

Familial Aggregation of Dementia With Lewy Bodies

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Background: Familial aggregation of dementia with Lewy bodies (DLB) remains unclear.

Objectives: To determine the degree of family aggregation of DLB by comparing DLB risk between siblings of probands with clinically diagnosed DLB and siblings of probands with clinically diagnosed Alzheimer disease in a cohort of Caribbean Hispanic families and to explore the degree of aggregation of specific clinical manifestations (ie, cognitive fluctuations, visual hallucinations, and parkinsonism) in DLB.

Design: Familial cohort study.

Setting: Academic research.

Patients: We separately compared risks of possible DLB, probable DLB, and clinical core features of DLB (cognitive fluctuations, visual hallucinations, and parkinsonism) between siblings of probands with clinically diagnosed DLB (n=344) and siblings of probands with clinically diagnosed Alzheimer disease (n=280) in 214 Caribbean Hispanic families with extended neurologic and neuropsychological assessment.

Main Outcome Measures: We applied general estimating equations to adjust for clustering within families. In these models, age and proband disease status were independent variables, and disease status of siblings was the measure of disease risk and the dependent variable.

Results: Compared with siblings of probands having clinically diagnosed Alzheimer disease, siblings of probands having clinically diagnosed DLB had higher risks of probable DLB (odds ratio [OR], 2.29; 95% confidence interval [CI], 1.04-5.04) and visual hallucinations (2.32; 1.16-4.64). They also had increased risks of possible DLB (OR, 1.51; 95% CI, 0.97-2.34) and cognitive fluctuations (1.55; 0.95-2.53).

Conclusions: Dementia with Lewy bodies and core features of DLB aggregate in families. Compared with siblings of probands having clinically diagnosed AD, siblings of probands having clinically diagnosed DLB are at increased risks of DLB and visual hallucinations. These findings are an important step in elucidating the genetic risk factors underlying DLB and in delineating DLB from other neurodegenerative diseases, such as Alzheimer disease.

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ALZHEIMER DISEASE (AD) IS the most common neurodegenerative disease causing dementia, and dementia with Lewy bodies (DLB) is the second most frequent, with a prevalence of 15% to 36% among cases at autopsy and an incidence of 0.1% a year among the general population.¹⁻⁴ Considerable confusion exists concerning the clinical, neuropathologic, and genetic delineation. Clinically, DLB is characterized by progressive dementia, visual hallucinations, fluctuating cognition, and parkinsonism,⁴ and it is sometimes difficult to differentiate DLB from other common dementias, particularly AD. Neuropathologically, there is overlap between DLB and AD: Lewy bodies occur in both conditions, particularly in the amygdala.

In turn, pathologic amyloid is frequently seen in DLB. The timing of specific symptoms that appear in the course of dementia can help distinguish between AD and DLB. Although visual hallucinations and parkinsonism tend to manifest in DLB from the beginning and hallucinations recur during the entire disease course, these symptoms are less frequent in AD and usually occur later in the disease.

Investigations exploring DLB occurrence in families reported a higher frequency of DLB among participants having a positive family history of dementia compared with participants not having such a family history.⁵ Frequency estimates for DLB were comparable to or higher than frequency estimates for AD.⁶ Psychosis, which includes the DLB core feature of visual hallucinations, is frequent among siblings of

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probands with AD and psychosis.^{7,8} These findings suggest that DLB or individual DLB symptoms may be under genetic influence and aggregate in families. However, the degree to which DLB and its symptoms aggregate in families remains to be determined. It is unclear whether familial aggregation differs between families predominantly affected by DLB or AD or whether it differs among the various core features of the heterogeneous DLB phenotype. Most previous studies exploring familial aggregation used DLB or dementia as the outcome of interest but did not specifically assess aggregation of DLB subfeatures, such as cognitive fluctuations, visual hallucinations, and parkinsonism. Separate analysis of subfeatures may better delineate the biologic mechanisms underlying the heterogeneous DLB phenotype.

The objective of this study was to examine the degree of family aggregation of DLB by comparing DLB risk between siblings of probands with clinically diagnosed DLB and siblings of probands with clinically diagnosed AD in a cohort of Caribbean Hispanic families. Using DLB as the phenotype, we also sought to individually explore the degree of aggregation of specific clinical manifestations (ie, cognitive fluctuations, visual hallucinations, and parkinsonism).

METHODS

Participants were members of a familial cohort of 214 Caribbean Hispanic families with at least 2 living first-degree relatives affected with AD. The sampling procedures were previously described in detail.⁹ Participants were recruited between January 1998 and December 2001 from clinics in the Dominican Republic and Puerto Rico, as well as the Alzheimer Disease Research Center Memory Disorders Clinic at Columbia University in New York City. In addition, we recruited Hispanic probands identified in the community-based Washington Heights–Inwood Columbia Aging Project in the northern Manhattan area of New York City¹⁰ when the informant reported family members with AD. Each participant underwent an in-person interview of general health and function, a structured neurologic and functional assessment, and a comprehensive neuropsychological test battery at the time of study enrollment and at each follow-up interval.

Clinical diagnoses of AD were made at a consensus conference of physicians and neuropsychologists and were based on guidelines from the National Institute of Neurological and Communicative Disorders and Stroke–the Alzheimer Disease and Related Disorders Association.¹¹ Clinical diagnoses of DLB were based on criteria by McKeith et al¹² and required the presence of progressive disabling cognitive impairment plus at least 1 of the following core features: (1) fluctuating cognition with pronounced variations in attention and alertness, (2) recurrent visual hallucinations, and (3) spontaneous motor features of parkinsonism. Diagnosis of DLB was made retrospectively. If an individual demonstrated dementia (as determined in the consensus conference) plus at least 1 DLB core feature, he or she was diagnosed as having possible DLB. If an individual demonstrated dementia plus 2 or 3 DLB core features, he or she was diagnosed as having probable DLB. To exclude individuals with questionable dementia, diagnoses of probable and possible AD and probable and possible DLB required a Clinical Dementia Rating of 1 or higher.¹³

Participants selected for this study were siblings of probands with clinically diagnosed possible and probable DLB (344

from 113 families) and siblings of probands with clinically diagnosed probable AD (280 from 101 families). The institutional review boards of Columbia University Medical Center and the New York Psychiatric Institute approved recruitment, informed consent, and study procedures for both cohorts.

CLINICAL ASSESSMENT

All participants, including probands and recruited family members, received medical, neurologic, and neuropsychological evaluations. To identify clinical features of DLB, we used a modified version of the Clinical Assessment of Fluctuation,¹⁴ a structured questionnaire evaluating DLB features, including symptoms such as cognitive fluctuations, visual hallucinations, and parkinsonism and the motor examination part of the Unified Parkinson's Disease Rating Scale.¹⁵ Cognitive fluctuations were not considered present when they were secondary to medication change. Spontaneous parkinsonism was deemed present when a participant scored 10 or higher on the motor examination part of the Unified Parkinson's Disease Rating Scale in the absence of neuroleptic treatment.

A comprehensive neuropsychological test battery was administered in Spanish. The test battery was developed to assess a broad range of cognitive functions and has been evaluated extensively among Hispanics.^{16,17}

APOLIPOPROTEIN GENOTYPING

APOE genotypes were determined as described by Hixson and Verner¹⁸ with slight modification.¹⁹ We classified participants as having at least 1 copy of APOE $\epsilon 4$ ($\epsilon 4/\epsilon 4$ or $\epsilon 4/-$) vs none ($-/-$).

STATISTICAL ANALYSIS

We first compared demographic and clinical characteristics between siblings of probands with AD and siblings of probands with DLB using analysis of variance for continuous variables and χ^2 test for categorical variables. Because AD or DLB status among individual members of a family cannot be treated as independent variables, we used generalized estimating equations²⁰ to assess familial aggregation of a diagnosis of DLB and the specific symptoms of interest (cognitive fluctuations, visual hallucinations, and parkinsonism) while accounting for familial clustering. In these analyses, the dependent variable was the disease status (DLB diagnosis or cognitive fluctuations, visual hallucinations, and parkinsonism) in siblings, and the independent variables were clinical proband DLB status (proband with DLB vs the reference [proband with AD]) and age (included as a continuous variable). Sex and educational status were included as covariates in subsequent analyses.

RESULTS

Demographics and clinical characteristics of the study groups are summarized in **Table 1**. Compared with siblings of probands having a clinical diagnosis of AD, siblings of probands having a clinical diagnosis of DLB had higher frequencies of DLB, visual hallucinations, and cognitive fluctuations. No differences were noted in age, sex, or educational level. Distributions of APOE $\epsilon 4$ genotypes between siblings of probands with DLB and siblings of probands with AD were also similar. No differences were noted in dementia frequency, dementia severity as measured by the Clinical Dementia Rating Scale, age at onset of dementia, dementia duration, or parkinson-

Table 1. Demographic and Clinical Characteristics Among Siblings of Probands Having Probable Alzheimer Disease (AD) vs Probands Having Dementia With Lewy Bodies (DLB)

Characteristic	Siblings of Probands With AD (n=280)	Siblings of Probands With DLB (n=344)	P Value
DLB, No. (%)			
Possible	46 (16.4)	80 (23.3)	.004
Probable	10 (3.6)	26 (7.6)	.009
Prevalent or incident dementia, No. (%)	194 (69.3)	255 (74.1)	.15
Cognitive fluctuations, No. (%)	32 (11.4)	53 (15.4)	.02
Parkinsonism, No. (%)	18 (6.4)	32 (9.3)	.19
United Parkinson's Disease Rating Scale, mean (SD) score	1.9 (4.6)	2.3 (5.3)	.39
Visual hallucinations % (SD)	13 (4.6)	31 (9.0)	.005
Age at baseline, mean (SD), y	72.7 (11.3)	72.9 (11.7)	.79
Female sex, No. (%)	159 (56.8)	197 (57.3)	.90
Education, mean (SD), y	5.7 (4.8)	6.2 (5.4)	.27
<i>APOE</i> ϵ 4 genotype, No. (%) ^a	82 (29.3)	134 (39.0)	.69
Age at onset of dementia, mean (SD), y	71.3 (11.5)	71.3 (12.5)	.98
Dementia duration, mean (SD), y	4.6 (4.9)	5.2 (5.8)	.25
Country of origin, No. (%)			
Puerto Rico	37 (13.2)	80 (23.3)	.004
Dominican Republic	237 (84.6)	260 (76.5)	
Elsewhere in the Caribbean	6 (2.1)	4 (1.1)	
Clinical Dementia Rating at baseline, No. (%)	(n=276)	(n=336)	
0	98 (35.5)	104 (31.0)	.30
0.5	49 (17.8)	80 (23.8)	
1	68 (24.6)	75 (22.3)	
2	31 (11.2)	33 (9.8)	
3	30 (10.9)	44 (13.1)	

^aGenotype of ϵ 4 ϵ 4 or ϵ 4/-.

Table 2. Differences in Neuropsychological Test Performance at Baseline Between Siblings of Probands With Alzheimer Disease (AD) and Siblings of Probands With Dementia With Lewy Bodies (DLB)

Variable	Unadjusted Score, Mean (SD)		P Value
	Siblings of Probands With AD (n=280)	Siblings of Probands With DLB (n=344)	
Total recall	19.3 (16.6)	20.6 (15.8)	.31
Delayed recall	2.4 (2.6)	2.6 (2.6)	.40
Delayed recognition	6.0 (4.7)	6.4 (4.6)	.34
Benton Visual Retention Test			
Recognition	3.2 (3.2)	3.2 (3.2)	.79
Matching	4.3 (3.7)	4.3 (3.7)	.84
Rosen Drawing Test	1.7 (1.6)	1.6 (1.5)	.39
Mini-Mental State Examination orientation	6.2 (3.9)	6.3 (3.8)	.94
Identities and oddities	8.5 (5.9)	9.1 (5.9)	.23
Wechsler Adult Intelligence Scale-Revised similarities	4.7 (3.4)	5.1 (3.6)	.17
Boston Naming Test	8.7 (5.6)	8.7 (5.5)	>.99
Category fluency	8.4 (6.0)	8.8 (6.0)	.46
Letter fluency	4.7 (4.4)	4.5 (4.4)	.66
Repetition	5.4 (3.3)	5.5 (3.2)	.86
Comprehension	3.1 (2.2)	3.0 (2.1)	.69

Table 3. Generalized Estimating Equation Analysis of Disease Risk Associated With Sibling Age at Follow-up Intervals Relative to Proband Dementia With Lewy Bodies (DLB) Status^a

Variable	Odds Ratio (95% Confidence Interval)	P Value
Probable DLB		
Sibling age	1.05 (1.01-1.09)	.01
Proband DLB status	2.29 (1.04-5.04)	.04
Possible DLB		
Sibling age	1.06 (1.04-1.09)	<.001
Proband DLB status	1.51 (0.97-2.34)	.07
Cognitive fluctuations		
Sibling age	1.01 (0.98-1.03)	.68
Proband DLB status	1.55 (0.95-2.53)	.08
Visual hallucinations		
Sibling age	1.04 (1.00-1.07)	.04
Proband DLB status	2.32 (1.16-4.64)	.02
Parkinsonism		
Sibling age	1.08 (1.04-1.12)	<.001
Proband DLB status	1.30 (0.67-2.50)	.44

^aAll models are adjusted for age, sex, and education. Probands with Alzheimer disease were used as the reference.

ism frequency. There were also no significant differences in neuropsychological test results between the study groups (**Table 2**).

The generalized estimating equation analysis demonstrated increased risks with age among siblings to develop DLB, visual hallucinations, and parkinsonism. Compared with siblings of probands having a clinical diagnosis of AD, siblings of probands having a clinical diagnosis of DLB had higher risks of probable DLB (odds ratio [OR], 2.29; 95% confidence interval [CI], 1.04-5.04; $P = .04$) and visual hallucinations (2.32; 1.16-4.64; $P = .02$) (**Table 3**). They also had increased risks of possible DLB (OR, 1.51; 95% CI, 0.97-2.34) and cognitive fluctuations (1.55; 0.95-2.53), although these were not statistically significant.

COMMENT

We observed a significant association between the clinical diagnosis of DLB in probands and the occurrence of DLB and core features of DLB in siblings. Compared with siblings of probands having AD, siblings of probands having DLB had approximately a 2.3-fold increased risk of probable DLB and visual hallucinations. They had almost a 1.5-fold increased risk of possible DLB and cognitive fluctuations, which approached significance. There was no difference in parkinsonism risk.

Previous studies^{5,6} found a higher frequency of DLB diagnosis among individuals having a positive family history of dementia compared with individuals having no such family history. Consistent with these studies, we found increased DLB risk among siblings of probands with a clinical diagnosis of DLB.

Strengths of this study are the many cohort families and family members who were comprehensively evaluated. Furthermore, diagnoses of probable AD and DLB were based not on a simple family history questionnaire but on complete in-person assessment of all participants (probands

and siblings) using neurologic and neuropsychological evaluation test batteries that were specially designed for diagnosis of cognitive impairment and dementia. A limitation of the study is the lack of histopathologic confirmation of diagnosis, which may lead to potential misdiagnosis of dementia subtypes. However, we tried to reduce heterogeneity by repeating analyses individually for specific clinical symptoms, including cognitive fluctuations, visual hallucinations, and parkinsonism. Another limitation is that low participant educational level may hinder interpretation of psychiatric symptom reporting, especially psychosis. Nevertheless, physicians evaluating individuals from this cohort (who are also Hispanic) are aware of this issue and try to differentiate between real hallucinations and cultural elements.

Our study findings strongly support that DLB and core features of DLB, such as visual hallucinations and cognitive fluctuations, are inherited and aggregate in families. This observation is an important step in elucidating the genetic risk factors underlying DLB and in delineating DLB from other neurodegenerative diseases such as AD.

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