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.

Arch Neurol. 2011;68(1):90-93

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...
related disorders association.11 Clinical diagnoses of dlb were
municative disorders and stroke—the alzheimer disease and
ence of physicians and neuropsychologists and were based on
perted neurologic and functional assessment, and a comprehen-
man in-person interview of general health and function, a struc-
tured family members with ad. Each participant underwent
festations (ie, cognitive fluctuations, visual hallucinations, and parkinson-
imism. separate analysis of subfeatures may better delineate the biologic mechanisms underlying the heterogeneous dlb phenotype.

The objective of this study was to examine the de-
egree 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 ex-
plore the degree of aggregation of specific clinical mani-
estations (ie, cognitive fluctuations, visual hallucina-
tions, and parkinsonism).

participants were members of a familial cohort of 214 carib-
bean hispanic families with at least 2 living first-degree rela-
tives affected with ad. the sampling procedures were previ-
ously described in detail.9 participants were recruited between
January 1998 and December 2001 from clinics in the Domini-
can republic and puerto rico, as well as the alzheimer dis-
ease research center memory disorders clinic at Columbia
university in new york city. In addition, we recruited his-
panic probands identified in the community-based Washing-
ton heights—inwood Columbia aging project in the northern
manhattan area of New york city10 when the informant re-
ported family members with ad. each participant underwent
an in-person interview of general health and function, a struc-
tured neurologic and functional assessment, and a comprehen-
sive neuropsychological test battery at the time of study en-
rollment and at each follow-up interval.

Clinical diagnoses of ad were made at a consensus confer-
ence of physicians and neuropsychologists and were based on
guidelines from the national institute of neurological and com-
municative disorders and stroke—the alzheimer disease and
related disorders association.11 Clinical diagnoses of dlb were
based on criteria by mcKeith et al4,12 and required the pres-
ence 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) recur-
rent visual hallucinations, and (3) spontaneous motor fea-
tures of parkinsonism. Diagnosis of dlb was made retrospec-
tively. 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 indi-
vidual 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 prob-
able 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 prob-
ands with clinically diagnosed possible and probable dlb (344
from 113 families) and siblings of probands with clinically di-
agnosed probable ad (280 from 101 families). the institu-
tional 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 modi-
ified version of the clinical assessment of fluctuation,14 a struc-
tured questionnaire evaluating dlb features, including symp-
toms 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 medica-
tion change. spontaneous parkinsonism was deemed present
when a participant scored 10 or higher on the motor exami-
nation part of the unified parkinson’s disease rating scale in
the absence of neuroleptic treatment.

A comprehensive neuropsychological test battery was ad-
ministered in Spanish. the test battery was developed to as-
sess a broad range of cognitive functions and has been evalu-
et extensively among Hispanics.16,17

Apolipoprotein genotyping
APOE genotypes were determined as described by Hixson and Ver-
nier18 with slight modification.19 we classified participants as hav-
ing at least 1 copy of APOE e4 (e4/e4 or e4/e3) vs none (−/−).

Statistical analysis
We first compared demographic and clinical characteristics be-
tween siblings of probands with ad and siblings of probands
with dlb using analysis of variance for continuous variables
and χ2 test for categorical variables. Because AD or dlb status
among individual members of a family cannot be treated as in-
dependent variables, we used generalized estimating equa-
tions20 to assess familial aggregation of a diagnosis of dlb and
the specific symptoms of interest (cognitive fluctuations, vi-
sual hallucinations, and parkinsonism) while accounting for
familial clustering. In these analyses, the dependent variable
was the disease status (dlb diagnosis or cognitive fluctua-
tions, visual hallucinations, and parkinsonism) in siblings, and
the independent variables were clinical proband dlb status (pro-
band with dlb vs the reference [proband with ad]) and age
(included as a continuous variable). Sex and educational sta-
tus were included as covariates in subsequent analyses.

results
Demographics and clinical characteristics of the study
groups are summarized in Table 1. compared with sib-
lings of probands having a clinical diagnosis of ad, sib-
lings of probands having a clinical diagnosis of dlb had
higher frequencies of dlb, visual hallucinations, and cog-
nitive fluctuations. No differences were noted in age, sex,
or educational level. distributions of APOE e4 geno-
types between siblings of probands with dlb and sib-
lings of probands with ad were also similar. No dif-
fferences were noted in dementia frequency, dementia severity
as measured by the Clinical Dementia Rating Scale, age
at onset of dementia, dementia duration, or parkinson-
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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Siblings of Probands With AD (n=280)</th>
<th>Siblings of Probands With DLB (n=344)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLB, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>46 (16.4)</td>
<td>80 (23.3)</td>
<td>.004</td>
</tr>
<tr>
<td>Probable</td>
<td>10 (3.6)</td>
<td>26 (7.6)</td>
<td>.009</td>
</tr>
<tr>
<td>Prevalent or incident dementia, No. (%)</td>
<td>194 (69.3)</td>
<td>255 (74.1)</td>
<td>.15</td>
</tr>
<tr>
<td>Cognitive fluctuations, No. (%)</td>
<td>32 (11.4)</td>
<td>53 (15.4)</td>
<td>.02</td>
</tr>
<tr>
<td>Parkinsonism, No. (%)</td>
<td>16 (6.4)</td>
<td>32 (9.3)</td>
<td>.19</td>
</tr>
<tr>
<td>United Parkinson’s Disease Rating Scale, mean (SD) score</td>
<td>1.9 (4.6)</td>
<td>2.3 (5.3)</td>
<td>.39</td>
</tr>
<tr>
<td>Visual hallucinations % (SD)</td>
<td>13 (4.6)</td>
<td>31 (9.0)</td>
<td>.005</td>
</tr>
<tr>
<td>Age at baseline, mean (SD), y</td>
<td>72.7 (11.3)</td>
<td>72.9 (11.7)</td>
<td>.79</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>159 (56.8)</td>
<td>197 (57.3)</td>
<td>.90</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>5.7 (4.8)</td>
<td>6.2 (5.4)</td>
<td>.27</td>
</tr>
<tr>
<td>APOE-ε genotype, No. (%)(^a)</td>
<td>82 (29.3)</td>
<td>134 (39.0)</td>
<td>.69</td>
</tr>
<tr>
<td>Age at onset of dementia, mean (SD), y</td>
<td>71.3 (11.5)</td>
<td>71.3 (12.5)</td>
<td>.98</td>
</tr>
<tr>
<td>Dementia duration, mean (SD), y</td>
<td>4.6 (4.9)</td>
<td>5.2 (5.8)</td>
<td>.25</td>
</tr>
<tr>
<td>Country of origin, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>37 (13.2)</td>
<td>80 (23.3)</td>
<td>.004</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>237 (84.6)</td>
<td>260 (76.5)</td>
<td></td>
</tr>
<tr>
<td>Elsewhere in the Caribbean</td>
<td>6 (2.1)</td>
<td>4 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Clinical Dementia Rating at baseline, No. (%)</td>
<td>(n=276)</td>
<td>(n=336)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Genotype of ε4/ε4 or ε4/−.

### 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)

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

\(^a\) All models are adjusted for age, sex, and education. Probands with Alzheimer disease were used as the reference.
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.

Accepted for Publication: February 26, 2010.

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Financial Disclosure: None reported.

Funding/Support: This work was supported in part by the Paul B. Beeson Career Development Award in Aging K23AG034350 (Dr Reitz) and by grant 2F30AG/15294-06 from the Blanchett Hooker Rockefeller Foundation (Dr Lee), by grants P01-AG07232 and R37AG15473 from the National Institute on Aging (Dr Mayeux), and by the Charles S. Robertson Gift from the Banbury Fund (Dr Mayeux).

Additional Contributions: We are grateful to the participating families, the paralitigants, and the patient’s families.