RESEARCH PAPER

Early neuropsychological discriminants for Lewy body disease: an autopsy series

Hiroshi Yoshizawa,1 Jean Paul G Vonsattel,1,2 Lawrence S Honig1,3,4

Objective To determine which neuropsychological test measures and which symptoms at presentation might best differentiate dementia with Lewy bodies (DLB) from Alzheimer’s disease (AD).

Methods Cases were from the Columbia University Alzheimer’s Disease Research Center, and included cases with pathological diagnosis of pure DLB (n=12), mixed DLB and AD (DLB+AD n=23) and pure AD (n=89) who had Clinical Dementia Rating 0, 0.5 or 1 at their first visit. Clinical symptoms and neuropsychological test measures were compared for pure DLB, DLB+AD and pure AD using univariate analysis of covariance and separate logistic regression analyses.

Results Visual hallucinations, illusions and extrapyramidal tract signs were more frequent as clinical features of the early stage of pure DLB compared with AD. The pure DLB patients showed more impaired visuospatial function than pure AD or DLB+AD patients whereas memory function was more severely impaired in pure AD or DLB+AD than in pure DLB. Analysis of memory subscores suggested that failure of retrieval was the major contributor to the memory deficit of DLB. Multiple logistic regression analysis showed that visuospatial function and delayed memory recognition were independent predictors of pure DLB from pure AD and from DLB+AD. But test measures did not discriminate between DLB+AD and pure AD.

Conclusions Visuospatial function was more affected in pure DLB than in AD while memory retrieval deficit was more affected in AD than in pure DLB, in the early stages of dementia. However, DLB+AD did not show significant neuropsychological difference from pure AD.

INTRODUCTION

Clinical discrimination of dementia with Lewy bodies (DLB) from Alzheimer’s disease (AD) is important for prognostication and may be important for treatment decisions as disease modifying therapies are developed. However, it is often difficult to distinguish DLB from AD, especially in the early stages as the clinical manifestations of DLB overlap those of AD.1

Although numerous studies have reported on the neuropsychological profile of DLB, many of these are based on examinations in the later stages of disease,2 3 and only a few studies are based on the earliest stages of dementia.4 5 There is a general consensus that memory function of DLB patient is relatively preserved compared with AD, but detailed profiles of memory function have been inconsistent.2 3 Also, many studies have not differentiated between persons with ‘pure’ DLB, without significant AD pathology, and mixed DLB and AD (DLB+AD), also known as Lewy body variant of AD.

The objectives of this investigation were (1) to outline the neuropsychological profile of the earlier clinical stages of autopsy confirmed pure DLB, DLB+AD and pure AD and (2) to elucidate best predictors among the neuropsychological testing at the initial visit for differentiation of DLB from AD.

METHODS

Case selection
This study is based on cases from the brain bank of the Alzheimer’s Disease Research Center (ADRC) at Columbia University. All ADRC participants are informed of the opportunity to participate in the brain bank. This research clinic referral based brain bank consists of 607 brains from autopsies performed during the period 1989–2010. Current autopsy rate is about 50%. Cases were selected for this study if they met a primary neuropathological diagnosis of DLB, AD or DLB+AD and presented with Clinical Dementia Rating5 (CDR) ≤1 and had neuropsychological testing at the initial visit. This resulted in a study set of 35 patients with DLB (12 patients with pure DLB without significant AD pathology and 23 patients with DLB+AD) and 89 patients with pure AD. The ADRC protocol was approved by the institutional review boards of the New York State Psychiatric Institute and Columbia University.

Clinical assessment
At the initial visit to our center, all patients had a medical history, physical and neurological examinations, and neuropsychological test battery. A modified form of the Unified Parkinson Disease Rating Scale6 was used to rate extrapyramidal motor signs. For this study, subjects with mild–moderate level of at least one motor sign were considered to have extrapyramidal tract signs. Visual hallucinations, illusions and other mental status were assessed by the Columbia University Scale for Psychopathology in Alzheimer’s Disease, which is a semi-structured informant based rating scale.7 Clinical diagnoses were made at a consensus conference of neurologists and neuropsychologists. Clinical diagnosis of AD was made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer’s Disease and Related Disorders Association.8 Clinical diagnosis of probable DLB required cognitive decline with ‘probable DLB’ based on the Consensus Guidelines for DLB.9

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Neuropsychological assessment
The neuropsychological test battery included the Mini-Mental State Examination, Selective Reminding Test (SRT), the 15 item Boston Naming Test, verbal fluency tests for letter (CFL) and category (animal), the five item Rosen Drawing Test (RDT) and the Digit Span subtest from the Wechsler Memory Scale-revised. SRT sub-measures used in this study included total recall (SRT-TR), long term retrieval (SRT-LTR), long term storage, delayed free recall (SRT-DR) and delayed recognition (SRT-DRcg). For multiple logistic regression analysis, T scores of the neuropsychological tests were used based on local age and education adjusted norms in our institute, except for Digit Span for which T scores were based on the National Alzheimer’s Disease Centers’ Uniform Data Set. We categorised Digit Span forward task as an indicator of working memory, STR-LTR as memory encoding, SRT-DR as memory retrieval and SRT-DRcg as memory storage. The difference between SRT-DRcg and SRT-DR was used as a measure of memory retrieval failure.

Neuropathological evaluation
Neuropathological assessment was performed as described previously, including haematoxylin–eosin, modified Bielschowsky silver stain and immunohistochemistry for beta-amyloid, phosphorylated tau and alpha-synuclein. All cases were rated according to Braak et al. The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) and National Institute on Aging–Reagan Institute (NIA-RI) criteria. All of the AD cases met the criteria of Braak stage ≥4 neurofibrillary pathological findings, and also met CERAD neuropathological criteria for definite AD. The pure AD cases showed no Lewy bodies other than in the amygdala. All of the DLB cases, including concomitant AD pathology cases (DLB+AD), met the consensus guidelines for establishing the neuropathological diagnosis of DLB. Cases with pure DLB did not demonstrate significant AD pathology (Braak stage≤3, and NIA-RI criteria low likelihood). According to the assessment of the likelihood of a clinical syndrome of DLB based on the Third Report of the DLB Consortium, all 12 of the ‘pure DLB’ cases had ‘high likelihood’, the 23 DLB+AD cases included five ‘low likelihood’, 15 ‘intermediate likelihood’ and three ‘high likelihood’, and of the 89 ‘pure’ AD cases, 10 had ‘low likelihood’ because of the presence of sparse Lewy bodies.

Statistical analyses
Baseline characteristics were compared among the three groups (pure AD, DLB+AD, pure DLB) using χ² tests or Fisher’s exact test for nominal data and analysis of variance (ANOVA) test for continuous variable. Univariate analysis of covariance (ANCOVA), with age at neuropsychological evaluation, gender, year of education and CDR score as covariates, was used to compare the raw scores of each neuropsychological test.

To identify independent predictors within neuropsychological variables for differentiation of pure DLB from pure AD, for differentiation of pure DLB from DLB+AD and for differentiation of DLB+AD from pure AD, all T scores of neuropsychological variables with p values<0.20 in the univariate analysis were included in the separate multiple logistic regression analysis using a forward stepwise method. Statistical analysis was performed using IBM SPSS V.19 (IBM Corp, New York, New York, USA).

RESULTS
Comparison of clinical features
The pure DLB group, DLB+AD group and pure AD group did not differ significantly for any of the demographic features (table 1). Multiple paired comparison demonstrated increased frequency of visual hallucinations in pure DLB compared with pure AD (Fisher’s exact test, p=0.002) and DLB+AD (p=0.005) (table 1). There was also increased frequency of extrapyramidal tract signs and visual illusions in pure DLB compared with pure AD at the initial presentation (Fisher’s exact test, p=0.001, p=0.018, respectively). No group differences were detected with regard to the other neuropsychiatric symptoms.

Table 1 Demographics of the patient groups

<table>
<thead>
<tr>
<th>Pathological group</th>
<th>DLB+AD (n=23)</th>
<th>Pure AD (n=89)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of onset (years)</td>
<td>68.5 (6.2)</td>
<td>66.0 (8.6)</td>
<td>0.695†</td>
</tr>
<tr>
<td>Age at initial visit (years)</td>
<td>71.9 (5.4)</td>
<td>69.8 (8.5)</td>
<td>0.749†</td>
</tr>
<tr>
<td>Age at death (years)</td>
<td>79.6 (7.0)</td>
<td>77.6 (10.4)</td>
<td>0.536‡</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>11.1 (3.7)</td>
<td>11.1 (4.9)</td>
<td>0.536‡</td>
</tr>
<tr>
<td>Education (years)</td>
<td>17.4 (2.2)</td>
<td>15.3 (4.6)</td>
<td>0.322‡</td>
</tr>
<tr>
<td>Gender (male %)</td>
<td>75.0</td>
<td>65.2</td>
<td>0.086§</td>
</tr>
<tr>
<td>Race (White/Black/Hispanic/other)</td>
<td>12/0/0/0</td>
<td>21/1/1/0</td>
<td>0.872§</td>
</tr>
<tr>
<td>Blessed Functional Activity Scale</td>
<td>2.8 (1.7)</td>
<td>2.3 (1.2)</td>
<td>0.450†</td>
</tr>
<tr>
<td>CDR†</td>
<td>0.63 (0.31)</td>
<td>0.70 (0.29)</td>
<td>0.377†</td>
</tr>
<tr>
<td><strong>Clinical symptoms (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal signs</td>
<td>54.5 (n=11)</td>
<td>19.0 (n=21)</td>
<td>0.002§</td>
</tr>
<tr>
<td>Visual hallucinations</td>
<td>44.4 (n=9)</td>
<td>0 (n=20)</td>
<td>0.002**</td>
</tr>
<tr>
<td>Illusions</td>
<td>33.3 (n=9)</td>
<td>5.0 (n=20)</td>
<td>0.020***</td>
</tr>
<tr>
<td>Delusions</td>
<td>11.1 (n=9)</td>
<td>11.8 (n=17)</td>
<td>0.564¶</td>
</tr>
<tr>
<td>Agitation</td>
<td>22.2 (n=9)</td>
<td>12.5 (n=16)</td>
<td>0.422‡</td>
</tr>
</tbody>
</table>

Values are presented as mean (SD) unless otherwise indicated. Bonferroni correction was applied to all paired comparisons.

*Pure DLB>pure AD, p=0.001; **pure DLB>pure AD, p=0.002; pure DLB>DLB+AD, p=0.005; †pure DLB>pure AD, p=0.018.
†CDR: Clinical Dementia Rating; AD, Alzheimer disease; ANOVA, analysis of variance; RDT, Digit Span subtest from the Wechsler Memory Scale-revised. "p<0.05; **p<0.01; †p<0.001; §Fisher’s exact test.
symptoms. Table 2 shows the initial clinical diagnoses at the first visit. More than half of the patients had initial diagnoses of ‘non-demented’ because their CDR was 0 or 0.5. Among patients with CDR 1, those in the pure AD pathology group were correctly clinically diagnosed as AD in 43 out of 46 cases (sensitivity 93.5%, specificity 42.9%). Among patients with CDR 1 who had DLB pathology, only two of 14 had a clinical diagnosis of DLB (see table 2; sensitivity 14.3%, specificity 100%).

Comparison of neuropsychological tests

The neuropsychological performance of the three subjects groups (pure DLB, DLB+AD and pure AD) differed only on RDT and SRT-DRcg, after controlling for age, gender, education and CDR (ANCOVA, p=0.004, p=0.001, respectively) (table 3). Multiple pairwise comparison of the three groups confirmed significant differences between pure AD and pure DLB (RDT, p=0.006 and SRT-DRcg, p=0.001). The pure AD group also had significantly lower RDT and higher SRT-DRcg scores than the DLB+AD group (p=0.005, p=0.044, respectively). The difference between SRT-DRcg and SRT-DR in the pure DLB group was significantly larger than in the pure AD group (p=0.038, post hoc analysis; p=0.043).

The neuropsychological performance of the four subject groups according to the DLB likelihood criteria (no likelihood, low likelihood, intermediate likelihood and high likelihood) were also compared (table 4). The ‘high likelihood’ group had significantly lower RDT scores than the ‘low likelihood’ group (p=0.013, post hoc analysis; p=0.007). The ‘no likelihood’ group had significantly lower SRT-DRcg scores than the ‘high likelihood’ group (p=0.003, post hoc analysis; p=0.002). The difference between SRT-DRcg and SRT-DR in the ‘high likelihood’ group was significantly larger than in the ‘no likelihood’ group (p=0.017, post hoc analysis; p=0.035).

Predictive value of neuropsychological tests

As RDT and SRT-DRcg were significantly different, we performed a logistic regression analysis using a stepwise forward selection method. The result showed that RDT and SRT-DRcg remained as independent predictors of pure DLB compared with pure AD in the final model (table 5). Similarly, these tests remained predictors of pure DLB versus DLB+AD (table 5). However, there were no predictors of DLB+AD versus pure AD.

DISCUSSION

Our autopsy based sample of cases with DLB with or without AD pathology in a research clinic cohort showed differences between DLB and AD with respect to clinical symptoms. We found that extrapyramidal tract signs, visual hallucinations and illusions were more frequent in pure DLB compared with pure AD of the early stage, as has been previously demonstrated.2–3 On neuropsychological testing, pure DLB patients showed greater visuospatial impairment than pure AD and DLB+AD patients, while they showed less memory recognition impairment than pure AD patients. These findings are consistent with prior studies.2–3 We did not find differences between DLB and AD in performance on the attentional task and verbal fluency task, although others have found this.2–4 This may be related to the measures used, or to our restriction of cases to those with presenting CDR=1 (ie, mild cases).

Overall memory testing using SRT immediate or SRT-DR did not show significant differences between pure DLB, DLB+AD and pure AD. However, on SRT-DRcg, pure DLB cases were significantly less impaired than pure AD cases and DLB+AD cases. Pure DLB cases showed a normal range in SRT-DRcg at their initial visit. More than half of the patients had initial diagnoses of ‘non-demented’ because their CDR was 0 or 0.5. Among patients with CDR 1, those in the pure AD pathology group were correctly clinically diagnosed as AD in 43 out of 46 cases (sensitivity 93.5%, specificity 42.9%). Among patients with CDR 1 who had DLB pathology, only two of 14 had a clinical diagnosis of DLB (see table 2; sensitivity 14.3%, specificity 100%).

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### Table 2 Clinical diagnosis at initial visit and performance of clinical diagnosis of dementia patients

<table>
<thead>
<tr>
<th>Pathological group</th>
<th>Pure DLB (n=12)</th>
<th>DLB+AD (n=23)</th>
<th>Pure AD (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia total</td>
<td>4</td>
<td>10</td>
<td>46</td>
</tr>
<tr>
<td>Probable AD</td>
<td>1</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>AD+other dementia</td>
<td>0</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>DB</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CBD</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Unclassified dementia</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Non-demented total</td>
<td>8</td>
<td>13</td>
<td>43</td>
</tr>
<tr>
<td>MCI</td>
<td>8</td>
<td>13</td>
<td>42</td>
</tr>
<tr>
<td>No cognitive decline</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathological group</th>
<th>DBL pathology (n=14)</th>
<th>Pure AD (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance of clinical diagnosis of dementia patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>14.3</td>
<td>93.5</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>100</td>
<td>42.9</td>
</tr>
</tbody>
</table>

AD, Alzheimer disease; CBD, corticobasal degeneration; DLB, Dementia with Lewy bodies; MCI, mild cognitive impairment.

### Table 3 Comparison of neuropsychological test scores

<table>
<thead>
<tr>
<th>Pathological group</th>
<th>Pure DLB (n=12)</th>
<th>DLB+AD (n=23)</th>
<th>Pure AD (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>24.4 (2.7)</td>
<td>21.8 (5.0)</td>
<td>21.2 (4.8)</td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span forward</td>
<td>5.75 (0.62)</td>
<td>5.74 (1.18)</td>
<td>5.69 (1.19)</td>
</tr>
<tr>
<td>Digit Span backward</td>
<td>4.08 (0.51)</td>
<td>3.52 (0.99)</td>
<td>3.54 (1.19)</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRT-TR</td>
<td>28.33 (7.66)</td>
<td>22.17 (8.51)</td>
<td>24.16 (6.68)</td>
</tr>
<tr>
<td>SRT-LTR</td>
<td>11.42 (7.79)</td>
<td>9.13 (8.73)</td>
<td>8.40 (8.18)</td>
</tr>
<tr>
<td>SRT-LTS</td>
<td>14.00 (9.46)</td>
<td>11.22 (10.96)</td>
<td>10.43 (10.12)</td>
</tr>
<tr>
<td>SRT-DR</td>
<td>2.67 (2.23)</td>
<td>1.43 (1.80)</td>
<td>1.24 (1.90)</td>
</tr>
<tr>
<td>SRT-DRcg</td>
<td>11.08 (0.90)</td>
<td>8.48 (2.37)</td>
<td>7.61 (2.99)</td>
</tr>
<tr>
<td>SRT-DRcg−SRT-DR</td>
<td>8.42 (2.02)</td>
<td>7.04 (2.14)</td>
<td>6.37 (2.40)</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal fluency</td>
<td>10.83 (6.37)</td>
<td>9.83 (5.61)</td>
<td>10.16 (6.21)</td>
</tr>
<tr>
<td>CFL letter fluency</td>
<td>11.22 (5.37)</td>
<td>9.77 (4.49)</td>
<td>10.46 (5.56)</td>
</tr>
<tr>
<td>BNT-15</td>
<td>14.25 (1.22)</td>
<td>12.70 (2.67)</td>
<td>12.83 (1.97)</td>
</tr>
<tr>
<td>Visuospatial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDT-5</td>
<td>2.50 (1.00)</td>
<td>3.30 (1.02)</td>
<td>3.07 (1.12)</td>
</tr>
</tbody>
</table>

Values are presented as mean (SD). Bonferroni correction was applied to all paired comparisons.

*Pure DLB>pure AD, p=0.001; pure DLB+DLB+AD, p=0.044; **pure DLB>pure AD, p=0.043; ***pure DLB-pure AD, p=0.006 and pure DLB+DLB+AD, p=0.005. AD, Alzheimer disease; BNT, Boston Naming Test; DLB, dementia with Lewy bodies; MMSE, Mini-Mental State Examination; RDT, Rosen Drawing Test; SRT, Selective Reminding Test; SRT-DR, SRT delayed free recall; SRT-DRcg, SRT delayed recognition; SRT-DRcg−SRT-DR, difference between SRT-DRcg and SRT-DR; SRT-LTR, SRT long term retrieval; STR-LTS, SRT long term storage; SRT-TR, SRT total recall.
presenting stage. Creating a ‘memory retrieval failure score’ by subtracting SRT-DR from SRT-DRcg, pure DLB cases also showed less impairment than pure AD. These finding suggest that DLB showed retrieval failure rather than a true encoding deficit, the latter of which is more characteristics of AD patients.

The underlying mechanism of memory function of DLB has not been fully elucidated. Prior investigators have similarly found that a deficit in retrieval plays a greater role in memory impairment of patients with DLB than AD.25 26 DLB patients show neuronal losses in the subcortical nuclei, perhaps affecting the frontal–subcortical circuit and this may be the mechanism of retrieval dysfunction. The principal pathology of AD is in the hippocampus, entorhinal cortex and the surrounding medial temporal areas, explaining the predominant dysfunction in memory encoding. The difference between delayed recall and recognition score may be helpful in differentiating DLB from AD.

We attempted to determine whether logistic regression analysis could provide improved discrimination of pure DLB versus DLB+AD versus pure AD. The result showed that RDT and SRT-DRcg were independent predictors of pure DLB pathology (table 5). Our result showed that visuospatial dysfunction and memory retrieval failure were helpful in distinguishing pathologically proven pure DLB from pure AD and also even from DLB+AD in the early stage, but discrimination of DLB+AD from pure AD was not achieved. Prior studies have shown that a diagnosis of DLB has high specificity but low sensitivity, and the reason for this may be because the phenotypes of some DLB patients are so close to AD.27 28 Our results confirmed that mixed pathology (DLB+AD) may challenge neuropsychological testing discrimination of DLB from AD.

In patients of mixed of DLB+AD pathology, the relative contribution of these two pathologies to clinical symptoms has not been clearly defined. Some have suggested that the Lewy body neuropathology significantly changes the cognitive presentation of AD.29 30 Others have suggested that Lewy and Alzheimer-type pathologies are co-contributors31 and some have suggested that the AD pathology is dominant in the mild to moderate stage of dementia.32–34 The DLB Consensus Guidelines1 included a table suggesting that a combination of high Lewy bodies with low AD pathology made it less likely. However, our comparison of neuropsychological performance according to likelihood criteria showed similar but less robust findings compared with the pathological grouping of DLB, mixed DLB+AD and pure AD. Our logistic regression analyses were broadly consistent with the ANOVA findings; we could not differentiate DLB+AD from pure AD by clinical and neuropsychological findings. The similarities in clinical features between DLB+AD and pure AD likely contribute to the low sensitivity and low accuracy in the clinical diagnosis of DLB.
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Our study has some limitations. First, this study involves a research clinic referral population and this may not be representative of the general population. Second, there are gender differences between DLB and AD subjects, but we have adjusted for these and, furthermore, reanalysis using a randomly selected AD group with the same percentage of males in the Lewy body groups did not change the results (data not shown). Third, the number of pure DLB was small. Further studies comparing DLB and AD in larger samples of autopsy verified patients would be useful. In the clinical setting, data on brain dopamine transporter imaging or cardiac iodine-123 metaiodobenzylguanidine scintigraphy might improve detection of Lewy pathology, and data on amyloid imaging could assist in the determination of AD pathology. Fourth, we do not have sufficient longitudinal neuropsychological test data to determine if rate of change measures might be more useful. Finally, the particular neuropsychological tests used in this study may not have been adequately comprehensive—for example, they are not tests of frontal or executive function such as the Wisconsin Card Sorting Test or Trail Making Test, which might have improved the clinical diagnosis.

In conclusion, data from our study suggest that: (1) in pure DLB, visuospatial function is more affected than in pure AD or DLB+AD, and in pure AD or DLB+AD, memory dysfunction is more severe than in pure DLB, even in the very mild stages of dementia; (2) memory dysfunction in DLB may represent retrieval more than encoding deficits; and (3) the clinical profile of mixed DLB+AD pathology is so similar to pure AD that it is difficult to clinically differentiate these groups at early stages of disease.

Contributors HY and LSH contributed to the study concept and design of the article, interpretation of the data, drafting the article and revising it. JPGV contributed to the pathological evaluation and review of the article.

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Competing interests None.

Ethics approval The study was approved by the institutional review boards of the New York State Psychiatric Institute and Columbia University.

Provenance and peer review Not commissioned; externally peer reviewed.

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