A pathological study of the association between Lewy body disease and Alzheimer's disease

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SUMMARY The possibility of an association between Parkinson's disease and Alzheimer's disease has been examined by studying the age-specific prevalence of Lewy bodies in the substantia nigra in a group of 273 control cases without Parkinson's disease and 121 cases of Alzheimer's disease. The substantia nigra was also studied in 14 cases of Down's syndrome, 13 of which had cortical Alzheimer pathology. Twelve (7.8%) of the controls aged over 60 years showed nigral Lewy bodies. There was mild nerve cell degeneration and/or an extranigral distribution of Lewy bodies, suggestive of presymptomatic Parkinson's disease. Twenty five (22.5%) of the Alzheimer's disease cases over 60 years showed Lewy bodies, but only 14 (14.0%) of these had mild nigral cell loss consistent with presymptomatic Parkinson's disease. No case of Down's syndrome had Lewy bodies. Counts of tangles and plaques in hippocampus, frontal and temporal cortex were lower in cases of Alzheimer's disease with Lewy bodies compared with those without, but cortical choline acetyltransferase (ChAT) activities were similar. This suggests that Lewy body degeneration in the nucleus basalis of Meynert contributes to the deficit of cortical ChAT, but not to the cortical Alzheimer pathology. The relatively small difference in the prevalence of Lewy bodies between controls and Alzheimer's disease could be explained by the additive effects of Lewy body and tangle pathology causing dementia, rather than a greater than chance association between Parkinson's disease and Alzheimer's disease.

Pathological studies have suggested that cortical neurofibrillary tangles and neuritic plaques are associated more frequently with Lewy bodies in the brainstem than could be explained on the basis of chance.¹⁻⁶ If correct this has two main implications. Firstly, that Alzheimer pathology may explain the increased prevalence of dementia in Lewy body-Parkinson's disease.⁷ Secondly, that Alzheimer's disease and Parkinson's disease may share pathogenetic or aetiological factors.

Most studies have examined the frequency with which Alzheimer's disease complicates Parkinson's disease, and depend on the accuracy and interpretation of quantitative assessments of tangles and plaques.⁸ Unfortunately there is no clear-cut quantitative threshold for the pathological diagnosis of Alzheimer's disease.⁹ In contrast, the presence of one or more Lewy bodies in sections of substantia nigra

of normal persons, aged over 50 years, is usually associated with degrees of nigral cell loss intermediate between normal and Parkinson's disease¹⁰ and an extranigral distribution of Lewy bodies identical to that found in Parkinson's disease.¹¹ This suggests that such cases represent a presymptomatic phase of Parkinson's disease and are consistent with the observation that striatal dopamine levels fall below 20% of normal values before symptoms develop.^{12,13} We have therefore compared the size of this "at risk" Parkinson's disease population (presymptomatic Parkinson's disease) in a group of 273 controls and 121 cases of Alzheimer's disease. In addition the substantia nigra in 14 cases of Down's syndrome was examined for Lewy bodies, because of its established association with the pathology of Alzheimer's disease.¹⁴⁻¹⁷

Materials and methods

Brains were examined from patients with Alzheimer's disease, Down's syndrome and a control population. The group of 121 cases of Alzheimer's disease were collected in three laboratories and therefore identified as Series 1 to 3. Forty

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Received 24 June 1988 and in revised form 24 September 1988.
Accepted 27 September 1988

Fig 1 Lewy body (eosinophilic body with halo) in pigmented cell of the substantia nigra. H&E stain, $\times 8200$.

cases in Series 1 were identified as having Alzheimer's disease on the basis of large numbers of neocortical plaques and tangles. The patients had documented histories of dementia and their brains were collected after death from psychiatric and general hospitals. In Series 2 (33 cases) and Series 3 (48 cases) the brains were obtained at necropsy from patients with progressive dementia residing in psychiatric hospitals. The neuropathological findings of numerous plaques and tangles in the neocortex, in the absence of significant cerebrovascular disease, confirmed the diagnosis of Alzheimer's disease. In the group of 14 cases of Down's syndrome, six were known to be trisomy 21 and all but one showed Alzheimer pathology.

Two hundred "control" brains were obtained from two neuropathology laboratories (Group 1). These patients had died from neurological disorders other than Parkinsonian syndromes and Alzheimer's disease. The remaining 73 cases (Group 2) were collected from a general hospital necropsy service, specifically for the purpose of the study.

Every brain was immersion fixed in formol-saline for a minimum period of three weeks. One block of substantia nigra was cut perpendicular to the axis of the brainstem. Blocks of locus coeruleus, nucleus basalis of Meynert, hippocampus, middle temporal gyrus (Brodmann area 21) and frontal cortex (Brodmann area 10) were also prepared. Sections of paraffin wax-embedded blocks were cut at thicknesses varying from $5\text{ }\mu\text{m}$ to $20\text{ }\mu\text{m}$. Most were cut at $7\text{ }\mu\text{m}$, but the brains of Alzheimer's disease Series 2 and those

of Down's syndrome were cut at $5\text{ }\mu\text{m}$, and those of Alzheimer's disease Series 3 cut at $16\text{ }\mu\text{m}$. Haematoxylin and eosin (H&E) stain was used in every case with adjacent cortical sections stained with Bielschowsky silver impregnation (Alzheimer's disease Series 1), modified Palmgren stain¹⁸ (Alzheimer's disease Series 2) or the Glee and Marsland modification of the Bielschowsky silver method (Alzheimer's disease Series 3). Additional sections were stained with Nissl cresyl violet.

Examination of the substantia nigra required an eyepiece graticule used at $\times 400$ magnification moved in parallel sweeps across the section. The amount of free melanin and cell destruction were estimated as mild, moderate or severe. The severity of cell loss was also estimated as mild (60–90% of cells remaining), moderate (20–60% of cells remaining) or severe (0–20% of cells remaining), and the cut off point for symptoms of Parkinson's disease was taken as 40% of cells remaining.^{19,20} Each cell was examined for Lewy bodies, which were defined as intracytoplasmic, eosinophilic bodies with haloes (fig 1). Sections of locus coeruleus, nucleus basalis, hippocampus and cerebral cortex were examined cell by cell for Lewy bodies.

In Series 2 the Palmgren stain was used to count plaques and tangles in sections of middle temporal gyrus ($5\text{ }\mu\text{m}$ thick) by the "nearest neighbour distance" method described by Aherne and Diggle.²¹ This technique measures distance between cells and provides a density measurement so that results are expressed as numbers of cells per area.²² In the

Table 1 Age-specific prevalence of Lewy bodies in Alzheimer's disease

Age (yr)	Series 1 Number 40	Series 2 33	Series 3 48	Total* 121	Corrected† 108
30-39	2/3	0/0	0/0	2/3 (66.7%)	0/1 (0%)
40-49	0/1	0/1	0/0	0/1 (0%)	0/1 (0%)
50-59	0/4	0/1	0/1	0/6 (0%)	0/6 (0%)
60-69	2/13	4/9	0/6	6/28 (21.4%)	4/26 (15.4%)
70-79	3/14	3/7	3/19	9/40 (22.5%)	5/36 (13.9%)
80-89	1/6	4/13	4/17	9/36 (25.0%)	4/31 (12.9%)
90-99	0/0	0/2	1/5	1/7 (14.3%)	1/7 (14.3%)
Prevalence over 60 years				25/111 (22.5%)	14/100 (14.0%)

*Includes "Parkinsonian" cases.

†Incidental cases only.

The numerator is the number of Alzheimer's disease cases with Lewy bodies; the denominator is the total number of Alzheimer's disease cases. Two cases in Series 1 of unknown age have been included in the seventh decade.

hippocampus plaques and tangles were counted in whole sections. In Series 3 the Glee's stain was used on sections (16 µm thick) of frontal cortex and middle temporal gyrus for plaque and tangle counts by the methods described by Mountjoy *et al.*²³ The plaque count was derived from a combination of two methods which showed a high degree of correlation. One was a random plaque count where plaques were counted in parallel strips perpendicular to the cortical

surface, the other a selected plaque count derived from counts found in areas of maximal plaque density. The frequency of tangles was estimated on a four-point scale (0 = absent, 1 = slight, 2 = moderate, 3 = severe) after the method of Corsellis.²⁴ It has been demonstrated that these tangle estimates when done on two separate occasions show a high degree of correlation.²³

Samples of middle temporal gyrus (Brodmann area 21)

Fig 2 Eosinophilic inclusion present in the subiculum in Patient 3. Unlike most Lewy bodies the demarcation between "body" and "halo" is abrupt (arrow), and the "halo" wide and pale. H&E stain, × 8200.

Fig 3 (a) Pale inclusion (arrows) in the temporal lobe. H&E stain, $\times 8000$. (b) Pale body (arrows) in the substantia nigra. H&E stain, $\times 6400$.

Table 2 Alzheimer's disease Series 2. Estimations of tangles and plaques in the middle temporal gyrus (Brodmann area 21) and hippocampus in 26 cases of Alzheimer's disease with and without Lewy bodies in the substantia nigra

	Lewy body neg cases (18) mean age 74.6 yr	Lewy body pos cases (8) mean age 77.5 yr	Difference as per cent of Lewy body neg cases
Temporal cortex plaques	18.6 (SD 10.9)	13.6 (SD 5.2)	27
Temporal cortex tangles	19.1 (SD 11.3)	13.6 (SD 5.8)	29
Hippocampus plaques	56.4 (SD 62.6)	37.6 (SD 28.4)	33
Hippocampus tangles	145.1 (SD 91.7)	131.3 (SD 58.0)	10

Temporal cortex plaque and tangle counts expressed as number per mm².

Hippocampal plaque and tangle counts expressed as number per section.

and frontal cortex (Brodmann area 10) were used for measurements of choline acetyltransferase (ChAT) activities.²⁵

Results

In Alzheimer's disease Series 1, mean age 68.6 years, there were three patients, aged 38, 38 (Patients 1 and 2) and 36 years at death, whose mother or sibling also had dementia (table 1). Lewy bodies were present in the substantia nigra in eight cases, in three of which, aged 38, 38 (Patients 1 and 2) and 80 years, the severity of nigral cell loss was sufficient to produce Parkinsonian features. One of the patients aged 38 years (Patient 1) exhibited a mask-like face and had numerous falls. The patient aged 80 years had muscular rigidity of the arms and a rest tremor of the right arm. As the association of Lewy bodies and nigral cell loss in excess of 60% is compatible with Parkinson's disease, these patients were not included as cases of presymptomatic disease.

The brain of Patient 1, a male of 38 years, showed severe neocortical changes of Alzheimer's disease with very numerous tangles and some amyloid deposits in the substantia nigra and ventral tegmental area. A single Lewy body was seen in the lateral substantia nigra zona compacta but none were found in the locus coeruleus, dorsal vagal nucleus or nucleus basalis. The brain of Patient 2, a female aged 38 years, showed tangles in the substantia nigra and locus coeruleus, with amyloid plaques in the substantia nigra, medulla, hypothalamus and nucleus basalis, and plaques alone in the thoracic spinal cord. Multiple Lewy bodies were present in the substantia nigra but not in the cerebral cortex, dorsal nucleus of the vagus, nucleus basalis or locus coeruleus. In another patient (Patient 3), a woman aged 61 years, there was severe cortical and

Table 3 Alzheimer's disease Series 3. Estimations of tangles and plaques, and of choline acetyltransferase (ChAT) in the frontal cortex (Brodmann area 10) and middle temporal gyrus (Brodmann area 21) in 48 cases of Alzheimer's disease with and without Lewy bodies in the substantia nigra

	Lewy body neg cases (40) mean age 74.0 yr	Lewy body pos cases (8) mean age 82.0 yr	Difference as percent of heavy body negative cases
B10 plaque count	1.00 (SD 0.95)	0.44 (SD 0.35)	56.0
B10 tangle count	2.10 (SD 2.00)	1.04 (SD 1.1)	50.5
B21 plaque count	1.07	0.38	64.5
B21 tangle count	2.17	1.9	12.4
B10 ChAT	4.03 (SD 2.09)	4.20 (SD 2.26)	—
B21 ChAT	2.83 (SD 2.34)	2.46 (SD 1.49)	—

Plaque counts derived from two measurements (see text).

Tangle counts on scale 0-4, absent-severe.

ChAT units, $\mu\text{mol/h/g}$ protein.

subcortical Alzheimer's disease with granulovacuolar degeneration in the ventral tegmental area. One isolated inclusion, vaguely resembling a Lewy body, was found in the subiculum with none elsewhere (fig 2).

Alzheimer's disease Series 2, mean age 75.4 years, was seven years older than Series 1 (table 1). The mother of one patient, a 48 year old woman, had histologically proven Alzheimer's disease. Lewy bodies were present in the substantia nigra of 11 cases, in seven of which there was moderate or severe loss of pigmented cells compatible with Parkinson's disease. Of the remaining four cases with Lewy bodies one had little cell loss and three had mild cell loss.

The nucleus basalis was examined in eight cases with nigral Lewy bodies and six Lewy body negative cases. Lewy bodies were found here in the Lewy body positive cases, in which the degree of cell loss ranged from moderate to severe. In Lewy body negative cases the degree of nucleus basalis cell loss was mild to moderate. Lewy bodies were found in the parahippocampal gyrus in six of eight Lewy body positive cases; and in eight of nine cases Lewy bodies were present in the middle temporal gyrus. In the single case without Lewy bodies in the middle temporal gyrus only a small section was examined. In the cerebral cortex cells that were swollen with ill-defined pale areas or inclusions were more numerous than those containing Lewy bodies (fig 3). Estimations of tangles and plaques in the temporal lobe and hippocampus showed consistently lower mean values (by 10% to 33%) for the Lewy body positive cases compared with cases of Alzheimer's disease alone (table 2).

Alzheimer's disease Series 3, mean age 78.6 years, was 10 years older than Series 1 (table 1). Lewy bodies were found in the substantia nigra in eight cases, in three of which nigral cell loss was moderate and in five it was mild. They also showed Lewy bodies in the locus

Table 4 Selected clinical and pathological details in 14 cases of Down's syndrome

Patient	Age (yr) sex	Mental age/ IQ*	Brain weight (g)
1	31 M	2/<30	1050
2	37 F	<2/30	1045
3	41 M	—	1245
4	53 M	3/30	870
5	57 M	4/—	Not recorded
6	59 M	4/<30	950
7	60 M	—	920
8	60 F	<2/<30	965
9	62 F	6/42	850
10	62 F	3/<30	960
11	64 M	2/<30	940
12	64 M	<2/<30	940
13	65 M	3.5/<30	Not recorded
14	71 M	2/44	1130

Paraffin sections were prepared at 5 µm thickness and stained for senile plaques and neurofibrillary tangles using a modified Palmgren's silver technique.¹⁸

*Based on the Wechsler Intelligence Test.

coeruleus. The middle temporal gyrus contained isolated Lewy bodies in two of the eight Lewy body cases, but none were found in the frontal pole cortex. The middle temporal gyrus was examined in 21 cases without nigral Lewy bodies and the frontal pole cortex in 31 cases without nigral Lewy bodies, and no Lewy bodies were found. Counts of tangles and plaques in the frontal and temporal cortex were 12% to 56% lower in the Lewy body positive cases. In contrast there were no differences in activities of ChAT (table 3).

Data on the age-specific prevalence of Lewy bodies in the three series of Alzheimer's disease were combined (table 1). The series were contaminated by a total of 13 cases in which nigral cell loss was severe enough to produce Parkinsonian features. Such patients may have been selected into these hospital-based studies because of difficulties with mobility. Their exclusion leaves 108 patients in which the prevalence of incidental Lewy body disease was 13% to 15% per decade in the seventh to tenth decades.

In the cases of Down's syndrome Patient 1 had no cerebral plaques or tangles and Patient 2 had numerous plaques, but few tangles (table 4). The remaining 12 cases had numerous neocortical plaques and tangles. In none of them were Lewy bodies found by searching one or two sections of substantia nigra.

A total of 14 of 273 "control" brains contained Lewy bodies in the substantia nigra, with similar proportions in the two groups examined (table 5). In eight of these 14 cases cell loss in the substantia nigra was mild in severity, but in six cases there was no obvious cell loss, although amounts of extraneuronal melanin were abnormally increased in three. As in Parkinson's disease Lewy bodies were also found in

Table 5 Age-specific prevalence of Lewy bodies in "control" brains

Age group (yr)	Group 1	Group 2	Total
10-19	0/5	0/0	0/5
20-29	0/16	0/1	0/17
30-39	0/15	0/2	0/17
40-49	0/26	0/1	0/27
50-59	2/48 (4.2%)	0/5 (0%)	2/53 (3.8%)
60-69	3/51 (5.9%)	0/13 (0%)	3/64 (4.7%)
70-79	2/23 (8.7%)	2/20 (10.0%)	4/43 (9.3%)
80-89	2/14 (14.3%)	3/25 (12.0%)	5/39 (12.8%)
90-99	0/1	0/6	0/7
100-109	0/1	0/0	0/1
Prevalence over 60 years	7/90 (7.8%)	5/64 (7.8%)	12/154 (7.8%)

The numerator is the number of Lewy body cases (incidental Lewy body disease), the denominator is the total number of cases examined.

the locus coeruleus, dorsal vagal nucleus and nucleus basalis.

Discussion

Most cases of Alzheimer's disease with Lewy bodies in the substantia nigra showed Lewy bodies in one or more locations elsewhere in the brain. They were most commonly found in the locus coeruleus, nucleus basalis and cerebral cortex reflecting the pattern seen in Parkinson's disease. The age-specific prevalence of presymptomatic Parkinson's disease occurring in Alzheimer's disease was similar to that in a group of control patients with neurological and non-neurological disorders. However, small differences remained in the seventh and eighth decades, despite excluding cases of combined Lewy body disease and Alzheimer's disease, with nigral cell loss sufficient to produce Parkinsonian features.

In Alzheimer's disease Series 2 and 3 the tangle and plaque counts in hippocampus, temporal and frontal cortex were consistently lower in those cases with brainstem Lewy bodies, with the smallest difference being for hippocampal tangle counts (Series 2). In contrast, the activities of ChAT in frontal and temporal cortex (Series 3) were no different suggesting that Lewy body degeneration in the nucleus basalis contributed to the cortical cholinergic deficit, but not to the number of cortical plaques and tangles. This observation agrees with recent studies which have not always found Alzheimer cortical pathology in cases of Parkinson's disease with dementia, although the nucleus basalis may be depleted and activities of cortical ChAT reduced.²⁶⁻²⁸ The differences in methodology applied to the three Series are not likely to have influenced outcome, but the consistent nature of the results between the Series tends to strengthen the observations.

Fig 4 Interactions between Alzheimer's disease (AD) and Parkinson's disease (PD). The inner ovals represent symptomatic cases of Alzheimer's disease and Parkinson's disease, the outer ovals include presymptomatic cases. Area 1 represents overlap between Alzheimer's disease and Parkinson's disease equivalent to the chance concurrence of these disorders. Areas 2 and 3 represent patients with modest Alzheimer pathology and nigrall Lewy bodies, many of whom have dementia, but not Parkinson's disease. Area 4 represents patients with Alzheimer's disease and nigrall Lewy bodies, but no Parkinson's disease. Area 5 represents patients with Parkinson's disease and modest Alzheimer pathology, many of whom have dementia.

Fig 5 Left-shift of the age-specific prevalence of Lewy bodies in Alzheimer's disease, because of dual pathologies responsible for dementia, and consequent reduced life expectancy.

In post-mortem studies of Alzheimer's disease there is a slight increase in the prevalence of incidental Lewy bodies, probably because of the inclusion of patients with dementia and cell loss in the nucleus basalis resulting from a combination of Lewy body disease with mild Alzheimer pathology (presymptomatic or borderline cases of Alzheimer's disease) (fig 4). The inclusion of cases of cortical Lewy body disease which is associated with dementia, even with little or no Alzheimer pathology,²⁹⁻³¹ may be another explanation. It is of note that the prevalence of cortical Lewy bodies in Series 2 and 3 was 59% (10/17). A slightly lower prevalence of 30% (16/54) has been found in unselected cases of Parkinson's disease.²⁹ Finally, a very small factor contributing to the excess frequency of Lewy bodies may be a reduced life expectancy, resulting from the co-existent pathologies (Lewy bodies and Alzheimer pathology) responsible for the dementia, shifting the age-specific prevalence of Lewy bodies to the left (fig 5).

The absence of Lewy bodies complicating the Alzheimer pathology of Down's syndrome provides additional support for the notion that Alzheimer's disease and Lewy body disease are not generally associated.

In a previous study Woodard¹¹ collected 96 brains with pathological features of Alzheimer's disease from persons aged over 50 years. In ten (10.4%) cases Lewy bodies were present in the substantia nigra or other locations in the brainstem. This can be compared with his prevalence figure of 8.8% (17/194) for all persons aged over 50 years, although a couple of these had Parkinsonian features. Another study consisted of 128 cases of senile dementia of the Alzheimer type and 68

cases of Alzheimer's disease, with mean age at death of 80.7 years and 65.4 years respectively.^{32,33} Lewy bodies were found in the substantia nigra or locus coeruleus in 15% or 22% respectively of the total (mean age 75.4 years), compared with a prevalence of 10% or 16% in 180 controls (mean age 74.3 years). These authors concluded that there was no evidence for an excess number of Lewy bodies in Alzheimer's disease.

In this study Patients 1 and 2 cannot be explained on the basis of additive lesions and selection bias. They showed familial Alzheimer's dementia presenting at a young age, with Lewy bodies present in the substantia nigra at death. Another young patient, aged 39 years, has been reported with Lewy body disease and Alzheimer's disease, but without other affected family members.³⁴ Thus there are a few rare, sometimes familial, cases where the pathologies of Alzheimer's disease and Lewy body disease coexist.

In Patient 3 the severe cortical pathology of Alzheimer's disease was associated with an isolated cortical neuronal inclusion resembling a Lewy body, in the absence of Lewy bodies in the brainstem. However, it lacked the precise morphology of a cortical Lewy body, and occurred in isolation in a region where cortical Lewy bodies are less plentiful. Furthermore cortical Lewy bodies have never been observed in the absence of brainstem Lewy bodies. Current evidence suggests that dementia with cortical Lewy bodies always forms part of the spectrum of Parkinson's disease.²⁹

This study fails to provide support for a greater than chance association between Alzheimer's disease and Parkinson's disease, except in rare cases. These rare cases join a small group of other disorders associated with Lewy bodies.³⁵⁻⁴⁰ The study emphasises the interaction of three major pathologies responsible for

dementia in Parkinson's disease: Alzheimer's disease, Lewy bodies and cell loss in the nucleus basalis, and cortical Lewy bodies.

WRGG was a Medical Research Council Training Fellow. We thank Dr R O Barnard and Professor P L Lantos for permission to study their cases, and Dr M N Rossor for providing the ChAT data and for helpful discussion.

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