coexistent mild to moderate cerebrovascular ischaemic changes, which have been symptomatic during life in three cases.

Quantification

All round ubiquitin and α synuclein positive structures in nucleated neurons were considered and counted as LB. LB counting was performed systematically throughout the selected areas (cingulate gyrus, entorhinal cortex, middle frontal cortex, and superior temporal cortex). The scanning for LB was conducted under a X40 objective. The α synuclein immunostained sections provided means to exclude globose tangles that are ubiquitin positive but negative for α synuclein, especially in the entorhinal cortex where several cases displayed AD changes. In cases without α synuclein immunostained sections (prior to 1997), τ immunostained sections were used to eliminate tangles from being mistakenly counted. The quantification was performed in all cases and areas by the same investigators.

In each case LB distribution and frequency was evaluated using the consortium guidelines LB scores¹³ and the cases were classified into brain stem dominant (score 0–2), limbic, or transitional (score 3–6) and neocortical (score 7–10) categories.

RESULTS

Clinical symptoms

Age at onset was 60.1 (10.1) years (range 36 to 81), and duration of the disease was 15.3 (5.5) years (range 5 to 28). The shortest disease duration was eight years with the exception of one patient (number 10) who died after five years from a rectal cancer. The cause of death was not established in every case, but most patients died of aspiration pneumonia or inanition; a few died of cancer or myocardial infarction. All patients were followed up throughout the course of the illness by a neurologist or geriatrician. Symptoms at onset were always those of parkinsonism and in 30 cases the onset was asymmetrical. During the disease course, akinesia and rigidity were present in all cases and classic resting tremor was noted in 29 (table 1).

They responded durably to levodopa treatment, and 21 developed motor fluctuations with abnormal involuntary movements. All patients continued to use levodopa and dopaminomimetics throughout the course of the illness and met the strict criteria for the clinical diagnosis of PD established by our group.⁵ One patient (number 38) underwent bilateral thalamic stimulation for severe tremor (the right side was treated 11 years after the disease onset, and the left side the following year). At the time of death, all patients were in Hoehn and Yahr stages three to five of disability.

Recurrent falls were reported in 12 cases, orthostatic hypotension in 11, visual hallucinations in 24 (accompanied also by auditory hallucinations in four cases), and systematised delusions in seven. Fluctuations in cognitive status and alertness, in a broad sense including variable cognitive performance as well as recurrent confusional, lethargic, or syncopal-like episodes, were reported in 13 cases.

At some time during the evolution of the disease 21 patients eventually developed different degrees of cognitive impairment (after a mean disease duration of 12.2 years). Clinical diagnosis at death was PD in 10 and PDD in 11, while pathology showed a picture consistent with limbic category of DLB in seven cases and with neocortical category in the other 14. In the remaining 17 patients no history of cognitive impairment was ever recorded in life and all of them had a clinical diagnosis of PD at death; in this subgroup, nine patients later revealed a neuropathological picture consistent with limbic category of DLB and eight with neocortical DLB (table 2).

DISCUSSION

We have shown that there are a number of patients with clinical PD and enough cortical LB to fulfil the current pathological criteria for DLB at postmortem examination who, either did not dement or who had only mild dementia after prolonged disease duration (up to 28 years in some cases). Similar cases have been also described in the literature.^{10 32 33} The detailed critic of DLB pathological consensus by Harding and Halliday³⁴ has already shown that these criteria are overly inclusive and tend to misclassify PD mainly as limbic DLB due to LB in the frontal association cortex. But, also taking this observation into account, it is noteworthy to point out the high number of clinically typical PD even with neocortical DLB (22) described in this series. Moreover, using the modern immunostaining techniques, virtually all cases of PD collected in our centre, whether or not dementia was present, have some cortical LB, as already shown by other studies.³⁵ This suggests that in PD the correlation between dense cortical LB load and dementia is not as strong as is still generally believed.^{19 36} There seems to be no clear threshold for cortical LB density distinguishing between demented and non-demented PD. Such data imply that the presence and quantity of cortical LB in PD patients is unrelated to that of cognitive impairment, and that LB in itself may not accurately represent or predict cognitive decline in this condition, for which the pathological/biochemical substrate remains to be determined.

The pathophysiological background of LB formation is still unknown, but it might involve an abnormal processing of α synuclein, which could, in turn contribute to neuronal degeneration in the affected areas. In fact, the notion that LB are markers for dying neurones may not be true,³⁷ and the conclusions regarding the role of LB follows that many are now arguing for amyloid and τ in AD and frontotemporal dementia, neuronal intranuclear inclusions in Huntington's disease and other trinucleotide repeat disorders, and ubiquitin inclusions in motor neuron disease. The presence of these inclusion bodies may indeed represent an adaptive or protective mechanism on the part of surviving cells, with cells that are unable to do this being those that are at most risk of disease, dying without leaving such pathological tombstones.³⁸ It further argues that the fundamental cause of the clinical dysfunction in these neurodegenerative conditions lies with cellular mechanisms yet to be elucidated.

We concede that the standard for clinical mental status evaluation of patients with suspected dementia is detailed neuropsychological testing, and this was not always available in the notes of the patients included in this study, leading to a possible underestimation of cognitive impairment. Indeed, mild deficits could be missed with these methods. Despite this limitation, common to all retrospective clinicopathological studies, we consider unlikely that a picture of full blown

dementia would have escaped ongoing serial specialist evaluation up to the time of death. In addition, the neuropsychological profile of the typical dementia accompanying longstanding PD differs in several aspects from the one considered typical for DLB, suggesting a somewhat different neuroanatomical substrate.¹⁵

Cortical LB is only one possible mechanism of dementia. A number of additional pathologies are thought to contribute to dementia in DLB such as Lewy neurites in the hippocampal CA2 region and neuritic plaque pathology.^{4 39} The role of AD brain changes has also been particularly emphasised in the past. In fact, recent studies have shown that the dementia of PD is less closely associated with AD neuropathological changes than was previously thought.^{40 41}

It has been suggested that immune mechanism may play a part in the pathogenesis of cognitive dysfunction in these conditions. Mackenzie has described activated microglia in demented patients with cortical LB, suggesting that a state of chronic inflammation may constitute an additional mechanism by which neurons may become dysfunctional.⁴² This finding has not as yet been corroborated.^{43 44} Finally, the regional distribution of LB more than their total cortical load could be critical; studies from different groups suggest that high densities of temporal⁴⁵ or parahippocampal^{4 46} LB indicate dementia in PD, regardless of additional pathologies. The selective involvement of some subcortical nuclei, such as the nucleus basalis of Meynert and the locus coeruleus, might also play an important part in the occurrence of dementia.^{47 49}

We were also able to analyse the parkinsonian features cases with pathology consistent with DLB; few papers in the past have concentrated specifically on this.^{18 50 51} Indeed, further characterisation might facilitate antemortem diagnosis, distinguishing simple PD from cases evolving to have PDD.^{52 54} We were unable to replicate other authors' findings, because in our series of cases fulfilling pathological criteria for DLB there was no difference in the occurrence of rest tremor, bradykinesia, rigidity, and asymmetry of signs. A good and sustained response to levodopa was frequent, in contrast with what has been recently reported by others in a smaller case series.¹⁹ Similarly, autonomic symptoms were as common as in patients with PD and no cortical involvement. Visual hallucinations, delusions, and transient confusional states were also frequent, but the long disease duration and the long term use of antiparkinsonian drugs in all cases may have been contributing factors.²¹ The over-representation of men in our series is in accord with other pathologically verified series of PD and DLB.^{32 55} Thus, we could not demonstrate that specific clinical features, in combination with reported differences in cognitive and psychiatric manifestations, may be used for diagnostic purposes in distinguishing PD from DLB in a clinical setting.

Clinical distinction of PD and DLB may have pathological relevance and even clinical importance: indeed, the same pathological picture of DLB can be manifest as a variety of clinical conditions ranging from a slowly progressive motor disorder to a severely disabling dementing illness often accompanied by significant motor disability. Further studies are needed to better define the spectrum of motor, cognitive, psychiatric, and autonomic symptoms associated with LB pathology and their response to treatment. This has become more important because of the increasing number of drugs, which can improve not only motor, but also cognitive and behavioural symptoms of this disease.^{56 57}

ACKNOWLEDGEMENTS

During this period C Colosimo was on leave from the La Sapienza University (Rome, Italy), funded by a European Neurological Society grant, and A J Hughes was on leave from the Austin and Repatriation Medical Centre (Heidelberg, Australia). The authors are indebted to S Daniel who performed several of the pathological studies and to A Evans for his valuable advice. The clinical details of the patients

included in this study are available on request. C Colosimo dedicates this work to his father, Enrico, who died while he was completing this paper.

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Competing interests: none declared

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