Cortical Lewy body dementia: clinical features and classification

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SUMMARY Seven patients, aged 65–72 years, are described with dementia and cortical Lewy bodies. In one patient a Parkinsonian syndrome was followed by dementia and motor neuron disease. In the remaining six patients dementia was accompanied by dysphasia, dyspraxia and agnosia. One developed a Parkinsonian syndrome before the dementia, in three cases a Parkinsonian syndrome occurred later, and in two cases not at all. All patients showed Lewy bodies and cell loss in the substantia nigra, locus coeruleus and dorsal vagal nucleus, as in Parkinson's disease. The severity of cell loss in the nucleus basalis varied from mild to severe. Lewy bodies were also present in the parahippocampus and cerebral cortex, but Alzheimer-type pathology was mild or absent, and insufficient for a diagnosis of Alzheimer's disease. Patients with moderate or severe dementia, some with temporal or parietal features, may have cortical Lewy body disease, Alzheimer's disease, or a combination of the two. Cortical Lewy body disease may be associated with dementia in Parkinson's disease more often than realised, but is not necessarily associated with extensive Alzheimer pathology.

Some patients with dementia, with aphasia, agnosia and apraxia do not have Alzheimer's disease or Pick's disease.^{1–5} This is also true for some patients with visuo-spatial and language deficits accompanied by a Parkinsonian syndrome.⁶ A number of reports indicate that dementia with or without Parkinsonian features may be associated with Lewy bodies in the cerebral cortex, often in association with neurofibrillary tangles and senile plaques.^{7,8} It has been suggested that the quantity of Alzheimer pathology, cortical Lewy body disease and severity of dementia are correlated, implying that Alzheimer's disease rather than cortical Lewy body disease, is the most likely cause of the dementia.^{9,10} However, dementia with Lewy bodies in the cerebral cortex can occur in the absence of tangles and plaques, and in the presence of Parkinson's disease^{11,12} and Hallervorden-Spatz disease.^{13–16} Lewy bodies in the cerebral cortex may be associated with dementia more frequently than recognised, and may help to explain dementia with temporal and parietal features.

We now report seven patients, representing a different series from that previously reported,⁸ who presented with memory failure, six of whom showed aphasia, apraxia or agnosia. Five also had a Parkinsonian syndrome. Various parts of the cerebral cortex contained Lewy bodies, but numbers of tangles and plaques were inadequate for the diagnosis of Alzheimer's disease.

Patients and methods

The seven cases examined were collected in one neuropathology laboratory. Six came from a group of approximately 110 brains of patients referred with dementia and a group of 30 referred with Parkinsonian disorders between 1980 and 1984. The brains were fixed in 10% formol-saline. Blocks were taken from the cerebral hemispheres (frontal, central, parietal, temporal and occipital regions), from the hippocampus, nucleus basalis of Meynert, hypothalamus, thalamus, striatum, midbrain, pons, medulla and cerebellum. Sections of 7 μ m and 14 μ m thickness were stained with haematoxylin and eosin (H and E), Nissl's cresyl violet, luxol-fast blue-cresyl violet, Holzer's stain, and impregnated with silver according to Bielschowsky, or Glees and Marsland.

In the cerebral cortex the number of Lewy bodies was counted directly at $\times 312$ magnification, in single 7 μ m-thick H and E-stained sections, by choosing a site at random and making five adjacent sweeps (each 0.38 mm wide) perpen-

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Table 1 Summary of clinical characteristics

Pt sex	Onset age years	Duration years	First symptom/sign	Later symptoms/signs
1.M	70	1.5	Failure of recent and remote memory	Spatial disorientation, dyspraxia, dysphasia, no Parkinsonian syndrome
2.M	68	2.5	Parkinsonian syndrome	Memory failure, spatial disorientation, prosopagnosia, dysphasia, colour agnosia, dyslexia
3.M	65	7	Short-term memory failure	Dyspraxia, dysphasia, Parkinsonian syndrome
4.M	72	7	Parkinsonian syndrome	Motor neuron disease, dementia
5.M	69	3.5	Memory failure	Dyspraxia, dysphasia, spatial disorientation, muscular rigidity
6.M	71	6	Memory failure	Dysphasia, Parkinsonian syndrome
7.F	66	0.5	Memory failure	Prosopagnosia, spatial disorientation, no Parkinsonian syndrome

dicular to the cortical surface from pia to white matter. The Lewy body was defined as an eosinophilic cytoplasmic inclusion with a halo. Pale bodies which fail to stain with eosin were not counted. Cortical sections of 14 μ m-thickness impregnated with silver according to Glees and Marsland were used to count plaques and tangles in the same way. Counts of Lewy bodies, plaques and tangles in the cortex were expressed as the number per mm² of cortical cross-sectional area.

In the substantia nigra counts of pigmented cells and cells with Lewy bodies were made in one or two unilateral 7 μ m-thick sections.

Case histories (summarised in table 1)

Case 1. A man aged 72 years at death worked as an industrial chemist until he retired at the age of 64 years. When he was aged 70 years his wife noted that his memory for recent events was poor. He failed to learn new information and had difficulty recalling names of longstanding acquaintances. He tended to forget his wife's name and had difficulty finding his way around the house. Within 18 months he was unable to shave and dress without help. Some weeks before presentation his wife noted that nocturnal myoclonic limb jerks greatly increased in frequency.

On examination he was disorientated and he had marked dyspraxia and nominal dysphasia. He named a telephone "a cabinet", and he called a magnifying glass "a barometer". He was unable to name other common objects, and could not recall his address in full. He was thought to be moderately demented. An EEG showed marked bilateral abnormalities with the dominant activity at 6 Hz and diffuse slow frequencies down to 2 Hz. A technetium 99 brain scan was normal, but a lumbar air encephalogram showed considerable enlargement of the ventricular system and pooling of air over the cortex. The degree of ventricular dilatation suggested hydrocephalus so a ventriculo-peritoneal shunt was inserted. His immediate post-operative recovery was satisfactory, but he died a month later from a pulmonary embolus.

Case 2. A 70 year old retired accountant had a radical total gastrectomy at the age of 55 years for an anaplastic gastric carcinoma. At the age of 63 years his blood film was macrocytic and serum and red cell folate levels were in the borderline range, with normal vitamin B12 levels. Thereafter he was given regular folate and vitamin B12 replacement and these levels remained above the normal range. At the age of 65 he retired, but often became muddled and believed he was still working. At the age of 68 years he developed rest tremor of the right hand with muscular rigidity of the limbs. He was

prescribed levodopa with a decarboxylase inhibitor (Sine-met). In the next 3 months he had difficulties with word finding and with recognising familiar faces. He developed spatial disorientation and impairment of short-term memory. At times he had visual hallucinations and urinary incontinence. Neuropsychological assessment showed his WAIS verbal IQ was 98, performance IQ 72, and full scale IQ 86. The low performance IQ and difficulty with the Face Hands test suggested parietal lobe damage. A low score in the Verbal Learning Test suggested verbal memory impairment. He was only partially orientated in time and place and showed perseveration of ideas. There was colour agnosia, dysphasia and dyslexia. His downgaze was poor, but horizontal gaze was normal.

One year from the onset he was moderately demented and he was unable to recall his previous occupation or his age. He was uncooperative, of labile mood, and had restless nights. He was admitted to a long-stay hospital where he remained until his death 2.5 years from the onset.

Case 3.¹⁷ This 72 year old man, an introverted and anxious person, worked as a school teacher until he retired at the age of 60 years. At the age of 56 years he developed bouts of irritability and depression, with mild memory failure. At the age of 65 years he had difficulty recalling previous conversations and tended to get lost. A year later his gait was slow and he often stumbled. He required help with dressing, became unkempt and forgetful. At 68 years he had poor short-term memory, poor concentration, mild dysphasia, dressing dyspraxia and constructional apraxia. He was orientated in month and year, but not for the day of the week and the date. He retained two out of three items at 30 seconds and one out of three at 60 seconds, was unable to do serial sevens, but could do serial threes rapidly. CT showed ventricular enlargement and prominent sulci.

By the age of 70 years he had visual and auditory hallucinations, global cognitive impairment, and was unable to care for himself. He showed naming difficulties for common objects, calling a pen "a cylinder". He showed paragrammatical speech with neologisms, disorientation in time and place and difficulties with both recent and remote memory. He was unable to copy simple drawings or a simple sentence. His WAIS vocabulary score was 50 and he performed poorly on tests of memory, language and parietal lobe function, confirming the diagnosis of dementia. An EEG showed a slow but symmetrical rhythm, at or below 8 Hz, frequent independent slow waves and occasional isolated bitemporal sharp waves. CT at 70 and 71 years suggested further enlargement of the lateral ventricles. His vocabulary

score fell to 39 by the age of 71 years. At the age of 72 years he had a shuffling gait, rest tremor and bradykinesia, but no muscular rigidity. Six months later he had several generalised convulsions and died 2 weeks later from bronchopneumonia.

Case 4. This 79 year old man was first examined after a fall at the age of 72 years. His responses to questions were delayed, but he was not thought to be significantly demented. He had a mask-like face, muscular rigidity of limbs, and a shuffling gait, which improved with levodopa. One year later he developed wasting and fasciculation of small hand muscles. Two years later higher doses of levodopa produced a further dramatic improvement in mobility. By the age of 78 years he was unaware of his disability, his memory was poor, and he was believed to be demented. He had lost weight and developed considerable proximal muscle wasting. There was minimal muscular rigidity in the arms, but tone in the legs was normal. There was wasting of muscles of the shoulders, thighs, hands and calves with fasciculations, absent tendon reflexes and extensor plantar responses. His gait was slow and shuffling. An EMG showed fasciculations in arms and legs with normal nerve conduction studies. The patient died 7 years later after a femoral fracture.

Case 5. This 72 year old man developed poor recent memory at the age of 69 years, and three years later showed dressing apraxia and spatial disorientation. He was unable to find his way around his home and often believed it was not his own. His recent memory was poor, he was unable to manipulate matches which he called "drawing pins", and he was unable to put on a pullover. He was apathetic and incontinent of urine, but at times he was agitated and given a few doses of haloperidol (1.5 mg). Three months later he was severely demented, unable to recognise his wife and unable to communicate. All his limbs were described as "very rigid". There were bilateral grasp and pout reflexes. He died 3.5 years after the onset of memory impairment.

Case 6. This 77 year old Polish man was assaulted at the age of 70 years and two ribs were fractured. A year later he became increasingly forgetful and tended to wander. Five years later he spoke only in Polish having once been fluent in English. He showed moderately severe dementia, but there was no muscular rigidity or bradykinesia. CT showed moderate diffuse cortical shrinkage and ventricular dilatation. A single dose of flupenthixol (20 mg intramuscularly) was given for nocturnal confusion, followed by haloperidol (0.5 mg daily). His dementia progressed and he developed a Parkinsonian syndrome complicated by venous and pressure ulcerations of the legs and flexion contractures of the knees. He died of bronchopneumonia 6 years from the onset.

Case 7. This 66 year old woman consumed 12 pints of beer daily in the year before she presented. At the age of 66 years she developed memory impairment with hallucinations and urinary incontinence over a period of 5 months. She failed to recognise faces, was disorientated and tended to wander. Thioridazine (50 mg daily) was prescribed. A random blood glucose was 23.5 mmol/l, but tests of liver function were normal. An EEG was diffusely abnormal with low voltage theta waves and occasional slow activity occurring bilaterally. CT showed mildly dilated cortical sulci. Glibenclamide, metformin, and chlorpromazine (100 mg as required) were prescribed. In the next month her dementia progressed rapidly so that she became restless, failed to recognise her family, language became incoherent and she

developed auditory hallucinations and incontinence of urine. She died 6 months from the onset.

Results

Pathological findings. Brain weights were not generally reduced (table 2). In Cases 1 and 2 cortical sulci were moderately widened, especially frontally, and temporal and frontal horns of the lateral ventricles were mildly dilated. In Cases 3 and 5 the lateral ventricles were moderately enlarged. In Case 7 there was mild fronto-parietal atrophy with moderate dilatation of the temporal horns of the lateral ventricles. All the brainstems showed pallor of the substantia nigra and locus coeruleus.

Microscopic examination in all cases showed moderate or severe cell loss with Lewy bodies in the substantia nigra (table 3, fig. a), locus coeruleus and dorsal vagal nucleus. Neuronal loss in the nucleus basalis varied from inapparent (Cases 2 and 4) to severe (Case 6). Cortical Lewy bodies were frequent in Cases 1, 2, 5-7 (fig. b). They were most numerous deeper in the parahippocampal gyrus, insular cortex, frontal and temporal lobes, and less frequent in parietal and occipital cortex. Lewy bodies never occurred in the hippocampus and were rare in the subiculum in Cases 5-7. None of the cases showed a conspicuous loss of cortical nerve cells and there was little gliosis. Many deep cortical cells without Lewy bodies showed abnormalities ranging from ill-defined cytoplasmic swelling to large pale inclusions. These pale inclusions were similar to those seen in the substantia nigra in these cases and in Parkinson's disease (fig. c and d). Their cerebral distribution followed that of Lewy bodies.

In Cases 1-5 the cortical Alzheimer-type pathology was generally mild and insufficient for a diagnosis of Alzheimer's disease (table 2). In Cases 1 and 2 plaques were infrequent in the parahippocampus and elsewhere in the temporal lobe, and were sparse or absent in other areas. Tangles were not found. In Cases 3-5 plaques were infrequent, and the occasional tangle was confined to the hippocampus and temporal lobe. In Cases 6 and 7 there were more plaques, and infrequent tangles in temporal and frontal cortex. The maximum numerical plaque density of 4/mm² falls short of published criteria for the diagnosis of Alzheimer's disease.¹⁸ In all cases neuronal loss and gliosis were not prominent and thinning of subcortical white matter did not occur. Granulovacuolar degeneration was absent in Cases 2-4, but was found in 13% of hippocampal pyramidal neurons in Cases 1 and 5, in 22% in Case 6, and 40% in Case 7. Occasional Hirano bodies were present in the hippocampus in Cases 1, and 4-7. Subcortical Alzheimer pathology was restric-

Table 2 Summary of pathology in the parahippocampus and cerebral cortex

		Patient						
		1	2	3	4	5	6	7
Brain weight g		1270	1410	1438	1414	1305	1147	na
Parahippocampus	LB	++	++	+	+	++	+++	++
	plaques	0	++	0	+	0	+++	+++
	tangles	0	0	0	0	0	++	+
Frontal	LB	+	++	0	++	+	++	++
	plaques	+	++	0	0	++	+++	na
	tangles	0	0	0	0	0	+	na
Temporal	LB	++	0	0	+	++	++	+
	plaques	0	0	0	++	+	++	+++
	tangles	0	0	0	+	0	0	0
Insular	LB	++	na	+	na	++	++	na
	plaques	0	na	0	na	+	++	na
	tangles	0	na	0	na	0	0	na
Occipital (mid-convexity)	LB	0	0	0	0	0	0	+
	plaques	++	++	0	0	+	+++	na
	tangles	0	0	0	0	0	0	na
Occipital (calcarine)	LB	0	+	0	0	0	0	0
	plaques	+	0	0	0	0	+++	0
	tangles	0	0	0	0	0	0	0

0 = absent in five successive sweeps (0.38 mm wide) from pia to subcortical white matter. Zero does not mean that a feature was entirely absent, but the sampled areas were sufficiently large to ensure that significantly high densities were not missed.

++ = mild, fewer than 0.3 per mm² of section area.

+++ = moderate, 0.3–3.0 per mm² of section area.

++++ = severe, 3.0–4.0 per mm² of section area.

LB = Lewy body.

na = not available.

ted to the occasional tangle in the brainstem, basal forebrain or hypothalamus.

Discussion

Seven patients of mean age 68.7 years (range 65–72) developed dementia. Six of them showed aphasia, apraxia, agnosia or spatial disorientation, suggestive of temporo-parietal dysfunction. The mean disease duration from onset to death was 4 years (range 0.5–7), which is shorter than the mean duration of 10–12 years in untreated Parkinson's disease before the levodopa era.¹⁹ Two cases (Cases 1 and 7), with short survival of 1.5 and 0.5 years respectively, had no evidence of a Parkinsonian syndrome, and three others (Cases 3, 5, 6) developed dementia before Parkinsonian features. Cases 2 and 3 showed a rest

tremor and the other three Parkinsonian cases had a bradykinetic-rigid syndrome. In Case 4 levodopa improved mobility and in Case 2 provoked confusion; it was not given in the other cases.

The subcortical distribution of Lewy bodies and neuronal loss was comparable with that of Parkinson's disease. In all cases there were Lewy bodies and pale inclusions in the cerebral cortex, but without enough plaques and tangles for Alzheimer's disease.^{18,20} Lewy bodies were located mostly in the parahippocampal gyrus, frontal, temporal and insular cortex. In Case 4 the motor neuron disease (MND) may have been coincidental. However, Delisle and Carpenter²¹ who compared proximal axonal swellings located in anterior horn neurons in MND and controls found that one of the 22 controls had Parkinson's disease with large and numerous axonal swellings, not dissimilar from MND. Sporadic MND has also been described with Lewy bodies in anterior horn cells.^{22,23} Hirano²² reported a 55 year old man with a clinical course of 11 years characterised by shuffling gait and muscle wasting. Widespread "neurofibrillary change", degeneration of cells of the substantia nigra and loss of anterior horn cells with intracytoplasmic inclusions, remarkably similar to Lewy bodies, were observed. The possibility arises, therefore, that rare cases of Parkinson's disease with anterior horn cell damage might be associated with Lewy body degeneration in anterior horn cells rather than representing a coincidental association between Parkinson's disease and

Table 3 Summary of pathology in the substantia nigra

Case	Count of pigmented cells	Count of pigmented cells with Lewy bodies
1	302	16
2	104	15
3	299	19
4	360	17
5	535	44
6	220	7
7	291	7

Mean nigral cell counts in 25 controls aged 60–79 years was 856.1 (SE.21.4).

Fig (a) Classical Lewy body in pigmented nerve cell of the locus coeruleus. H and E, $\times 3125$. (b) Lewy body in temporal cortex. H and E, $\times 5000$. (c) Pale body (arrows) in pigmented cell of the substantia nigra. H and E, $\times 3125$. (d) Pale inclusions (arrows) in temporal cortex. H and E, $\times 5000$.

classical MND. One relevant patient described by Delisle *et al* developed MND at the age of 36, followed by extrapyramidal rigidity and dementia a few months before death at the age of 49 years.²⁴ There were moderate numbers of cortical Lewy bodies, with mild Alzheimer pathology, and loss of anterior horn motor neurons with Lewy bodies in the spinal cord, but probably not in surviving motor neurons (slides reviewed by WRGG). Extension of Lewy bodies into anterior horn cells in Parkinson's disease has therefore not been shown. Indeed all recorded patients with MND accompanied by Lewy bodies in anterior horn cells have not been accompanied by Lewy bodies in the brainstem,^{22,23} so these disease entities may be mutually exclusive.

Many previous reports of patients with cortical Lewy bodies and dementia have come from Japan. Okazaki *et al*¹⁷ first reported patients aged 68 and 70 years at death with dementia, Parkinsonian features and multiple cortical Lewy bodies. Although 21 other similar cases, aged 26–72 years, have been described,^{8–12} few characteristics of the dementia have been reported. One patient had topographical amnesia²⁵ and another had bradyphrenia.²⁶ In most cases a Parkinsonian syndrome developed with the dementia, but in four cases dementia was the sole clinical feature for the 3–10 year duration of the disease.^{27–30} The importance of neocortical neurofibrillary tangles and senile plaques has usually been stressed, but in seven cases these were sparse or absent.^{7,12,28,31–34} Among seven recently described, two cases had dyscalculia, dyspraxia or topographical disorientation.^{35,36} Cortical Alzheimer pathology was described as mild or absent in six out of 13 cases.^{35–37} Another report emphasises the temporo-parietal clinical features and the complete absence of Alzheimer changes in one case.⁸ Additional evidence supporting a possible association of cortical Lewy bodies and dementia comes from four reports of patients with Hallervorden-Spatz disease. These cases had multiple cortical Lewy bodies and pale inclusions, and no plaques or tangles.^{13–16}

The classification of our cases depends upon the observation that the distribution of the brainstem pathology was identical to that in Parkinson's disease. Up to 30% of patients with Parkinson's disease have occasional Lewy bodies in the temporal lobe,^{38–40} and some cases have a few Lewy bodies in both temporal and frontal lobes.^{9,10,38} Indeed some such patients have had dementia, but the relative importance of cortical Lewy bodies and Alzheimer changes in these cases is not clear. In this study the cases of idiopathic Lewy body disease have had moderate or severe cortical Lewy body involvement (with the exception of Case 3 which had mild involvement) with little Alzheimer pathology, and they appear to form part of a spectrum

of cortical Lewy body disease in Parkinson's disease.

Studies based on clinical observation alone have stressed the high prevalence of bradykinesia and muscular rigidity in Alzheimer's disease,^{41–43} although in most cases these signs occur late in the disease and are of uncertain significance. In contrast the prevalence of moderate and severe dementia complicating Parkinson's disease has been estimated at about 20%,⁴⁴ although some believe this figure to be excessive,⁴⁵ implying that the prevalence of dementia may be about twice the 5–7% rate in the normal population. Moderate or severe forms of dementia in Parkinson's disease seem to be indistinguishable from that in Alzheimer's disease^{46,47} and are usually accompanied by deteriorating performance in language and visuo-spatial tasks.^{47,48} In the absence of significant Alzheimer changes pathological changes associated with cortical Lewy bodies may be responsible in some cases.

Neuropathological studies have suggested an association between Alzheimer's disease and Parkinson's disease,^{49–51} but quantitative estimates of neocortical tangles and plaques usually fall short of those established in controlled series of Alzheimer's disease.^{18,19,52} Further studies failed to show that tangles, plaques and dementia correlate in Parkinson's disease as they do in Alzheimer's disease.^{53–55} There is now evidence that in Parkinson's disease cell loss and Lewy bodies in the nucleus basalis⁵⁶ are associated with cortical cholinergic deficiency and dementia in the absence of a significant correlation with cortical Alzheimer pathology.^{57–59} Nevertheless Alzheimer pathology may be a contributory factor and reports continue to appear showing that some demented Parkinsonians have pathological features of both Alzheimer's disease and Parkinson's disease.^{60,61} Other reports emphasise that some patients presenting with dementia, with or without a Parkinsonian disorder, show the pathology of Parkinson's disease in the absence of Alzheimer pathology.^{3,6,62} In these cases the possibility of cortical Lewy body pathology may have been overlooked.^{4,6}

Our observations of patients with temporo-parietal clinical features, dementia, cortical Lewy bodies and sparse tangles and plaques suggest that the presence of cortical Lewy bodies may have an important and previously neglected association with the dementia of Parkinson's disease. Future clinico-pathological studies of dementia in Parkinson's disease should consider the effects of cortical Lewy bodies in addition to the two other important lesions; notably, cortical Alzheimer pathology, and nerve cell loss in the nucleus basalis associated with Lewy bodies.

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