

# Hallucinations and signs of parkinsonism help distinguish patients with dementia and cortical Lewy bodies from patients with Alzheimer's disease at presentation: a clinicopathological study

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## Abstract

**Objectives**—To compare, in a retrospective clinicopathological study, the presentation features of patients with dementia and cortical Lewy bodies (Lewy body dementia) with those of patients with Alzheimer's disease.

**Methods**—From a population of 426 cases from the dementia brain bank, 39 cases of Lewy body dementia and 61 cases of Alzheimer's disease with presentation details were identified.

**Results**—The Lewy body dementia group had significantly more frequent hallucinations (23% *v* 3%,  $P = 0.006$ ) and signs of parkinsonism (41% *v* 5%,  $P < 0.0001$ ) than the Alzheimer's disease group. The Lewy body dementia group also had a greater proportion of men (62% *v* 34%,  $P = 0.013$ ).

**Conclusion**—Hallucinations and signs of parkinsonism help distinguish Lewy body dementia from Alzheimer's disease at presentation. These indicators may not be very sensitive, because they were reported for less than half of the patients with Lewy body dementia.

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Interest in cortical Lewy bodies found on neuropathological examination of the brains of demented patients has increased in recent years. Even though there has not been much agreement on the nosology of the condition, with different researchers using various terms ranging from Lewy body dementia to the Lewy body variant of Alzheimer's disease (for reviews, see Hansen and Galasko<sup>1</sup> and Lennox<sup>2</sup>), there have been many reports that indicate that dementia associated with cortical Lewy bodies is relatively common, with 14%–20% of demented patients having cortical Lewy bodies at necropsy.<sup>3-6</sup>

By contrast with the presentation symptoms and signs of Alzheimer's disease, the Newcastle research group<sup>7</sup> has reported that in their experience with cases of Lewy body dementia confirmed at necropsy "80% present with a syndrome of fluctuating cognitive impairment associated with hallucinations (usually visual), and with parkinsonian features which are often precipitated by neuroleptic

drugs". These symptoms and signs have been so characteristic that the Newcastle group<sup>8</sup> has included them as key features of a proposed set of clinical criteria for the antemortem diagnosis of the condition which they have termed "senile dementia of Lewy body type".

In addition to the Newcastle criteria, at least two other research groups have recently proposed antemortem clinical criteria for the diagnosis of Lewy body dementia. Both the Nottingham Group for the Study of Neurodegenerative Disease<sup>9</sup> and the San Diego group<sup>10</sup> have presented criteria that include the presence of multiple parkinsonian features, with the second group indicating that the criteria should be applied to patients with mild to moderate dementia. Neither emphasises the psychiatric features as prominently as the Newcastle group.

Despite the claims of these research groups regarding parkinsonian and psychiatric features at presentation, few independent series have investigated how often patients with Lewy body dementia present with such signs or symptoms. Moreover, those that have included presentation details have not described as high a frequency of parkinsonian or psychiatric features. For example, in their necropsy series of 65 patients with clinically diagnosed Alzheimer's disease Förstl *et al*<sup>11</sup> reported that the early symptoms of the eight that were found to have "the Lewy body variant of Alzheimer's disease" were "uncharacteristic" when compared with a matched group with Alzheimer's disease. No particular differences in the presence of hallucinations or fluctuations in the course of illness were noted, and the only distinctive feature of the patients with cortical Lewy bodies was the development of severe rigidity.

Another necropsy series that included descriptions of the first symptoms and signs of patients with Lewy body dementia was reported by Gibb *et al*<sup>12</sup>; however, their series included both cases of dementia and cases of parkinsonian disorders. Out of 140 cases, seven with "cortical Lewy body dementia" were identified, with two having early memory impairment associated with psychiatric features and two presenting with a parkinsonian syndrome.

One necropsy series with a relatively high frequency of parkinsonian and psychiatric features at presentation was reported by the Nottingham group.<sup>13</sup> Their study, however, was not limited to cases of dementia and also

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included cases with extrapyramidal syndromes. Fifteen of 57 such cases were found to have "diffuse Lewy body disease", with the presentations of four of the 15 including psychiatric features such as hallucinations. Nine of the 15 presented with Parkinson's disease with or without mild cognitive impairment, and the remaining two presented with cognitive impairment alone.

Considering the relative paucity of research into the presenting clinical features of patients with Lewy body dementia, we conducted a retrospective study of the cases in our dementia brain bank to identify those with cortical Lewy bodies to review their presentations. Our primary objective was to determine how often key features included in the recently proposed clinical criteria<sup>8-10</sup> were reported for patients with Lewy body dementia relative to those with Alzheimer's disease. In addition to an overall group of patients with cortical Lewy bodies, we subcategorised our cases into groups according to the concomitant presence of Alzheimer's changes and the relative concentration of cortical Lewy bodies to allow readers to consider different pathological definitions of Lewy body dementia. To minimise confounding factors such as infarcts, we included only cases that demonstrated cortical Lewy bodies, Alzheimer's pathology, or both.

#### Patients and methods

We retrospectively reviewed all 476 cases of dementia received in the Ramsey Foundation-Alzheimer's Treatment and Research Center Brain Bank from August 1988 to the end of July 1992. Brain tissue from these cases had been referred to us for the neuropathological diagnosis of a demented patient's illness. Our referral sources were diverse and included primary physicians, neurologists, hospitals, academic centres, and nursing homes primarily located in the midwest of the United States. Most of the specimens comprised the entire brain; a few consisted only of histopathological slides or selected tissue samples. If frozen specimens had been received or if the specimens had been obtained soon after death, one cerebral hemisphere was removed and frozen for research purposes. After each brain was received, medical records were requested for documentation of the patient's medical history.

All cases in this study had a neuropathological report detailing the gross and microscopical examinations of at least one hemisphere, the brainstem, and the cerebellum, and medical records indicating that the patient had a progressive dementing illness. Two patient populations were determined for comparison that were as devoid of other dementing pathology as possible, one with cortical Lewy bodies and the other with Alzheimer's disease without cortical Lewy bodies. To focus our study on patients that presented with dementia rather than on all patients with disease associated with Lewy bodies, we excluded patients with clinical Parkinson's disease, defined as those who were treated with medication for signs of

parkinsonism before the onset of dementia. The few patients in our brain bank with clinical Parkinson's disease were identified but not included in the data analysis. Otherwise, selection was not influenced by clinical diagnoses or characteristics.

#### CLINICAL METHODS

The records for each case were reviewed to determine if there was documentation of the patient's presentation for dementing illness, defined as the first time that a patient's symptoms or signs of cognitive impairment or associated psychiatric pathology were considered by a physician. The physician's report at the time of presentation must have included a history, physical examination, assessment, and plan considering the symptoms or signs. Parkinsonian or extrapyramidal features were considered present if the examining physician mentioned any sign of parkinsonism, including but not limited to such terms as shuffling gait, masked facies, bradykinesia, loss of postural reflexes, increased muscle tone, or any tremor. The use of neuroleptic medication in association with the presentation was documented, and any exaggerated or unexpected response to neuroleptic drugs was recorded. Parkinsonian or extrapyramidal features noted with the use of neuroleptic drugs were not included as signs of parkinsonism. The records were also reviewed for additional key features included in the Newcastle criteria<sup>8</sup> that were reported at presentation or to have occurred in the preceding year, including prominent fluctuation in cognitive status or level of consciousness, hallucinations, and any unexplained falls or episodes of syncope. Hallucinations were recorded only if the term "hallucination" was used. When available, presentation examinations by neurologists were also analysed in a separate subcategory.

Although not specifically included in their criteria, the Newcastle group<sup>8</sup> reported that depression occurs significantly more often in Lewy body dementia at presentation. We therefore recorded if patients were diagnosed with and treated for depression in association with the dementia presentation or in the preceding year.

Severity of disease at the time of presentation was graded according to DSM-III-R criteria<sup>14</sup> on review of the records. Either a "mild", "moderate", or "severe" rating was assigned, with mild indicating that the patient retained the capacity for independent living, moderate indicating that some degree of supervision was necessary, and severe indicating that continuous supervision was required. If the available clinical information for a particular case was insufficient to establish a severity rating with confidence, the less severe grade was assigned.

#### PATHOLOGICAL METHODS

The tissue was fixed, sectioned, and grossly inspected, and histopathological sections were then systematically taken from the neocortex of the frontal (two sections), parietal, and occipital lobes, and from the amygdala, hip-

pocampus, corpus striatum, thalamus, mid-brain including the substantia nigra (at least two sections at different levels), pons, medulla, and cerebellar cortex and stained with haematoxylin and eosin and Bielschowsky silver stains. The identification of cortical and subcortical Lewy bodies was based on their characteristic size, location, and staining properties, consistent with published descriptions.<sup>15</sup> All cases were reviewed by both neuropathologists (K-HY and JHS).

Cases in which Lewy bodies were noted in subcortical sections but not the cortex with haematoxylin and eosin were further studied by preparing a slide, using an antiubiquitin stain, of the medial temporal lobe including the hippocampus and parahippocampal gyrus. Cases in which no Lewy bodies were noted with haematoxylin and eosin were likewise further studied with antiubiquitin stain if either moderate or more severe degeneration of the substantia nigra was noted or if there were atypical clinical features.

Quantitative estimates of the density of senile plaques and neurofibrillary tangles were made from the silver stained sections. Counts of Lewy bodies were made from sections stained with either haematoxylin and eosin or antiubiquitin.

Cases showing cortical Lewy bodies were considered as a single overall group and were also subcategorised according to the presence or absence of Alzheimer's changes in the neocortex and the density of cortical Lewy bodies. The "cortical Lewy body only" subgroup comprised cases with cortical Lewy bodies and < 25 senile plaques and < 10 neurofibrillary tangles per 100 × magnification field, the "cortical Lewy body and senile plaque" subgroup comprised cases with cortical Lewy bodies and ≥ 25 senile plaques and < 10 neurofibrillary tangles, and the "cortical Lewy body and Alzheimer's disease" subgroup comprised cases with cortical Lewy bodies and ≥ 25 senile plaques and ≥ 10 neurofibrillary tangles. A "high concentration of cortical Lewy bodies" subgroup comprised cases with a mean cortical Lewy body count > 5 in at least five 100 × fields irrespective of the presence of senile plaques or neurofibrillary tangles. The Alzheimer's disease control group included all cases received during the study period with no cortical Lewy bodies and ≥ 25 senile plaques and ≥ 10 neurofibrillary tangles in the neocortex.

We excluded cases that exhibited any gross or microscopical dementing pathology other than Lewy bodies or Alzheimer's changes—such as infarcts of any size, haemorrhages, contusions, Pick bodies, neoplasms, and vascular malformations. Cases that had evidence of extra-axial pathology, such as subdural haematomas and meningiomas, were also excluded. The presence of any degree of atherosclerosis, arterioarteriolar sclerosis, rarefaction of the cerebral white matter, or amyloid infiltration of the vessels was allowed, provided that there were no gross or microscopical infarcts. Ventricular dilatation was not a reason for exclusion. Cases showing pathologi-

cal evidence of acute or subacute infarcts or haemorrhages (having occurred within weeks of the patient's death) were not excluded.

#### STATISTICAL ANALYSIS

Differences between patient groups were analysed with unpaired Student's *t* tests for continuous variables and Fisher's exact tests for counted variables. Two sided *P* values were used for all comparisons, with significance defined at the *P* = 0.05 level. Data for subgroups were analysed if the differences between the overall cortical Lewy body group and the Alzheimer's disease control group were significant.

#### Results

Of the 476 cases received during the study period, 50 were excluded due to inadequate tissue (19), inadequate records (29), or records not documenting that the patient was demented (two). Ninety (21%) of the remaining 426 were found to have cortical Lewy bodies with or without other pathology. An additional four had Lewy bodies in the substantia nigra but no cortical Lewy bodies. Only one case was identified that had cortical Lewy bodies but no Lewy bodies in the substantia nigra in two sections. This case also had severe substantia nigra neuronal loss and gliosis. Twenty two of the 90 (24%) had high concentrations of cortical Lewy bodies.

Forty of the 90 cases with cortical Lewy bodies were excluded from further study due to microscopical or gross infarcts (34), unclassified degeneration (two), a meningioma (one), a subdural haematoma (one), a metastatic neoplasm (one), and alcoholic degeneration (one). One additional case was excluded due to treatment for clinical Parkinson's disease before the onset of dementia. The remaining 49 cases had cortical Lewy bodies without other dementing pathology except senile plaques or neurofibrillary tangles. Presentation details were available for 39 of these 49, comprising the overall cortical Lewy body group.

There were 83 cases identified out of the 426 that had Alzheimer's disease without other dementing pathology. Presentation details were available for 61 of these, comprising the Alzheimer's disease control group.

Table 1 gives the presentation details for the cortical Lewy body and Alzheimer's disease groups. A significant difference was noted between the two groups in reports of hallucinations, with these being reported for nine of the cortical Lewy body group (23%) and only two of the Alzheimer's disease group (3%). Six of the patients with cortical Lewy bodies had visual hallucinations; no descriptions of the hallucinations of the other three were mentioned. Descriptions of the hallucinations of the patients in the Alzheimer's disease group were not mentioned, although one was included due to hallucinations after a seizure.

Signs of parkinsonism at presentation were reported for less than half of the cortical Lewy body group (15 of 37 as reported by all physi-

Table 1 Key features reported at presentation

Symptoms and signs at presentation	AD group	CLB group	P value
Any fall or syncopal episode in preceding year	4 n = 60	4 n = 39	0.71
Prominent fluctuation	2 n = 60	3 n = 39	0.38
Hallucinations	2 n = 60	9 n = 39	0.006
Treatment for depression	4 n = 60	7 n = 39	0.11
Any sign of parkinsonism	3 n = 59	15 n = 37	< 0.0001
Two or more of above symptoms or signs	0 n = 60	10 n = 39	< 0.0001
Any sign of parkinsonism reported by neurologist	3 n = 34	13 n = 28	0.0011
Treatment for parkinsonism	0 n = 61	1 n = 39	0.39
Men/women	21/40	24/15	0.013
Mean age of onset in years (SD)	68.0 (9.1) n = 61	69.7 (5.7) n = 39	0.30

Values are numbers of cases with features reported. Groups include patients of all dementia severity.

AD = Alzheimer's disease; CLB = cortical Lewy bodies.

cians or 13 of 28 as reported by neurologists), but they were reported statistically more often than for the Alzheimer's disease group (three of 59). One patient from the cortical Lewy body group was being treated for parkinsonism at the time of presentation to a physician for dementia, with the records documenting that the onset of symptoms of dementia had preceded the onset of the parkinsonism.

Ten of the 39 patients with cortical Lewy bodies (26%) had two or more of the key features (fall or syncopal episode, fluctuation, hallucinations, depression, or parkinsonian signs) at presentation by contrast with none of the patients with Alzheimer's disease. Four patients with cortical Lewy bodies had three key features whereas there were none in the patients with Alzheimer's disease. Eight of the cortical Lewy body group were treated with neuroleptic medication in association with their presentations, with no cases of exaggerated or unexpected responses being noted.

The cortical Lewy body group also had a greater proportion of men 24 of 39 (62%) v 21 of 61 (34%) for the Alzheimer's disease group.

Table 2 presents the data for the patients with only mild or moderate severity of dementia. Consistent with the findings in table 1,

hallucinations, signs of parkinsonism, and two or more features were statistically more frequent in the cortical Lewy body group than in the Alzheimer's disease group. Three patients with cortical Lewy bodies had three key features.

Table 2 also includes data categorised according to the cortical Lewy body subgroups. On the assumption that clinicians would be more interested in presentation details of patients with mild or moderate dementia, excluding those with severely advanced conditions, the subgroup data are included in table 2 rather than table 1. With the exception of the cortical Lewy body and Alzheimer's disease subgroups, each of the subgroups reflected essentially the same significant differences relative to the Alzheimer's disease group as the overall mild-moderate cortical Lewy body group. A remarkable finding was that the cortical Lewy body only subgroup contributed relatively greater numbers of cases with hallucinations and cases with two or more features than the other subgroups, with three of four (75%) having such reports. The cortical Lewy body and Alzheimer's disease subgroup contributed only one or none of the key features, with no features reaching significance.

All 15 cases in the Alzheimer's disease group for which key clinical features were reported were examined for cortical Lewy bodies using antiubiquitin stain; no additional cases with cortical Lewy bodies were identified.

## Discussion

Albeit in a minority of cases, our results support the claims of the Newcastle group<sup>7</sup> that many patients with Lewy body dementia present with a syndrome very different from the "typical" patient with Alzheimer's disease. Twenty six per cent of those with Lewy body dementia presented with two or more of the key features, by contrast with none of those with Alzheimer's disease. Those with Lewy body dementia had hallucinations and signs of parkinsonism reported more often than those with Alzheimer's disease, and they were noted to have a male predominance.

Table 2 Key features reported at presentation for patients with mild or moderate dementia

Symptoms and signs at presentation	Mild-moderate AD group	Mild-moderate CLB group	P value	CLB subgroups							
				CLB only	P value	CLB+SP	P value	CLB+AD	P value	High concentration CLB	P value
Hallucinations	1 n = 40	7 n = 29	0.008	3 (2) n = 4 (2)	0.0012	4 (2) n = 20 (6)	0.038	0 n = 5 (1)	1.00	4 n = 9	0.0027
Any sign of parkinsonism	1 n = 41	10 n = 28	0.0003	2 (2) n = 4 (2)	0.018	7 (2) n = 19 (6)	0.0008	1 (0) n = 5 (1)	0.21	4 n = 9	0.0025
Two or more symptoms or signs (see table 1)	0 n = 40	8 n = 29	0.0005	3 (2) n = 4 (2)	0.0003	5 (2) n = 20 (6)	0.0028	0 n = 5 (1)		4 n = 9	0.0006
Any sign of parkinsonism reported by neurologist	1 n = 21	9 n = 22	0.0093	2 (2) n = 4 (2)	0.057	6 (2) n = 16 (4)	0.029	1 (0) n = 2 (0)	0.17	4 n = 6	0.004

Values are numbers of cases with features reported. The CLB only subgroup column includes cases with CLBs and < 25 senile plaques (SPs) and < 10 neurofibrillary tangles (NFTs) per 100 × magnification field in the neocortex; the CLB and SP subgroup column includes cases with CLBs and ≥ 25 SPs and < 10 NFTs; the CLB and AD subgroup column includes cases with CLBs and ≥ 25 or more SPs and ≥ 10 NFTs. Numbers in parentheses indicate number of cases with mean CLB count greater than five in at least five 100 × magnification fields, summarised in the high concentration CLB subgroup column. P value is statistical comparison with the AD column. P values in the high concentration CLB column were not adjusted for multiple comparisons.

On the other hand, our results do not support the Newcastle group's report<sup>7</sup> that 80% of patients with Lewy body dementia present with fluctuating cognitive impairment associated with hallucinations and parkinsonian features. Whereas 23% were reported to have had hallucinations at presentation, the other key symptoms of falls, syncope, and prominent fluctuation were reported less often and with no greater frequency than for the patients with Alzheimer's disease. Less than 50% of the patients had signs of parkinsonism documented at presentation, whether reported by neurologists or by all the physicians irrespective of specialty. Moreover, the Newcastle claim that depression occurs more often in Lewy body dementia at presentation<sup>8</sup> was not supported by our data.

This relatively low frequency of recognition of parkinsonism at presentation also suggests that the clinical diagnostic criteria for Lewy body dementia proposed by the Nottingham<sup>9</sup> and San Diego<sup>10</sup> groups would not be very sensitive for distinguishing early disease, as both require the presence of multiple parkinsonian features.

It must be emphasised that our data collection was retrospective, and the true frequency of occurrence of many of the key symptoms and signs likely was higher. We acknowledge that the absence of reports of falls, syncope, and fluctuation cannot be used to argue that they did not occur. Furthermore, our patient population may not have been representative of all cases of Lewy body dementia, as those that may have had a very rapid course and florid psychiatric features could have been neuropathologically diagnosed through other channels. Nevertheless, our data suggest that such features were not prominent in the presentations of most of the patients with Lewy body dementia.

Another explanation for the difference between our results and those of the Newcastle group<sup>8</sup> is that our patient population was very different from theirs. Our patients were referred from a wide variety of sources by contrast with the Newcastle patients, most of whom were in psychogeriatric units.<sup>4</sup> By selecting similar patients from our brain bank the frequency of reports of psychiatric symptoms would undoubtedly have been higher.

Even in a retrospective study such as this, in which respondents were not systematically asked if certain symptoms had occurred, the reports of hallucinations at presentation in 23% of the patients with Lewy body dementia are very remarkable. Whether patients of all severities, only patients of mild or moderate severity, or only patients in the cortical Lewy body subgroups are considered, hallucinations were more often reported for patients with cortical Lewy bodies than for patients with Alzheimer's disease. Surprisingly, the only exception to this finding was in the subgroup of patients with Lewy body dementia that included Alzheimer's disease (the cortical Lewy body and Alzheimer's disease subgroup), in which no hallucinations were docu-

mented. It is of particular interest that visual hallucinations were specifically mentioned in most of these reports. With the precaution that this study did not assess the occurrence of hallucinations in other dementing illnesses, this finding strongly suggests that visual hallucinations occurring early in a dementing illness argue against Alzheimer's disease as being the sole aetiology.

An incidental finding was the greater tendency for Lewy body dementia to afflict men, by contrast with Alzheimer's disease. Although this tendency has been mentioned by other investigators,<sup>8,16-18</sup> only Galasko *et al*<sup>19</sup> have reported it as significant relative to Alzheimer's disease.

That all of the cases were not examined with antiubiquitin stain is a potential weakness in this study, raising the possibility that the percentage of our dementia cases with cortical Lewy bodies may actually have been higher than 21%. Because we found excellent correlation between the slides stained with antiubiquitin and those stained with haematoxylin and eosin regarding the identification of cortical Lewy bodies, we doubt that the percentage would have been substantially higher. Furthermore, whether or not a more rigorous search for cortical Lewy bodies would have increased the frequency of key feature recognition is not known, for many of the new cases of Lewy body dementia would most likely have been derived from the present Alzheimer's disease group. More judicious scrutiny of the cases with Alzheimer's disease with key features (with additional antiubiquitin slides) could have increased the frequency if some were discovered to have cortical Lewy bodies.

We caution that our results are primarily germane to the study of dementia and represent only part of the total range of disease associated with Lewy bodies. Although the numbers were small, we excluded patients that were treated for Parkinson's disease before onset of the dementia. Similarly, our study did not include patients who may have harboured Lewy bodies but were asymptomatic.<sup>20</sup>

Our results suggest that clinical differences may exist between the cortical Lewy body subgroups, but the few cases in each group limit convincing analysis. Previous studies that mention presentation details are very difficult to compare in this regard because of the lack of standardisation of criteria and objectives. As examples, the Nottingham group<sup>13</sup> did not fully describe their neuropathological findings in their report, and the study by the Newcastle group<sup>8</sup> included cases with cortical Lewy bodies and senile plaques, the study by Gibb *et al*<sup>12</sup> included cases with cortical Lewy bodies only, and the study by Förstl *et al*<sup>11</sup> included cases with cortical Lewy bodies and senile plaques or Alzheimer's disease. None of these studies specifically excluded cases with Lewy body dementia with other neuropathology.

In summary, our results corroborate the advice of the Newcastle group<sup>7</sup> that "clinicians should be aware of the broad spectrum of clinical presentations of cortical Lewy body

disease". Many patients with Lewy body dementia indeed presented with symptoms and signs different from the patient with Alzheimer's disease. In particular, the occurrence of hallucinations in association with their presentations is very noteworthy. On the other hand, many did not seem to be different from Alzheimer's disease, at least regarding the features we studied. Furthermore, the recently proposed criteria<sup>8-10</sup> for the clinical diagnosis of Lewy body dementia would seem not to be very sensitive in its early detection. Further work is needed to confirm our findings and to develop better clinical criteria for its early diagnosis.

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