Published in final edited form as:
Arch Neurol. 2008 December ; 65(12): 1634–1639. doi:10.1001/archneur.65.12.1634.

Comparison of Clinical Manifestation in Familial Alzheimer's disease and Dementia with Lewy Bodies

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Abstract

Background—The clinical delineation of Dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) remains unclear.

Objective—To compare the neuropsychological profiles of patients with clinically diagnosed Dementia with Lewy bodies (DLB) and Alzheimer's disease (AD).

Methods—We first compared measures of memory, orientation, language, executive, visual perception and visual construction function between persons with DLB and AD in two Caribbean Hispanic cohorts, including a family dataset (DLB =89; AD: n=118) and an epidemiologic dataset (DLB: n=70; AD: n=157). DLB in the family sample was further divided into i) families with two or more affected family members (DLB), or ii) one affected family member (DLB). To determine whether observed differences in cognitive profiles were driven by heritable factors, we then repeated the analyses in the epidemiologic cohort excluding all familial cases. We applied general linear models adjusting for age, sex, education, disease duration, and APOE-ε4 genotype.

Results—Persons with DLB were in both cohorts more severely impaired in orientation, visual construction and non verbal reasoning after controlling for potential confounders. Persons with 2 or more DLB cases per family had the most severe impairment in episodic and semantic memory, followed by those with one DLB case per family, then by those with AD. When familial AD and DLB cases were excluded from the analysis in the epidemiologic cohort, the differences between the AD and DLB groups persisted but were attenuated.

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Conclusions—Compared to persons with AD, persons with DLB are more severely impaired in various cognitive domains, particularly orientation, visual perception and visual construction. The difference appears strong in familial rather than sporadic DLB. Whether this divergence in cognitive functions is caused by gene-gene or gene-environmental interactions remains unclear.

INTRODUCTION

Dementia with Lewy bodies (DLB) may be the second most common type of degenerative dementia after Alzheimer disease (AD), accounting for 15 to 25% of dementia cases at autopsy (1,2). There is considerable confusion concerning its clinical, neuropathological and genetic delineation from other types of dementia, in particular AD. Clinically, DLB is characterized by progressive cognitive decline accompanied by recurrent visual hallucinations, fluctuating attention and cognition, and motor features of parkinsonism (3). Neuropathological hallmarks are alpha-synuclein-positive Lewy bodies and Lewy neurites predominantly located in brainstem, subcortical nuclei, limbic cortex and neocortex (3-5). However, Lewy bodies and Lewy neurites may occur not only in DLB but also in persons with AD (6), and many patients with DLB have some degree of AD pathology (3).

Establishing the correct diagnosis would have ramifications for treatment. While patients with DLB respond to cholinesterase inhibitors with improvement in cognitive and psychiatric symptoms (7), they show a propensity to have exaggerated adverse reactions to neuroleptic drugs, with a significantly increased morbidity and mortality (8,9).

Better characterization of neuropsychological profiles of DLB and AD could help differentiate both disorders and increase diagnostic sensitivity and specificity. Most previous studies observed a more severe impairment in visual spatial abilities, attention and executive functions in persons with DLB compared to persons with AD (10-12). However controversies exist regarding memory function. While most investigators found DLB patients to have relatively preserved verbal episodic memory (13-19), other found episodic memory to be equally impaired (20-22), Concerning working memory, most prior studies showed similar deficits (20,28,30,31) or more severe deficits (13,17,21) in persons with DLB than AD. Finally, semantic memory has also been reported to be similarly impaired in persons with DLB and with AD (13-15,17,20,[21],[23],24,26-29,31).

The objective of the present study was to compare cognitive profiles in DLB and AD among Caribbean Hispanic families and a population-based epidemiologic cohort that have extended neuropsychological test batteries. We also explored whether differences in cognitive profiles were potentially related to heritable factors.

METHODS

Subjects and settings

The first cohort included one family member with DLB or with AD selected from each family participating in a Caribbean Hispanic family study of dementia, and the second cohort included participants from an epidemiologic study with extended follow up. We restricted the second cohort to those whose self-report ethnicity was Caribbean Hispanic. All participants underwent an in-person interview of general health and function, a structured neurological and functional assessment and a comprehensive neuropsychological test battery.

For the family cohort, 207 Caribbean Hispanic families with a history of AD in at least two living first-degree relatives were recruited between 1998 and 2001. The sampling procedures have been previously described in detail (32). AD diagnosis was made at a

consensus conference of physicians and neuropsychologists, it was based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) (33), and required a Clinical Dementia Rating Scale (CDR) ≥ 1 (39). Multiple sources were used to recruit families. We recruited from clinics in the Dominican Republic and Puerto Rico, as well as the Alzheimer's disease Research Center Memory Disorders Clinic at Columbia University in New York City. In addition, we recruited Hispanic probands identified in the epidemiologic study in northern Manhattan (34) when the informant reported family members with dementia. DLB diagnosis, based on McKeith consensus guidelines, required the presence of a progressive disabling cognitive impairment and one or more of the following clinical features: 1) Fluctuating cognition with pronounced variations in attention and alertness; 2) Recurrent visual hallucinations; and 3) Motor features of Parkinsonism (3). Familial DLB was defined as one or more family members affected with DLB. Specifically, for the present study, a single individual with DLB or AD was selected from each family, leading to inclusion of 118 AD cases and 89 DLB cases in the final analytic sample. From the 89 DLB cases, 69 (77.5%) had one case affected with DLB per family, and 20 (22.5%) had two or more family members affected with DLB.

Participants in the epidemiologic cohort were from a random sample of Medicare recipients 65 years or older and residing in northern Manhattan. The sampling procedures have been described elsewhere (35). Participants were recruited at two points (1992−1994 and 1999−2002). They have been followed up at approximately 18-month intervals with similar assessments at each interval. For the present study we used information from 591 Hispanic participants: 157 AD cases, 70 DLB cases and 364 non-demented controls. Of these, 103 AD cases and 40 DLB cases had a negative family history of dementia in 1st degree relatives (sporadic cases) based in a structured family history interview. AD and DLB criteria were similar to definitions in the family sample. Controls were defined as participants without evidence of cognitive impairment based on neuropsychological and clinical examinations, and a CDR of zero.

The institutional review boards of Columbia University Medical Center and the New York Psychiatric Institute approved recruitment, informed consent, and study procedures of both cohorts.

Clinical Assessment

In both cohorts all participants underwent an in person interview of general health and function, and medical and neurological examination. To identify DLB clinical features, we used the Semiquantified Clinical Fluctuating Cognition (FC) Rating Scale (36), a questionnaire assessing visual hallucinations, and the motor part of the Unified Parkinson's Disease Rating Scale (mUPDRS) (37,38). Spontaneous parkinsonism was deemed present when the person scored greater or equal to 10 on the mUPDRS in the absence of neuroleptic treatment.

Neuropsychological assessment

A comprehensive neuropsychological test battery was given in Spanish. The battery of neuropsychological tests used had been developed and evaluated extensively in Hispanics (40-42). It was designed to assess a broad range of cognitive functions including orientation (10 orientation items from the MMSE) (43), verbal memory (total recall, delayed recall, and delayed recognition sub tests of the Buschke Selective Reminding Test) (44), nonverbal memory (a multiple-choice version of the Benton Visual Retention Test) (45), verbal reasoning (Similarities subtest of the Wechsler Adult Intelligence Scale, Revised [WAIS-R]) (46), nonverbal reasoning (Identities and Oddities subtest of the Mattis Dementia Rating

Scale) (47), naming (15-item version of the Boston Naming Test) (48), verbal fluency (letter and category fluency tasks), auditory comprehension (first six items version of the Complex Ideational Material subtest of the Boston Diagnostic Aphasia Examination) (49), repetition (high-frequency phrases from the Boston Diagnostic Aphasia Examination Repetition of Phrases subtest) (49), visuoconstructional skills (five-item version of the Rosen Drawing Test) (50), and visual perception skills (four-choice matching version of the Benton Visual Retention Test) (45).

APOE genotyping

APOE genotypes were determined as described by Hixson and Vernier (51) with slight modification (52). We classified persons as homozygous or heterozygous for the APOE ε4 allele or not having any ε4 allele.

Statistical analysis

After determining AD, DLB and control groups, we selected the neuropsychological information from the first interval of assessment in which the person was diagnosed with dementia (CDR ≥ 1or questionable dementia (CDR 0.5) for the dementia group, and the last interval of assessment was selected for the control group. DLB was further divided into i) families with two or more persons affected, or ii) families with one person affected. All analyses were performed separately for the family and epidemiologic samples. Unaffected non demented individuals from the epidemiologic study were used as the comparison group for family and epidemiologic cohorts.

We first compared demographic and clinical characteristics between persons with2 or more individuals with DLB in the family, a single patient with DLB in the family, AD and non-demented controls using ANOVA for continuous variables and χ^2 tests for categorical variables. We then used ANOVA and general linear models to compare measures of memory, orientation, language, executive and visual-spatial function between persons with DLB and AD. We performed first unadjusted models and subsequently models adjusted for age, sex, education, APOE-ε4 genotype and disease duration. To further assess whether observed differences in cognitive profiles are driven by heritable factors , we then repeated the analyses in the epidemiologic cohort excluding all familial cases. All analysis was performed using SPSS version 15.0.

RESULTS

In the family cohort, compared with persons without dementia, patients with DLB or AD had lower levels of education, were more often carriers of an APOEe4 allele, were less often smokers, more frequent alcohol consumers, and had less often hypertension, diabetes or myocardial infarction (table 1). The DLB group in the family cohort had more severe dementia cases than the AD group. In the epidemiologic sample there were no differences in demographics or risk factors between AD, DLB and non demented subjects, with the exception of smoking which was less frequent in persons with DLB than persons with AD or non demented subjects.

As expected because we used the McKeith clinical criteria (3), persons with DLB had more fluctuations in cognition, hallucinations, and parkinsonism with a higher mUPDRS score than the AD or control groups. There were no differences in age, education, sex, APOE-ε4 genotype, age at onset of dementia or disease duration between persons with AD and DLB in either cohort.

In both samples persons with DLB were more impaired in orientation, visual perception, and visual construction tasks than persons with AD (table 2). In the family cohort, we observed a

gradient, particularly in episodic and semantic memory, with the most severe impairment in persons with 2 or more family members affected with DLB, followed by families with a single individual with DLB in the family, and then followed by persons affected with AD. When familial AD or DLB cases were excluded from the analysis in the epidemiologic cohort, the differences between the AD and DLB groups were attenuated and became non-significant (Data not shown). We finally repeated these analyses adjusting for age, sex, education, APOEe4 genotype and duration of dementia. In both samples, all associations remained unchanged, with the exception of letter fluency in the family sample, and Benton matching in the epidemiologic cohorts, which were slightly attenuated.

DISCUSSION

Persons with DLB were more severely impaired than persons with AD, particularly in orientation, visual perception and visual construction abilities. Individuals from families with two or more persons affected with DLB had the most severe memory impairment, followed by individuals from families with one person affected with DLB, and then by persons with AD. The differences between DLB and AD groups were attenuated in the epidemiologic cohort when familial cases were excluded.

The cognitive profiles of DLB and AD are consistent with the reported patterns of pathological changes. The neuropathological basis of DLB includes neuronal loss and the presence of Lewy bodies in subcortical nucleus, frontal, temporal, and parietal lobes. This pathological pattern could explain the predominant attentional, executive, and visuospatial dysfunction found in this disease (53). Neuritic degeneration in the CA2−3 region of the hippocampus, what has been reported to be a specific histopathologic feature of Diffuse Dementia with Lewy bodies (54,55), and reduction of dopaminergic projection to the striatum (56), might explain the memory impairment found in DLB. Functional changes in the occipital and temporal lobes, evidenced by hypoperfusion and hypometabolism (57-61), could be related to the perceptual deficit noticed in persons with DLB. Key hallmarks of AD are amyloid plaques, neurofibrillary tangles and neuropil threads predominantly occurring in the hippocampal formation and neocortex. In particular hippocampal dysfunction is thought to underlie the memory impairment in AD.

Most previous neuropsychological studies have shown that persons with DLB had more severe impairments in visual construction, visual perception, attention, and executive functions than persons with AD (10-12). Semantic memory has consistently been reported to be similarly impaired in persons with DLB and with AD (13-15,17,20,[21],[23],24,26-29,31). Concerning episodic and working memory, studies however, are inconsistent. While some investigators found persons with DLB to perform better than persons with AD in episodic memory, (13-19) others found no differences between these groups (20,21,30,62). Concerning to working memory, most prior studies showed similar deficits (20,28,30,31) in DLB and AD, or more severe deficits (13,17,21) in persons with DLB than AD.

Consistent with previous findings (10-12), in this study persons with DLB performed worse than those with AD on visual perception and visual constructive tasks. In contrast to earlier studies that observed more severe episodic memory impairment in patients with AD than with DLB (13,14,16-19,36), we observed similar impairment in AD and DLB cases in the epidemiologic cohort, and more severe impairment in DLB cases than AD cases in the family sample. Semantic memory was equally impaired in persons with AD or DLB in the epidemiologic sample as it has been reported before (13-15,17,20,[21],[23],24,26-29,31); but was more severely impaired in persons with DLB than with AD in the family sample.

A possible explanation for the higher severity of memory dysfunction in DLB than AD in the family cohort is that the pathology underling familial DLB is not only diffuse Lewy body disease but rather Lewy body disease in addition to AD pathology (Lewy Body Variant of AD) while AD cases may predominately have AD pathology only. It has been suggested (64), that the co-occurrence of AD and LB pathology is associated with a greater degree of dementia than found in pure AD or pure DLB. This leads to the potential of an additive or synergistic effect of AD and Lewy body pathologies on memory function and other cognitive domains such as visuospatial or executive function. The fact that in both samples the cognitive deficit was more severe in familial than sporadic cases suggests that genetic factors may underlie these changes.

Alternative explanations accounting for the differences between studies can be methodological issues. For instance, the inclusion of subjects with clinical rather than pathologically confirmed diagnosis could have resulted in misclassification of AD or DLB. Sensitivity of DLB diagnosis still remains poor because of the variability and overlap of symptoms between AD and DLB, but also because it has been proven difficult to characterize and assess the core clinical features of cognitive fluctuations and visual hallucinations. Given the difficulty in teasing apart the contribution of other deficits in processes outside the cognitive domain assessed, it could also be possible that, the poor memory performance in persons with DLB was secondarily to attention or perception impairment rather than memory failure itself. Finally, we cannot exclude the possibility that the attenuation of associations after exclusion of familial cases in the epidemiologic cohort was driven by a smaller sample size and reduced statistical power. However, considering the consistency of these findings with the observation s in the family cohort, we consider this unlikely.

It is important to point out that both cohorts were based on participants coming from communities with a high prevalence of risk factors for morbidity and mortality, such as diabetes and hypertension. If these factors are differentially associated with DLB and AD, this could have resulted in an imprecise estimate of the difference in neuropsychological profiles between AD and DLB. However, we consider this unlikely as in both cohorts the vascular burden between AD and DLB groups was similar.

One limitation of this study is that this is a cross-sectional design. Some of the strengths are the relatively large sample size and the fact that we studied two different cohorts that were especially designed for the diagnosis of cognitive impairment and had extensive neuropsychological assessment.

Compared to AD, DLB is associated with more severe impairment in various cognitive domains, particularly in orientation, visual perception and visual construction. The primary difference is strongest among individuals with familial DLB. Whether this divergence in cognitive functions is caused by gene-gene or gene-environmental interactions remains unclear and needs to be investigated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the participants of the study. This work was supported by grants from the National Institute of Health and the National Institute on Aging: P01-AG07232 and R37-AG15473 (RM) and, and 2P30AG/15294-06 (RL), the Blanchett Hooker Rockefeller Foundation, Charles S. Robertson Gift from the Banbury Fund (RM).

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Table1

Demographic, risk factors and clinical characteristics of the familial and sporadic DLB

	FAMILIAL SAMPLE			EPIDEMIOLOGICAL SAMPLE		
	AD (n=183)	**Sporadic DLB (n=69)**	**Familial DLB (n=20)**	**AD (n=157)**	**DLB (n=70)**	**Control (n=364)**
Age at evaluation, mean (SD)	77.6 (9.5)	77.4 (10.6)	74.5 (10.5)	80.0 (7.2)	81.0 (8.0)	80.0 (7.5)
Female, n (%)	132 (72.1)	50 (72.5)^{a}	10 (50.0)$^{*\int}$	104 (66.2)	47 (67.1)	245 (67.3)
Education years, mean (SD)	5.0 (5.1)^{b}	4.6 (5.5)^{b}	5.0 (4.6)^{b}	6.8 (4.3)	6.2 (4.3)	7.0 (4.8)
APOE −/4 or 4/4 genotype, n (%)	98 (54.1)^{b}	39 (57.4)^{b}	8 (42.1)	42 (31.3)	21 (32.8)	73 (22.7)
Age at onset, mean (SD)	73.6 (10.1)	72.2 (10.9)	69.3 (10.9)	81.1 (7.7)	80.9 (7.6)	n/a
Duration of disease (yrs), mean (SD)	4.0 (5.2)	5.4 (5.8)	5.2 (4.8)	1.6 (3.9)	1.9 (2.6)	n/a
CDR, n (%)						
0	0	0	0	0	0	364 (100)
0.5	18 (9.8)	6 (8.7)	0	47 (29.9)	18 (25.7)	0
1	82 (44.8)	14 (20.3)	6 (30.0)	86 (54.8)	35 (50.0)	0
2	53 (29.0)	11 (15.9)	6 (30.0)	15 (9.6)	13 (18.6)	0
3	30 (16.4)	38 (55.1)	8 (40.0)	9 (5.7)	4 (5.7)	0
Hypertension, n (%)	86 (47.8)^{a}	30 (44.8)^{b}	6 (30.0)^{b}	120 (76.9)	57 (83.8)	278 (77.2)
Diabetes, n (%)	28 (15.6)^{a}	10 (14.5)^{b}	3 (15.0)	39 (25.0)	24 (35.3)	93 (25.8)
Myocardial Infarction, n (%)	12 (6.6)^{a}	2 (3.0)^{b}	2 (10.0)	17 (10.9)	13 (18.6)	45 (12.6)
Smoking, n (%)	45 (26.8)^{a}	15 (23.8)^{b}	5 (25.0)	61 (43.3)	19 (29.7)^{a}	145 (43.9)
Alcohol, n (%)	15 (8.2)	7 (10.8)^{b}	5 (25.0)^{*b}	10 (6.4)	2 (2.9)	16 (4.4)
Fluctuation cognition, n (%)	0	20 (76.9)^{**b}	12 (85.7)^{**b}	0 (0.0)	32 (45.7)^{**b}	8 (2.2)
Visual hallucinations, n (%)	0	14 (56.0)^{**b}	12 (85.7)^{**b}	0 (0)	18 (33.3)^{**b}	2 (1.2)
Other hallucinations, n (%)	1 (2.0)	8 (32.0)^{**b}	8 (57.1)^{**b}	6 (8.6)	15 (29.4)^{**b}	12 (7.1)
Delusions, n (%)	0	4 (14.8)^{**b}	2 (14.3)^{**b}	0	2 (3.6)	0
mUPDRS (0−44), mean (SD)	1.2 (1.8)	15 (10.9)^{**b}	10.2 (10.3)$^{**\int b}$	2.6 (2.7)^{b}	10.6 (7.7)^{**b}	1.2 (2.2)
Repeated fall, n (%)	3 (6.0)	7 (25.9)^{*a}	2 (14.3)	12 (17.6)	10 (30.3)^{b}	22 (11.2)
Neuroleptic sensitivity, n (%)	0	1 (3.7)	1 (7.1)			
Transient Alteration of Consciousness, n (%)	0	3 (11.5)^{*b}	5 (41.7)$^{**\int b}$	0	1 (3.0)	2 (1.0)

‡ used as control group in the analyses of both, the epidemiological and familial sample

[a] statistical differences at a 0.05 level compared to control group

[b] statistical differences at a 0.01 level compared to control group

[*] statistical differences at a 0.05 level compared to AD group

[**] statistical differences at a 0.01 level compared to AD

[∫] statistical differences at a 0.05 level compared to sporadic DLB. SRT, Selective Reminding Test. BVRT, Benton Visual Retention Test. BDAE, Boston Diagnostic Aphasia Examination. MMSE, Mini-Mental State Examination. WAIS-R, Wechsler Adult Intelligence Scale, revised.

Table 2

Differences in neuropsychological test performance between persons with AD, DLB and non-demented controls in the familial sample and the epidemiological sample.

	FAMILIAL SAMPLE			EPIDEMIOLOGICAL SAMPLE		
	AD (n=183)	**Sporadic DLB (n=69)**	**Familial DLB (n=20)**	**AD (n=157)**	**DLB (n=70)**	**Control (n=364)**
SRT Total recall (0−72)	11.2 (11.4)	5.2 (9.4) **	4.0 (7.8) **	18.3 (8.0)	17.3(9.3)	40.0 (7.9)
SRT Delayed recall (0−12)	0.9 (1.5)	0.5 (1.1) *	0.3 (0.6)	1.5 (1.4)	1.1 (1.3)	5.5 (1.9)
SRT Delayed recognition (0−12)	3.6 (4.0)	1.7 (3.4) **	1.4 (2.9) *	6.7 (3.2)	5.5 (3.4) *	11.1 (1.4)
BVRT Matching (0−10)	2.6 (2.9)	1.2 (2.5) **	1.8 (3.4)	3.9 (3.1)	3.0 (2.8) *	7.9 (2.6)
BVRT Recognition (0−10)	1.7 (2.2)	0.6 (1.3) **	1.1 (2.6)	2.5 (2.0)	1.9 (2.3) *	6.0 (2.6)
Rosen Drawing Test (0−5)	1.0 (1.4)	0.4 (0.9) **	0.3 (0.8) *	1.3 (1.0)	0.9 (1.0) **	2.4 (1.1)
Identities and Oddities (0−16)	6.9 (6.0)	3.5 (5.6) **	3.8 (6.1) **	10.3 (5.2)	8.5 (5.6) *	14.0 (3.1)
MMSE Orientation (0−10)	3.9 (3.5)	1.7 (2.9) **	1.6 (2.9) **	7.0 (2.5)	5.7 (2.9) **	9.5 (0.9)
Boston Naming Test (0−15)	6.3 (5.5)	3.0 (4.9) **	2.5 (4.7) **	9.7 (4.4)	8.7 (4.9)	13.4 (2.8)
BDAE Repetition (0−8)	4.3 (3.4)	2.2 (3.4) **	1.6 (3.1) **	6.5 (1.9)	5.8 (2.4) *	7.7 (0.8)
BDAE Comprehension (0−6)	1.7 (1.8)	0.8 (1.4) **	1.2 (2.2)	3.1 (1.6)	2.6 (1.7) *	5.0 (1.1)
Letter Fluency (≥ 0)	2.0 (3.0)	1.1 (2.4) *	0.8 (1.9)	4.2 (3.1)	3.1 (2.8) *	9.2 (5.4)
Category Fluency (≥ 0)	5.1 (4.6)	2.3 (3.9) **	1.8 (3.4) **	8.1 (3.1)	7.3 (3.9)	13.5 (3.3)
WAIS-R Similarities (0−28)	1.8 (3.2)	0.9 (2.4) *	1.1 (2.9)	3.0 (2.9)	2.6 (2.6)	9.9 (6.5)

‡ used as control group in the analyses of both, the epidemiological and familial sample; AD and DLB cases from both cohorts presents statistical differences in all domain assessed compared to control group at a 0.01 level; There were not statistical differences between sporadic DLB and familial DLB

* statistical differences at a 0.05 level compared to AD group

** statistical differences at a 0.01 level compared to AD; SRT, Selective Reminding Test. BVRT, Benton Visual Retention Test. BDAE, Boston Diagnostic Aphasia Examination. MMSE, Mini-Mental State Examination. WAIS-R, Wechsler Adult Intelligence Scale, revised.