Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2005;20:89–94
DOI: 10.1159/000086472

Accepted: January 29, 2005
Published online: June 23, 2005

The Alzheimer Variant of Lewy Body Disease: A Pathologically Confirmed Case-Control Study

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Key Words
Alzheimer-type dementia · Lewy body dementia · Histopathology

Abstract
The objective of the study was to identify clinical features that distinguish patients with dementia with Lewy bodies (DLB), who were classified as Alzheimer's disease (AD) patients, from patients with AD. We examined a group of 27 patients from our memory clinic, originally diagnosed with AD, of whom 6 were postmortem found to have DLB. For the present study, we compared cognitive, noncognitive and neurological symptoms between the two groups. We found that there were no differences on ratings of dementia and scales for activities of daily living. Patients with DLB performed better on the MMSE and the memory subtest of the CAMCOG, but there was no difference in any other cognitive domain. Furthermore, genetic risk factors, including family history of dementia or allele frequency of the apolipoprotein ε4, did not discriminate between the two groups, and there were no differences on CCT scans. Taken together, our findings suggest that Lewy body pathology may be present in patients who do not show the typical clinical features which distinguish DLB from AD.

Introduction

In 1990, the Lewy body variant of Alzheimer's disease (AD) [1], also termed senile dementia of Lewy body type [2] or dementia with Lewy bodies (DLB) [3], was described as a distinct neuropathological and clinical form of dementia in the elderly. Autopsy studies have shown that in 15–25% of elderly patients with dementia, Lewy bodies (LBs) are found in the cortex and brainstem in addition to various degrees of Alzheimer-type pathology. According to these studies, DLB may be the second most common cause of dementia after AD [1, 2, 4–6].

As noted in the initial descriptions of the condition, patients with DLB share many clinical features with typical AD including age, family history, history of onset, symptoms, duration of disease, mental status and degree of brain atrophy [7]. Symptoms that distinguish DLB from AD without Lewy body pathology are disproportional impairment of attention, executive function and visuospatial performance as well as mild extrapyramidal findings [1]. In studies on patients who met clinical and pathological criteria for AD, however, no consistent association has been found between the presence of LBs and the frequency of these clinical features [3].

In addition to progressive dementia, the clinical consensus criteria [7] emphasize fluctuation of attention and alertness, recurrent visual hallucinations and spontane-

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ous motor features of Parkinsonism. Impairment of memory may be absent at early stages. Using these criteria, the sensitivity of the clinical diagnosis is 78%, and the specificity is 64% as compared with neuropathological findings [8]. This is consistent with the finding that two thirds of patients with pathologically confirmed DLB have less than two core clinical features [8].

Here, we report on a small group of patients who fulfilled clinical criteria for AD [9] but were identified as having DLB at postmortem examination. The study was designed to determine whether classification of DLB as AD might have been avoided if distinguishing features had been observed, or whether there is a variant of DLB that cannot be separated from AD on clinical grounds.

Methods

Patients

From 1988 to 1992, we conducted a prospective study which was designed to investigate the natural course and possible subtypes of AD [10]. A total of 90 patients were enrolled and re-examined at 12-month intervals for up to 3 years. All patients underwent a thorough diagnostic evaluation, which included psychiatric interview, physical examination, laboratory screening, cranial computed tomography and apolipoprotein E genotyping [11].

Clinical Assessments and Diagnosis

The clinical documentation included information on age, age at onset, years of education at school and family history of dementia. Impairment of cognitive function was assessed using the cognitive section (CAMCOG) of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) [12], which incorporates the Mini-Mental State Examination (MMSE). Out of 8 subscales of this standardized interview, 5 were considered in the present study (orientation, language, memory, praxis and perception). The CAMDEX protocol also provides information on activities of daily living (ADL) obtained from an informant (orientation in and around the home, performing household chores, handling money, eating, dressing, bladder and bowel control). For the present analysis, these variables were combined into an ADL score, higher values indicated greater impairment. Furthermore, informant ratings of non-cognitive symptoms were taken from the CAMDEX standardized interview (hallucinations, paranoid ideation and fluctuating attention). These symptoms were rated as present or absent.

Neurological signs were documented in a standardized form. Of 10 signs recorded, gait disorder and increased muscle tone were selected and combined in a neurological score for the present analysis. Tremor was recorded as part of the CAMDEX documentation. Severity of dementia was rated on the Dementia Scale (DS) [13], the Global Deterioration Scale (GDS) [14] and the Clinical Dementia Rating (CDR) [15].

Based on this extensive information, a consensus diagnosis of AD was made by two experienced clinicians according to ICD-10 research criteria [9]. A probable AD was diagnosed using the NINCDS-ADRDA criteria [16]. In 1996, Rasmussen et al. [17] showed that these diagnoses are 90% accurate. At the time of study, diagnostic criteria for DLB were not available, since they were only introduced in 1992 [18]. Patients who had marked neurological symptoms or a history of cerebrovascular accidents were not included.

Neuropathological Evaluation and Diagnostic Criteria

Brains were fixed in 4% formalin in phosphate-buffered saline for at least 14 days. Representative blocks were embedded in paraffin and processed for routine histology. Sections (4 μm) were cut and stained with hematoxylin and eosin, according to Gallyas and Bielschowsky silver impregnation. Immunohistochemistry was performed with anti-tau antibody AT8 (dilution 1:100; Innogenetics, Ghent, Belgium), anti-synuclein antibody 15G7 (dilution 1:10), anti-β amyloid peptide antibody (1:100; Dako, Glostrup, Denmark) and anti-ubiquitin antiserum (1:300; Dako). Antibody binding was detected using the Dako alkaline phosphatase/anti-alkaline phosphatase system and neufuchsin as chromogen.

The pathological diagnosis was made using established international criteria. Alzheimer's pathology was classified using the CERAD pathologic criteria, based on semiquantitative analysis of neuritic plaques [19], as well as the Braak and Braak classification, based on the distribution of neurofibrillary tangles and neuropil threads [20].

Distribution and frequency of LBs were evaluated according to consensus guidelines for diagnosing DLB [7]. The number of LBs was counted in the therein defined brain regions using α-synuclein immunohistochemistry and was converted into scores of 0 (no LBs), 1 (1–4 LBs) and 2 (>5 LBs) for each area. Based on the total score, cases were divided into 3 subtypes: brainstem predominant, limbic and neocortical.

The neuropathological diagnosis of DLB was made if LBs were present in the diagnostic areas, irrespective of the severity of AD pathology.

The diagnosis of dementia lacking distinctive histopathology (DLDH) and corticobasal degeneration (CBD) was made according to McKhann et al. [21] and Dickson et al. [22], respectively.

Postmortem diagnosis was attempted in as many patients as possible. Of the 66 patients who had died between 1988 and 1997, autopsy was obtained in 27 cases. The clinical diagnosis of AD was confirmed in 19 patients, 6 patients had additional Lewy body pathology and were classified as DLB. Two patients showed no AD-related pathology and were diagnosed as DLDH or CBD. Neuropathological information is shown in table 1.

Apolipoprotein E Genotyping

The apolipoprotein E genotype was determined according to the procedures described previously [23].

Data Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences [24], version 10.0. Demographic data, severity ratings (MMSE, DS, GDS, CDR), CAMCOG subscores, ADL, BEH and neurological scores were compared between AD and DLB patients applying χ^2 tests for frequencies and linear regression analysis for group means, controlling for age at onset and education.

Table 1. Neuropathological information

Case	Sex	Age	Diagnosis	CERAD	Braak and Braak stage	LB pathology
1	F	72	AD	C	VI	none
2	M	74	AD	C	V	none
3	F	68	AD	C	VI	none
4	F	73	AD	C	VI	none
5	F	78	AD	C	VI	none
6	M	83	AD	C	VI	none
7	M	80	AD	C	VI	none
8	F	70	AD	C	V	none
9	M	63	AD	C	V	none
10	F	70	AD	C	V	none
11	F	71	AD	C	VI	none
12	F	72	AD	C	VI	none
13	F	89	AD	C	IV	none
14	M	81	AD	C	V	none
15	F	83	AD	C	V	none
16	F	81	AD	C	V	none
17	F	84	AD	C	V	none
18	F	63	AD	C	VI	none
19	F	70	AD	C	VI	none
20	F	79	DLB	C	V	neocortical
21	F	85	DLB	C	V–VI	neocortical
22	F	80	DLB	C	V–VI	neocortical
23	F	79	DLB	C	V	neocortical
24	F	85	DLB	C	V	neocortical
25	F	80	DLB	C	V–VI	neocortical
26	F	78	DLDH	0	I	none
27	M	69	CBD	B	II	none

Results

Demographic Data

Patients with AD and DLB did not differ significantly regarding gender distribution and years of education. However, DLB patients were significantly older than AD patients (table 2). A family history of dementia was found in 26% in AD and 33% in DLB cases (table 3).

Apolipoprotein E Genotype

Of the 19 patients with AD, 14 were carriers of the apolipoprotein E ε4 allele, whereas only 3 of 6 patients with DLB were ε4 positive. The ε4 allele frequency was 0.42 in the AD group and 0.50 in the DLB group. This difference was not statistically significant (p = 0.12) (table 3).

Cranial Computed Tomography

Brain atrophy was seen in 13 out of 17 patients with AD (76%) for whom CT scans were available and in 5 patients with DLB (83%). This difference did not reach statistical significance (table 3).

Table 2. Demographic data

Variable	AD (n = 19)	DLB (n = 6)	p value
Females:males	15:4	5:1	0.82
Family history, yes:no	5:14	2:4	0.74
Education, years	9.5 ± 1.7	9.0 ± 1.8	0.51
Age at onset, years	66.2 ± 7.9	74.4 ± 3.7	0.03

Figures for education and age at onset are expressed as mean ± SD.

Table 3. Genetic variables and cranial computed tomography (CCT) findings

Variable	AD	DLB	p value
ApoE ε4 allele frequency	0.42	0.50	0.12
Brain atrophy on CCT	0.77	0.83	0.73
Family history of dementia	0.26	0.33	0.74

Severity of Dementia

Although they were significantly older, patients with DLB achieved a higher cognitive performance on the MMSE than patients with AD (table 4). Due to the small sample size, the difference of 4 points on the scale was not of statistical significance. General severity of dementia, as assessed using the DS, GDS or CDR, was not different between the two diagnostic groups.

Cognitive Ability

There was no statistically significant difference on any CAMCOG subscale between the two diagnostic groups (table 4). Fluctuation of attention was not observed in either group.

Noncognitive Symptoms

Hallucinations were present in 2 out of 6 patients with DLB and in 1 out of 19 patients with AD. This difference fell short of reaching statistical significance (table 4).

ADL and Neurological Symptoms

There were no statistically significant differences between the diagnostic groups with regard to these symptoms (table 5). Furthermore, tremor was absent in both groups.

Table 4. Psychopathological symptoms

Variable	AD (n = 19)	DLB (n = 6)	p value
MMSE	14.9 ± 4.9	18.8 ± 3.2	0.06
DS	12.2 ± 4.8	14.7 ± 4.3	0.09
GDS, 4/5/6	3/13/3	1/4/1	1.00
CDR, 1/2/3	8/10/1	3/3/0	0.82
Orientation	3.1 ± 1.9	5.0 ± 3.4	0.94
Language	17.5 ± 5.7	18.7 ± 7.4	0.82
Memory	3.6 ± 3.3	7.5 ± 3.7	0.10
Praxis	6.7 ± 2.6	6.2 ± 3.1	0.67
Perception	4.6 ± 3.2	4.3 ± 2.1	0.89
Delusions, no/yes	17/2	4/2	0.23
Hallucinations, no/yes	19/1	4/2	0.13
ADL	7.0 ± 4.4	8.0 ± 4.2	0.66

Figures are expressed as mean ± SD, except for GDS, CDR, delusions and hallucinations.

Table 5. ADL and neurological symptoms

Variable	AD (n = 19)	DLB (n = 6)	p value
ADL	7.0 ± 4.4	8.0 ± 4.2	0.66
Neurological symptoms, no/yes	17/2	6/0	0.41

Figures for ADL are expressed as mean ± SD.

Discussion

The present study refers to a highly selected group of patients who were referred to a university memory clinic for diagnostic evaluation. All patients included in this study fulfilled ICD-10 research criteria for AD [9]. At postmortem examination, AD was confirmed in 19 of these patients, but 6 subjects were found to have DLB. All cases classified as DLB had severe Alzheimer-related pathology (CERAD C and Braak and Braak stage V–VI) in addition to significant Lewy body counts in diagnostically important areas. In the present paper, we compare cognitive, noncognitive and neurological symptoms between the two groups at the time of enrollment. The objective of the study was to identify clinical features that distinguish patients with DLB who were classified as AD from patients with AD.

Patients with DLB were significantly older at onset of symptoms than AD patients. On ratings of dementia severity, the two groups were identical, the majority of patients showing a moderate degree of intellectual impairment. Furthermore, there was no difference in the ability to carry out ADL. On the MMSE, however, patients with DLB had higher average scores than patients with AD, suggesting that their cognitive performance was better. This is consistent with a nonsignificantly higher score on the memory subtest of the CAMCOG. There was no difference between the groups in any other cognitive domain. This indicates that the profile of cognitive abilities may not be useful for the differentiation between AD and DLB.

Even though present clinical diagnostic criteria for DLB were not available at the time of our study, we feel confident that the clinical assessment covered all the important early signs of DLB. Typical symptoms, such as fluctuating attention, visual hallucinations and tremor, are part of the CAMDEX interview, and neurological symptoms with focus on additional features of Parkinsonism were recorded in a standardized form. Parkinsonian symptoms, in particular tremor, gait disorder and increased muscle tone, were absent in both groups. Another major feature of DLB [7] was absent in the DLB group, namely fluctuating attention. Furthermore, hallucinations were only present in one third of these individuals. There have been previous comparisons between AD and DLB in patients with neuropathologically confirmed diagnosis, which also did not find any differences regarding cognitive impairment, hallucinations and fluctuating attention [25]. A recent study comes to the similar conclusion that patients with significant tangle pathology who are pathologically assigned a DLB diagnosis were clinically indistinguishable from AD [26]. On the other hand, there are authors who report that visual hallucinations are more common in DLB [27, 28] and suggest that the distinction between AD and DLB may be improved by greater emphasis on hallucinations [29]. Furthermore, some studies found a significantly higher impairment of attention in patients with DLB [30] and more fluctuations of attention compared with patients who suffered from AD [31, 32]. Fluctuating attention also has a significant impact on ADL [33].

Genetic risk factors also did not discriminate between the groups; approximately one third of the DLB and AD patients had a positive family history of dementia, and the apolipoprotein E ε4 allele frequency was elevated above control values to a similar extent in both groups. This finding is consistent with several other studies which also found no difference in the ε4 allele frequency between AD and DLB [34–36]. In addition, the frequency of atrophic changes seen on CT scans was not different

between the two groups. Previous studies have found a strong correlation between DLB and occipital deficits in cerebral perfusion [37] and glucose metabolism [38, 39]. However, as was the case in the present study, no changes in occipital brain structure were seen [40] and the CT or MRI findings did not differ between the two types of dementia [41].

Taken together, our findings suggest that Lewy body pathology may be present in patients who do not show any of the clinical features which distinguish DLB from AD according to present diagnostic criteria. This is consistent with the sensitivity of these criteria of 78%, which has been found in clinicopathological correlations [8]. Diagnostic sensitivity may possibly be improved by including more sensitive tests of attention and executive ability in the neuropsychological evaluation and by using the full range of diagnostic possibilities, such as positron emission tomography [39, 42, 43], brain perfusion scintigraphy [44] and liquor markers [45–47].

Acknowledgement

This study was supported in part by the Federal Ministry of Research and Technology, grant No. 701770/3 and the Federal Ministry of Education and Research, grant No. 01/GI9999/1.

We thank Iryna Pigur for excellent experimental assistance.

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