Comparison of Clinical Manifestations in Alzheimer Disease and Dementia With Lewy Bodies

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Background: The clinical delineation of dementia with Lewy bodies (DLB) from Alzheimer disease (AD) remains unclear.

Objectives: To compare neuropsychological profiles in DLB and AD among Caribbean Hispanic family members and participants in a population-based epidemiologic sample using extended neuropsychological test batteries and to explore whether these differences were related to heritable factors.

Design: Cross-sectional study.

Setting: Clinics in northern Manhattan (New York City), the Dominican Republic, and Puerto Rico.

Patients: We compared measures of memory, orientation, language, and executive and visuospatial functioning between patients with DLB vs AD in 2 Caribbean Hispanic cohorts, including a family sample (89 patients with DLB and 118 patients with AD) and an epidemiologic sample (70 patients with DLB and 157 patients with AD). Patients with DLB in the family sample were further categorized as patients having at least 2 family members with DLB or as patients having 1 family member with DLB.

Main Outcome Measures: To determine whether observed differences in cognitive profiles were driven by heritable factors, we repeated analyses in the epidemiologic sample after excluding familial cases. We applied general linear models adjusted for age, sex, educational level, disease duration, and apolipoprotein E ε4 (OMIM 104310) genotype.

Results: Patients with DLB in both samples were more severely impaired in orientation, visuoconstruction, and nonverbal reasoning after controlling for potential confounders. Patients having at least 2 family members with DLB had the most severe impairment in memory, followed by patients having 1 family member with DLB, and then by patients with AD. After excluding familial AD and DLB cases in the epidemiologic sample, the differences between the groups persisted but were attenuated.

Conclusions: Compared with patients having AD, patients having DLB are more severely impaired in various cognitive domains, particularly orientation and visuospatial functioning. The difference seems stronger in familial DLB than in sporadic DLB. Whether this divergence in cognitive functions is caused by gene-gene or gene-environmental interactions remains unclear.

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versaries remain regarding memory function. Although most investigators have found that patients with DLB have preserved episodic memory, others have found it to be equally impaired. Concerning working memory, prior studies showed similar or more severe deficits in patients having DLB compared with patients having AD. Finally, semantic memory has been reported to be similarly impaired in patients with DLB and in patients with AD.

The objective of the present study was to compare neuropsychological profiles in DLB and AD among Caribbean Hispanic family members and participants in a population-based epidemiologic sample using extended neuropsychological test batteries. We also explored whether these differences were related to heritable factors.

METHODS

SUBJECTS AND SETTINGS

The first cohort included 1 family member with DLB or 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-reported race/ethnicity was Caribbean Hispanic. All participants underwent an in-person interview of general health and function, a structured neurologic and functional assessment, and a comprehensive neuropsychological test battery.

For the family sample, 207 Caribbean Hispanic families having at least 2 living first-degree relatives with AD were recruited between June 30, 1998, and June 30, 2001. The sampling procedures have been previously described in detail. Alzheimer disease diagnosis was made at a consensus conference of physicians (R.L., M.M., I.Z.-J.-V., and R.M.) and neuropsychologists based on criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA). It required a Clinical Dementia Rating Scale (CDR) score of 1 or higher. We recruited subjects from clinics in the Dominican Republic and in Puerto Rico, as well as from the Alzheimer Disease Research Center Memory Disorders Clinic at Columbia University, New York City. In addition, we recruited Caribbean Hispanic probands identified in the epidemiologic study in northern Manhattan (New York City) when the informant reported family members with dementia.

Dementia with Lewy bodies diagnosis was based on clinical criteria by McKeith et al and required the presence of progressive disabling cognitive impairment and at least 1 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. The DLB diagnosis was made retrospectively and blinded to the neuropsychological assessment. Therefore, if an individual had dementia (as determined in the consensus conference) plus at least 1 of the DLB core features, the individual was retrospectively assigned a diagnosis of DLB.

Familial DLB was defined as 1 or more family members with DLB (ie, included in this definition were probands with DLB who had 1 or more family members with DLB, as well as probands with DLB who had a family member with dementia diagnosed as other than DLB). The reason to include the latter in the familial DLB group is this: if, in a family there is 1 family member with DLB and another family member with dementia (although he or she does not manifest DLB features at that time), it is probable that the family member will develop DLB symptoms later in life. Therefore, we considered it more reasonable to categorize such subjects as having familial DLB rather than sporadic DLB.

For the family sample, a single individual with DLB or AD was selected from each family, leading to inclusion of 118 patients with AD and 89 patients with DLB in the final analytic sample. Among 89 patients having DLB, 69 (77.5%) had 1 family member with DLB, and 20 (22.5%) had at least 2 family members with DLB.

Participants in the epidemiologic sample were from a random sample of Medicare recipients 65 years or older residing in northern Manhattan. The sampling procedures have been described elsewhere. Participants were recruited at 2 time points (1992-1994 and 1999-2002). They have been followed up at approximately 18-month intervals with similar assessments at each interval. For the epidemiologic sample, we used information from 591 Caribbean Hispanic participants, including 157 patients with AD cases, 70 patients with DLB, and 364 nondemented control subjects. Of these, 103 patients with AD and 40 patients with DLB had a negative family history of dementia in first-degree relatives (sporadic cases) based on a structured family history interview. The 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 with a CDR score of 0.

The institutional review boards of Columbia University Medical Center and New York Psychiatric Institute approved the recruitment and study procedures. Informed consent was obtained from both samples.

CLINICAL ASSESSMENT

In both samples, all participants underwent an in-person interview of general health and function, as well as medical and neurologic examinations. To identify clinical features of DLB, we used the Semiquantified Clinical Fluctuating Cognition Rating Scale, a questionnaire assessing visual hallucinations, and the motor function part (part III) of the Unified Parkinson’s Disease Rating Scale. Spontaneous parkinsonism was deemed present when the patient scored at least 10 on the motor part of the Unified Parkinson’s Disease Rating Scale in the absence of neuroleptic treatment.

NEUROPSYCHOLOGICAL ASSESSMENT

A comprehensive neuropsychological test battery was given in Spanish. The battery of neuropsychological tests had been developed and evaluated extensively among Hispanics. It was designed to assess a broad range of cognitive functions that included the following: orientation (10 orientation items from the Mini-Mental State Examination), verbal memory (Total Recall, Delayed Recall, and Delayed Recognition subtests of the Selective Reminding Test by Buschke and Fuld), nonverbal memory (a multiple-choice version of the Benton Visual Retention Test), verbal reasoning (Similarities subtest of the Mattis Dementia Rating Scale), naming (15-item version of the Boston Naming Test), verbal fluency (Letter and Category Fluency Tasks), auditory comprehension (first 6 items of the Complex Ideational Material subtest of the Boston Diagnostic Aphasia Examination), repetition (high-frequency phrases from the Boston Diagnostic Aphasia Examination repetition of phrases subtest), visuoconstruction skills (3-item version of the Rosen Drawing Test), and visual perception skills (4-choice matching version of the Benton Visual Retention Test).
APOE GENOTYPING

Apolipoprotein E (APOE) genotypes were determined as described by Hixson and Vernier with slight modification. We classified patients as having at least 1 copy of APOE ε4 or none.

STATISTICAL ANALYSIS

After determining the AD, DLB, and control groups, we selected neuropsychological information from the first assessment in which a patient was diagnosed as having dementia (CDR score, ≥1) or questionable dementia (CDR score, 0.5) for the AD and DLB groups, and the last assessment was selected for the control group. The DLB group was further divided into patients having at least 2 family members with DLB or patients having 1 family member with DLB. All analyses were performed separately for the family and epidemiologic samples. Unaffected nondemented individuals from the epidemiologic study served as the control group for the family and epidemiologic samples.

Using analysis of variance (ANOVA) for continuous variables and χ2 test for categorical variables, we first assessed demographic and clinical characteristics in the following: (1) patients having at least 2 family members with DLB, (2) patients having 1 family member with DLB, (3) patients with AD and controls in the family sample, and (4) patients with DLB and AD and controls in the epidemiologic sample. We then used ANOVA and general linear models to compare measures of memory, orientation, language, and executive and visuospatial functioning in patients with DLB vs in patients with AD. We first performed unadjusted models and subsequently models adjusted for age, sex, educational level, 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 sample after excluding all familial cases. All analyses were performed using commercially available statistical software (SPSS version 15.0; SPSS Inc., Chicago, Illinois).

RESULTS

In the family sample, compared with patients without dementia, patients with DLB or AD had lower educational levels, were more often carriers of an APOE ε4 allele, were less often smokers, were more frequent alcohol consumers, and had less frequent hypertension, diabetes mellitus, and myocardial infarction (Table 1). In the family sample, the patients with DLB had more severe dementia than the patients with AD. In the epidemiologic sample, there were no differences in demographics or risk factors among the patients with AD and DLB and controls except for smoking, which was less frequent in patients with DLB than in patients with AD or in controls.

As expected, because we used clinical criteria by McKeith et al, patients with DLB had more fluctuations in cognition, hallucinations, and parkinsonism and a higher motor score on the Unified Parkinson's Disease Rating Scale than patients with AD or controls. There were no differences in age, sex, educational level, APOE ε4 genotype, age at onset of dementia, or disease duration between patients with AD vs DLB in either sample.

In both samples, patients with DLB were more impaired in orientation, visual perception, and visuocognitive tasks than patients with AD (Table 2). In the family sample, we observed a gradient, particu-
Consistent with previous findings, our patients with DLB performed worse than patients with AD on visual perception and visuconstructive tasks. In contrast to earlier studies that observed more severe episodic memory impairment in patients with AD vs DLB, we observed similar impairment in patients with AD and DLB in the epidemiologic sample and observed more severe impairment in patients with DLB vs AD in the family sample. Semantic memory was equally impaired in patients with DLB vs AD in the family sample. Rather Lewy body disease in addition to AD (Lewy body variant of AD), while patients with AD may have AD pathologic features only. It has been suggested that cooccurrence of AD and DLB pathologic conditions is associated with a greater degree of dementia than that found in pure AD or pure DLB. This implies an additive or synergistic effect of AD and Lewy body pathologic features on memory function and other cognitive domains such as visuospatial or executive functioning. The fact that in both samples the cognitive deficit was more severe in familial cases than in sporadic cases suggests that genetic factors may underlie these changes.

Alternative explanations accounting for the differences between study findings can be methodological issues such as ascertainment bias. For instance, the inclusion of patients with clinical diagnoses rather than pathologically confirmed diagnoses could have resulted in misclassification of AD or DLB. Sensitivity of DLB diagnoses remains poor because of the variability and overlap of symptoms between AD and DLB and because it is difficult to characterize and assess the core clinical features of cognitive fluctuations and visual hallucinations.

### Table 1. Demographic and Clinical Characteristics of Patients With Alzheimer Disease (AD), Patients With Dementia With Lewy Bodies (DLB), and Control Subjects in the Family and Epidemiologic Samples

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AD (n=118)</th>
<th>With DLB (n=69)</th>
<th>With DLB (n=29)</th>
<th>AD (n=157)</th>
<th>DLB (n=70)</th>
<th>Control Subjects (n=364)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at evaluation, mean (SD), y</td>
<td>78.2 (9.3)</td>
<td>77.4 (10.6)</td>
<td>74.5 (10.5)</td>
<td>79.3 (7.4)</td>
<td>80.0 (7.9)</td>
<td>79.4 (7.5)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>86 (72.9)</td>
<td>50 (72.5)</td>
<td>10 (50.0)</td>
<td>104 (66.2)</td>
<td>47 (67.1)</td>
<td>245 (67.3)</td>
</tr>
<tr>
<td>Educational level, mean (SD), y</td>
<td>4.6 (4.7)</td>
<td>4.6 (5.5)</td>
<td>5.0 (4.6)</td>
<td>6.8 (4.3)</td>
<td>6.3 (4.3)</td>
<td>7.0 (4.8)</td>
</tr>
<tr>
<td>APQE -/4 or 4/4 genotype, No./total No. (%)</td>
<td>63 (53.8)</td>
<td>39 (58.4)</td>
<td>8 (41.2)</td>
<td>41 (26.9)</td>
<td>15 (24.6)</td>
<td>93 (27.8)</td>
</tr>
<tr>
<td>Age at onset, mean (SD), y</td>
<td>74.1 (10.3)</td>
<td>72.3 (11.0)</td>
<td>69.4 (11.0)</td>
<td>81.8 (7.4)</td>
<td>82.1 (8.1)</td>
<td>…</td>
</tr>
<tr>
<td>Duration of disease, mean (SD), y</td>
<td>4.3 (5.4)</td>
<td>5.4 (5.8)</td>
<td>5.2 (4.8)</td>
<td>2.4 (4.2)</td>
<td>2.6 (4.8)</td>
<td>…</td>
</tr>
<tr>
<td>Origin</td>
<td>Puerto Rico</td>
<td>8 (7.0)</td>
<td>12 (17.9)</td>
<td>8 (40.0)</td>
<td>22 (19.1)</td>
<td>9 (17.0)</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>107 (93.0)</td>
<td>55 (82.1)</td>
<td>12 (60.0)</td>
<td>93 (80.9)</td>
<td>44 (83.0)</td>
<td>170 (73.9)</td>
</tr>
<tr>
<td>Clinical Dementia Rating Scale score, No. (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>364 (100.0)</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>7 (5.9)</td>
<td>6 (8.7)</td>
<td>0</td>
<td>50 (31.8)</td>
<td>18 (25.7)</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>59 (50.0)</td>
<td>14 (20.3)</td>
<td>6 (30.0)</td>
<td>84 (53.5)</td>
<td>35 (50.0)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>35 (29.7)</td>
<td>11 (15.9)</td>
<td>6 (30.0)</td>
<td>15 (9.6)</td>
<td>13 (18.6)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>17 (14.4)</td>
<td>38 (55.1)</td>
<td>8 (40.0)</td>
<td>8 (5.1)</td>
<td>4 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>55 (46.6)</td>
<td>30 (43.5)</td>
<td>6 (30.0)</td>
<td>120 (76.4)</td>
<td>57 (81.4)</td>
<td>278 (76.4)</td>
</tr>
<tr>
<td>Diabetes mellitus, No. (%)</td>
<td>18 (15.3)</td>
<td>10 (14.5)</td>
<td>3 (15.0)</td>
<td>39 (24.8)</td>
<td>24 (34.3)</td>
<td>93 (25.5)</td>
</tr>
<tr>
<td>Myocardial infarction, No. (%)</td>
<td>7 (5.9)</td>
<td>2 (2.9)</td>
<td>2 (10.0)</td>
<td>17 (10.8)</td>
<td>13 (18.6)</td>
<td>45 (12.4)</td>
</tr>
<tr>
<td>Smoking, No. (%)</td>
<td>30 (25.4)</td>
<td>5 (7.2)</td>
<td>5 (25.0)</td>
<td>61 (38.9)</td>
<td>19 (27.1)</td>
<td>145 (39.8)</td>
</tr>
<tr>
<td>Alcohol consumption, No. (%)</td>
<td>9 (7.6)</td>
<td>7 (10.1)</td>
<td>5 (25.0)</td>
<td>10 (6.4)</td>
<td>2 (2.9)</td>
<td>16 (4.4)</td>
</tr>
<tr>
<td>Fluctuation cognition, No. (%)</td>
<td>0</td>
<td>20 (29.0)</td>
<td>12 (60.0)</td>
<td>0</td>
<td>32 (45.7)</td>
<td>8 (2.2)</td>
</tr>
<tr>
<td>Visual hallucinations, No. (%)</td>
<td>0</td>
<td>14 (20.3)</td>
<td>12 (60.0)</td>
<td>0</td>
<td>18 (25.7)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Other hallucinations, No. (%)</td>
<td>0</td>
<td>8 (11.6)</td>
<td>8 (40.0)</td>
<td>6 (3.8)</td>
<td>15 (21.4)</td>
<td>12 (3.3)</td>
</tr>
<tr>
<td>Delusions, No. (%)</td>
<td>0</td>
<td>4 (5.8)</td>
<td>2 (10.0)</td>
<td>0</td>
<td>3 (4.3)</td>
<td>0</td>
</tr>
<tr>
<td>Motor part of the Unified Parkinson's Disease Rating Scale score, range 0–44, mean (SD)</td>
<td>1.0 (1.7)</td>
<td>15.4 (10.9)</td>
<td>10.2 (10.3)</td>
<td>2.6 (2.7)</td>
<td>10.6 (7.7)</td>
<td>12.2 (2.2)</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein E; ellipsis, not applicable.

- a Served as control group in the family and epidemiologic samples.
- b Statistical difference at P < .05 compared with controls.
- c Values do not sum to 69 and 118, respectively, because 2 individuals each were from places other than Puerto Rico and the Dominican Republic.
- d Statistical difference at P < .05 compared with patients having AD.
Given the difficulty in teasing apart the contributions of other deficits in processes assessed outside of the cognitive domain, it could be that the poor memory performance in patients with DLB was secondary to attention or perception impairment rather than memory failure itself. It could also be argued that these differences in cognitive function between patients with AD vs DLB were due to the fact that patients with DLB were more demented than patients with AD. A measure for severity of dementia is the CDR score. However, because the CDR score is partly based on cognitive function, adjustment by the CDR score would be circular and would diminish differences between DLB and AD. Because of that, we preferred to adjust by disease duration rather than by severity of dementia. Finally, we cannot exclude the possibility that the attenuation of associations after exclusion of familial cases in the epidemiologic sample was driven by smaller sample size and reduced statistical power. However, considering the consistency of these findings with the observations in the family sample, we consider this unlikely.

It is important to point out that both samples were composed of participants from communities with high prevalences of risk factors for morbidity and mortality such as diabetes mellitus 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 because in both samples the vascular burden between patients with AD and DLB was similar.

A limitation of this study is the lack of histopathologic confirmation. We tried to avoid potential misdiagnosis by including in the AD group only patients with probable AD who did not meet DLB criteria (ie, did not manifest hallucinations, fluctuations, or significant parkinsonism).

A strength of this study is the large sample size. Furthermore, we studied 2 different samples that were especially designed for the diagnosis of cognitive impairment and had extensive neuropsychological assessment. Compared with AD, DLB is associated with more severe impairment in various cognitive domains, particularly in orientation, visual perception, and visuospatial 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.

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