Published in final edited form as:

Neurobiol Aging. 2010 October ; 31(10): 1805–1813. doi:10.1016/j.neurobiolaging.2008.09.017.

Prodromal clinical manifestations of neuropathologically confirmed Lewy body disease

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Abstract

The mild cognitive impairment (MCI) stage of dementia with Lewy bodies (MCI-DLB) has not yet been defined, but is likely to differ in the MCI stage of Alzheimer's disease (MCI-AD). To determine whether clinical features distinguish MCI-DLB and MCI-AD, 9 cases of neuropathologically confirmed MCI-DLB and 12 cases of MCI-AD were compared. No significant differences were found between MCI-DLB and MCI-AD cases in age at death, gender, ApoE status, education, time followed while clinically normal, or duration of MCI. MCI-DLB and MCI-AD cases differed clinically in the expression of Parkinsonism ($P = 0.012$), provoked hallucinations or delirium ($P = 0.042$), or the presence of any of these noncognitive symptoms of DLB ($P < 0.0001$). Letter fluency ($P = 0.007$) was significantly lower and Wechsler Logical Memory I ($P = 0.019$) was significantly higher in MCI-DLB compared to MCI-AD cases. These data demonstrate the feasibility of differentiating underlying pathologic processes responsible for cognitive decline in the preclinical disease state and suggest that further refinement in diagnostic criteria may allow more accurate early detection of prodromal DLB and AD.

Keywords

Mild cognitive impairment; Alzheimer's disease; Dementia with Lewy bodies

1. Introduction

The clinical phenotype of early, predementia, dementia with Lewy bodies (DLB) is unknown. Early clinical changes that predate the development of a symptom complex sufficient to meet DSM-IV criteria for dementia likely occur in all slowly progressive degenerative disease states, such as Alzheimer's disease (AD) and DLB (Busse et al., 2003, 2006; Jicha and Petersen, 2007; Lambon Ralph et al., 2003; Panza et al., 2007; Petersen,

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Conflict of interest The authors report no conflicts of interest.

2007; Winblad et al., 2004). The early predementia clinical state of AD, characterized by amnesic difficulties, is embodied by the proposed diagnostic criteria of mild cognitive impairment (MCI-AD) (Jicha and Petersen, 2007; Petersen, 2007; Winblad et al., 2004). While there is much debate as to the usefulness and specific criteria for the diagnosis of MCI, the recognition that such a clinical entity exists has spurred research into the early predementia detection of AD. Such research endeavors have proved useful in the identification of individuals at risk for the development of AD (Bruscoli and Lovestone, 2004; Chong and Sahadevan, 2005; Griffith et al., 2006; Modrego, 2006; Petersen, 2007; Petersen et al., 1999, 2001; Winblad et al., 2004). These discoveries have allowed the development of the first wave of secondary prevention trials for AD (Petersen et al., 2005). Elucidation of the predementia, clinical phenotype of DLB (MCI-DLB) may be similarly useful in the study of the clinical progression of disease, and allow early therapeutic intervention for persons with DLB.

Lewy body pathology (LBP) is found in the postmortem brain of all individuals who have suffered from Parkinson's disease (PD) and DLB. LBP is also seen in some cases of AD (termed the Lewy body variant of AD, LBV), and in the brains of normal persons who have been autopsied (Del Tredici et al., 2002; Dickson, 2002; Lippa et al., 1994; McKeith et al., 2004; McKeith, 2006; Parkkinen et al., 2005). The latter observation suggests that the pathological features of DLB may predate clinical diagnosis in many cases. It further supports the rationale for early, clinical, predementia detection of disease states related to the pathological development of LBP in the brains of affected individuals.

The clinical phenotype of DLB is characterized by the presence of at least two of the three core clinical criteria: (1) Parkinsonism; (2) early hallucinations, delusions, and paranoia; and (3) severe fluctuations in cognitive state. The diagnosis of DLB is also supported by the findings of: (1) depression, (2) hypersensitivity to neuroleptics, and (3) REM sleep behavior disorder (RBD) (McKeith, 2006). While these features can also be seen in other pathological disease states such as AD, early manifestation of these symptoms raises the index of suspicion of DLB in the discerning clinician.

A diagnosis of Parkinson's disease that predates the development of cognitive or psychiatric symptoms by more than 1 year shifts the diagnosis from DLB to PD dementia (PDD) (Lippa et al., 2007; McKeith, 2006). Although there remains some debate as to the validity of such distinction, diagnostic criteria seeking to establish uniformity between clinicians have supported this approach (Lippa et al., 2007; McKeith, 2006). The determination of the degree of Parkinsonism necessary to shift the clinical diagnosis is purely subjective (Lippa et al., 2007; Louis and Bennett, 2007). The clinical acuity, methods, and operational definition used to determine a diagnosis of Parkinsonism may differ significantly between clinicians and centers (Lippa et al., 2007). Likewise, early psychiatric features of DLB are often attributed to primary psychiatric conditions and fluctuations to medical illness. Mild Parkinsonism, psychiatric features, and hallucinations can be seen in many individuals that do not exhibit the hallmark pathological features of DLB at autopsy. It is unclear to what degree these clinical features are predictive of pathological DLB in the predementia disease state.

The neuropsychological profile of clinical DLB is characterized by prominent involvement of frontal attentional/executive and parieto-occipital visuospatial pathways (Collerton et al., 2003; Crowell et al., 2007; Ferman and Boeve, 2007; Ferman et al., 2006; Guidi et al., 2006; Hanyu et al., 2006; McKeith, 2006; Metzler-Baddeley, 2007; Mondon et al., 2007; Preobrazhenskaya et al., 2006; Williams et al., 2007). The clinical profile of predementia DLB has not been elucidated, but is likely to involve these same neuroanatomic areas, albeit to a lesser degree.

The present study uses prospectively collected clinical data to examine the clinical features of neuropathologically proven DLB cases in the early, predementia clinical disease state. The findings support the hypothesis that MCI-DLB can be identified and differentiated from MCI-AD, years before clinical dementia is apparent.

2. Methods

2.1. Subjects

The subjects studied in this report were from the University of Kentucky Alzheimer's Disease Center (UK-ADC) Normal Control Clinic. Inclusion criteria are minimum age 65 years; cognitive and neurological normality by enrollment examination; designated informant for structured interviews; willingness to undergo annual cognitive testing, and physical and neurological examinations; and brain donation to the UK-ADC at death. Excluded are individuals with a history of substance abuse (including alcohol); major head injury; major psychiatric illness; medical illnesses that are nonstable, impairing, or that have an effect on the CNS; chronic infectious diseases; stroke or TIA; encephalitis; meningitis; or epilepsy. Annual standardized assessment includes extensive medical, cognitive, social, and functional evaluations as previously described (Schmitt et al., 2001). All subjects were contacted at 6-month intervals, had detailed cognitive function testing annually, and had neurologic and physical examinations biannually or annually. The mental status testing of our subjects has been described previously (Schmitt et al., 2001). Since 2005 we have used the standard test battery required by the National Alzheimer's Coordinating Center for all NIA-funded Alzheimer's Disease Centers that includes most of the above, plus others (<https://www.alz.washington.edu/NONMEMBER/v2forms.html>).

The present study represents 21 subjects from this cohort. All were found to be neurologically normal at enrollment. Nine of these subjects met neuropathological criteria for neocortical DLB (without evidence for significant AD pathology or vascular disease) and 12 met neuropathological criteria for AD (without evidence for DLB pathology or significant vascular disease) at the time of autopsy.

2.2. Retrospective identification of predementia cognitive decline

Individual clinical charts and the UK ADC database were reviewed for each case selected or excluded from the present study. Cases identified as not demented were included in this analysis. Because the prospective diagnosis of MCI was not entertained before 2001 at our center, a systematic approach to MCI was developed for all cases coming to autopsy prior to this time.

The diagnosis of MCI followed the guidelines of the 2nd International Consensus Panel on MCI, Stockholm, Sweden (Winblad et al., 2004). Charts were specifically reviewed for: (1) the presence of a memory complaint or objective evidence of longitudinal decline (>1.5 S.D. below baseline), (2) objective evidence of memory impairment on formal testing (>1.5 S.D. below mean age and education matched scores (using the UK ADC database normative values), and (3) generally intact global cognition and functional activities.

The presence or absence of noncognitive features of disease (Parkinsonism, hallucinations, delusions, paranoia, delirium, depression, or fluctuations in cognitive status) were considered only if prospectively collected data positively affirmed or denied their presence. No assumptions regarding symptom presence or absence were made on the basis of nondocumented observations. While it is possible that many of the subjects could have had symptoms or lack of symptoms that were not documented prospectively that may have biased the present analysis, the documented opinions of the examining clinician always held

precedence in this analysis. Onset dates of recorded symptoms or cognitive test score decline were included as variables in the analysis where appropriate.

Operational definitions for symptom involvement are as follows:

1. Parkinsonism—any motoric symptom that involved gait, slowness of movement, rigidity, or tremor, without a sufficiently documented medical cause for these abnormalities (severe osteoarthritis documented by X-ray, CT, or MR scan; peripheral neuropathy, degenerative disk disease and myelopathy documented by X-ray, CT, or MR scan; structural abnormality secondary to congenital or traumatic defect). Gait instability alone without evidence for clear extrapyramidal involvement documented by the examining physician was insufficient to meet criteria for Parkinsonism by our criteria.
2. Provoked psychiatric features—hallucinations, delusions, or paranoia required no previous history of psychiatric disease including schizophrenia, bipolar disorder, or severe depression.
3. Fluctuations—required use of the term “fluctuations,” descriptions of episodic confusion, or staring spells not associated with seizure-like activity or known history of seizure disorder.

A search of the UK ADC database identified 15 autopsy cases that met the neuropathological criteria for pure neocortical DLB without significant neuropathological comorbidity including NIA-Reagan definite AD classification (The National Institute of Aging, Reagan Institute Working Group, 1997), Braak stage greater than IV (Braak and Braak, 1991), significant cerebrovascular disease defined as: (i) presence of ischemic or hemorrhagic infarcts of any size, in any location; (ii) moderate or severe atherosclerotic disease defined as >50% stenosis of extra- or intracranial vessels; and (iii) moderate or severe microvascular disease using the criteria of Esiri et al. (1997) as follows, moderate to severe lipohyalinosis without myelin pallor or microvascular infarcts or severe lipohyalinosis or the presence of microinfarcts related to arteriosclerotic disease) (McKeith, 2006). These charts were reviewed for evidence of predementia cognitive decline. Nine of these fifteen subjects met criteria for further inclusion in this study (MCI-DLB). The same database was additionally examined for all autopsy cases submitted to the National Alzheimer's Coordinating Center that met current neuropathological criteria for AD without significant neuropathological comorbidity including any evidence for LBD or significant cerebrovascular disease as described above. Retrospective chart review of prospectively collected clinical data, before the overt diagnosis of dementia, was performed on 16 consecutive cases, resulting in the identification of 12 cases that showed evidence for predementia cognitive decline meeting criteria for MCI-AD.

2.3. Validation of the methodology for retrospective diagnosis

Because most autopsy subjects were evaluated before 2001, when the prospective diagnosis of MCI was routinely applied to all UK ADC subjects, we had to develop, validate, and use a methodology for the accurate application of this diagnosis based on retrospective chart review.

Charts from 8 prospectively diagnosed MCI and 14 normal control subjects were reviewed and all references to annual diagnoses were removed. The data for these subjects were identical to those obtained in the UK ADC since its inception in 1989. These charts were then screened in a blinded fashion by an examining neurologist resulting in retrospective diagnoses of either normal, MCI, or dementia for each longitudinal evaluation (methodology identical to that described above). Sensitivity (100%), specificity (87.5%), positive predictive value (100%), negative predictive value (93.3%), and diagnostic accuracy

(95.5%) for the retrospectively identified and prospectively applied diagnoses were determined.

2.4. Tissue sampling and processing

Fresh brain weights were determined at the time of autopsy. Specimens for histologic evaluation included 21 different brain regions. The sections were taken from the left cerebral hemisphere at the time of autopsy from the following regions and fixed in 4% formaldehyde: frontal pole (Brodmann area 10), middle frontal gyrus (area 9), gyrus rectus (area 11), temporal pole (area 38), superior and middle temporal gyri (areas 21, 22), inferior parietal lobule (areas 39, 40), occipital lobe (areas 17, 18), anterior cingulate gyrus (area 24), and posterior cingulate gyrus (area 23). Specimens were also taken from the hippocampus at the level of the lateral geniculate nucleus, entorhinal cortex, amygdala, ambient gyrus, basal ganglia, nucleus basalis of Meynert, thalamus, midbrain, and cerebellum. Similar sections were taken from the right hemisphere of most cases following fixation of the brain including additional sections from the cerebellum, midbrain, pons, and medulla. All specimens were processed in the usual manner and sections were cut at 8 μ m thickness. Sections were stained with hematoxylin and eosin and the modified Bielschowsky method. The Gallyas stain was used for sections of the entorhinal cortex, hippocampus, and amygdala. All sections of the cortex and ventromedial temporal lobe structures were stained with 10D-5 or the amyloid beta antibody (Novacaster, Newcastle, United Kingdom).

For assessment of LBP, the alpha-synuclein mouse monoclonal antibody (Novacaster) immunohistochemistry was used. Immunohistochemistry for alpha-synuclein was performed on 10 μ m sections that were pretreated with formic acid, blocked in 15% filtered horse serum in automation buffer, incubated with primary antibody for 1 h, and developed with the avidin–biotin complex using Nova Red (Vector Laboratories, Burlingame, CA) as the chromagen.

Neurofibrillary tangles, diffuse plaques, and neuritic plaques were counted using Bielschowsky-stained sections of frontal area 9, middle temporal gyrus, inferior parietal lobule, and occipital area 18. Diffuse and neuritic plaques were quantified as previously described in the amygdala, CA1, subiculum, and entorhinal cortex using the Bielschowsky stained sections (Nelson et al., 2007). Gallyas stained sections were used to quantify neurofibrillary tangles in hippocampal CA1, subiculum, amygdala, and entorhinal cortex. Khachaturian [ADRDA, Alzheimer's Disease and Related Disorders Association] (Khachaturian, 1985), Consortium to Establish a Registry for Alzheimer's Disease [CERAD] (Mirra et al., 1991), National Institute on Aging–Reagan Institute [NIA–Reagan] (The National Institute on Aging Reagan Institute Working Group, 1997), and Braak (Braak and Braak, 1991) criteria were used to categorize AD pathology in these subjects, and are presented independently in Table 1.

The semiquantitation of LBP in the different brain regions of varying size presented some difficulties. For example, the small locus ceruleus/subceruleus compared to the larger and less compact amygdala or neocortex or the elongated substantia nigra made it difficult to set specific numbers for LB or Lewy neuritis (LN). In addition, in the olfactory bulb, olfactory tract, and hippocampal CA2-3, LN predominated the findings. Thus, there was considerable subjectivity included in the scoring of severity. With this in mind, LBP was semiquantitated on a scale of 0–3 with 1 + (mild) being from 1 to 2 LB/20 $\times$ field and a few LN in the region being studied (cases with a single LB were not included); 2 + (moderate) being 3–6 LB/20 $\times$ field, and scattered to mild LN per region; and 3 + (severe) being >6 LB/20 $\times$ field and moderate or severe LN per region. Only cases meeting full neuropathologic criteria for neocortical DLB (Braak et al., 2004; McKeith, 2006) were included in the present analysis.

as MCI-DLB cases. MCI-AD cases were completely devoid of LBP in all sections examined.

Quantitative assessment of neurofibrillary tangles, diffuse and neuritic plaques were performed independently of the final neuropathological evaluation as described previously (Nelson et al., 2007). Final neuropathological diagnoses, and verification of the contribution of coexistent vascular and LBP was performed by a single neuropathologist (WRM) ensuring uniformity of the application of diagnostic criteria and the relative contributions of coexistent pathological features.

2.5. Statistical analysis

Standard descriptive and comparative analyses were performed and included mean, standard deviations, mode, Student's *t*-test, Mann–Whitney *U*-test, and Fisher exact test where appropriate.

The level for statistical significance was set at $P < 0.02$ to reduce the likelihood of type I error given the multiple comparisons made.

3. Results

Nine cases meeting neuropathological criteria for neocortical DLB (McKeith, 2006), and fulfilling our inclusion/exclusion criteria, were identified in the UK ADC brain bank derived from persons enrolled while cognitively normal that came to autopsy between 1989 and 2006. These subjects all had LBP extending from the brainstem, through limbic areas, and into neocortical areas sufficient to warrant the pathological diagnosis of DLB without criteria for clinical dementia. While none of these cases met NIA-RI criteria for high likelihood of AD, 3 met intermediate criteria, 3 met criteria for low likelihood of AD, and 3 were completely devoid of any significant AD pathological features (Table 1). Seven cases had sufficient number of diffuse senile plaques to meet the outmoded Khachaturian criteria for AD (Table 1). At least moderate levels of neuritic or dense-cored plaques were found in 6 cases (Table 1). Braak staging of neurofibrillary pathology revealed only minimal involvement of the hippocampus and medial temporal lobe structures, in the range typically seen in the normal aged population in our cases (Table 1).

Retrospective chart review and use of the prospectively collected clinical records allowed the diagnosis of MCI (Petersen et al., 2001; Winblad et al., 2004) or dementia (Knopman et al., 2001) to be applied to 9 of the 15 unselected DLB cases identified. Six cases with neuropathological findings for neocortical DLB had no charted evidence for cognitive decline (40% of total cases) despite rigorous surveillance and annual examinations. Of the 9 cases identified with cognitive decline, five met criteria for dementia by the time of death and autopsy. Four of these subjects expired while the clinical diagnosis was MCI-DLB.

For comparison, the database was searched for all cases meeting NIA-RI criteria for high-likelihood of AD. Sixteen consecutive cases were screened for evidence of clinical cognitive decline using identical methodology. Twelve cases had evidence for clinical cognitive decline and met criteria for MCI at some point before death and autopsy (Table 1). These cases all had Braak stages of V or VI, and all met CERAD criteria for definite AD but did not meet criteria for clinical dementia (Table 1). None of these cases had any evidence for LBP in any brain region studied (Table 1). Seven of these cases progressed to dementia and a clinical diagnosis of AD by death (Table 1). Five of these subjects died while the clinical diagnosis was MCI-AD (Table 1).

Comparative analyses demonstrate that the experimental groups are matched for age, gender, education, time followed while cognitively normal, and time from the diagnosis of MCI to dementia or death (Table 1). Several subjects in each group had no available ApoE genotyping to allow a full analysis. None of the 6 MCI-DLB cases with genotyping results were positive for the e4 allele. In contrast, 5 of the 10 MCI-AD cases with genotyping results were positive for at least one e4 allele, although this finding was not significant (Table 1).

Postmortem interval averaged less than 6 h for these subjects and no statistical differences between MCI-DLB and MCI-AD were seen (Table 1). Gross brain weight was lower in MCI-AD cases, but this difference did not reach significance ($P = 0.07$, Student's *t*-test). All measures of AD pathology were higher in the MCI-AD group than in the MCI-DLB group (Table 1), with the exception of diffuse plaques, which were present in comparative densities in each of the experimental groups ($P = 0.34$, Fisher exact test).

Comparisons of clinical data, between groups during the time when the diagnosis was MCI, demonstrated equivalent MMSE and CDR scores (Table 2). MCI-DLB subjects performed worse than MCI-AD subjects on the task of phonemic fluency (Controlled Oral Word Association Test, $P = 0.007$), but better on the WMS I Immediate Paragraph Recall test (Wechsler Memory Scale-Logical Memory I, $P = 0.019$) (Table 3). The groups did not differ on cognitive test score for Category fluency (animal naming), CERAD word list learning, or Trailmaking B test (Table 3). There was a trend, albeit not significant, for better performance on the Boston Naming Test and CERAD Word List Delayed Recall for the MCI-DLB subjects (although four of the nine MCI-DLB subjects scored worse on the CERAD Word List Delayed Recall than the mean of MCI-AD subjects). MCI-DLB subjects also showed a trend towards slower times to completion on the Trailmaking A test (Table 3).

Noncognitive symptoms including subtle signs of Parkinsonism, provoked hallucinations/delusions/paranoia, and fluctuations were only seen in the MCI-DLB group in the prodementia stage of disease (Table 2). Onset of these symptoms after the transition from MCI to dementia was not included in the present analysis. The presence of Parkinsonism was the only noncognitive feature that differed significantly between groups (Table 2). Because some MCI-DLB cases were associated with Parkinsonism and others with provoked hallucinations/delusions/paranoia and fluctuations, we analyzed the presence or absence of any noncognitive symptoms with the presence of MCI-DLB, and again found a significant association of these noncognitive symptoms with MCI-DLB rather MCI-AD in the prodementia state (Table 2).

4. Discussion

This study is the first to our knowledge to use rigorously obtained prospective clinical data from neuropathologically confirmed cases of DLB in an effort to characterize the prodementia or prodromal phase of DLB. All subjects were cognitively and neurologically normal at initial enrollment, followed longitudinally, and eventually came to autopsy. The present data demonstrate the feasibility of differentiating MCI-DLB from MCI-AD. Significant differences in both cognitive measures and noncognitive symptoms were found between experimental groups.

The present data also demonstrate the feasibility of a retrospective application of the MCI diagnosis in cases where adequate prospectively collected data exist. Using identical methodology to that in the present analysis, we were able to obtain a positive predictive value of 100%, a negative predictive value of 93.3%, and an overall diagnostic accuracy of 95.5% (onset ± 1 year from prospective diagnosis). While we missed a single case of

prospectively diagnosed MCI using our retrospective methodology, the diagnosis was accurate in all cases in which the diagnosis was applied retrospectively. Thus, while we may “undercall” MCI using the retrospective methodology, it is highly accurate when applied. It is possible that in the current study we may have missed the diagnosis of MCI in other cases in the autopsy series or that the duration of MCI may have varied by a year in either direction skewing these results in the present analysis.

Reliance on simple demographic measures such as age, education, and gender are insufficient in the differentiation of MCI-DLB from MCI-AD. While duration of MCI did not differ significantly between MCI-DLB and MCI-AD, there was a trend for a shorter duration of the MCI phase of DLB suggesting a more rapid course. Some studies in the literature have similarly suggested that a course characterized by more rapid progression of decline is characteristic of DLB (Ferman and Boeve, 2007; McKeith et al., 2004). The present study advances these findings into the prodromal phase of disease and a shortened duration of MCI duration may have prognostic value in future studies. Variability in the retrospectively determined date of onset for MCI and small sample size are the major confounds in this analysis.

Noncognitive symptoms analyzed in this study include the core features of DLB including Parkinsonism, fluctuations, and psychiatric features such as hallucinations, delusions, and paranoia (McKeith, 2006). In our series we found that the signs and symptoms of Parkinsonism were always mild, precluding a diagnosis of PD in all cases (Louis and Bennett, 2007). By design, we excluded cases with overt Parkinsonism as this would confound the present data with cases representing PDD rather than DLB according to current consensus criteria (Lippa et al., 2007; McKeith, 2006). None of the cases included developed sufficient Parkinsonism during the stage of MCI to warrant either diagnosis or treatment of symptoms. As such, these cases more clearly met criteria for DLB than for PDD. While subtle changes indicating possible underlying α -synuclein pathology, as seen in the subjects with MCI-DLB might be considered common in the elderly population examined in this study, it is intriguing that no such symptoms were found in the MCI-AD group. While gait changes were found in 3 of 12 MCI-AD subjects, underlying medical causes including spinal stenosis ($n = 1$) or severe skeletal malformation resulting from uncontrolled degenerative osteoarthritis ($n = 2$) were found. In contrast, the subtle Parkinsonian features seen in the MCI-DLB cases were without reasonable medical explanation.

Fluctuations in this study were characterized as affirmative comments of unprovoked staring spells or periods of confusion with normal cognition intervening. One-third of the MCI-DLB and none of the MCI-AD subjects exhibited this characteristic symptom of DLB in the MCI or preclinical phase of disease. While the presence or absence of this symptom did not reliably differentiate groups in the present study, the data suggest that careful attention to such symptoms may help with the underlying prediction of pathological features in MCI-DLB. Our routine collection of data has not included questions regarding such symptomatology and all reports of episodes meeting our criteria for fluctuations were offered spontaneously from caregivers. Taking this into consideration, it is possible that this symptom is much more prevalent than we describe herein, and deserves further consideration as a possible indicator of MCI-DLB in other series that have systematically addressed the issue of fluctuations in the early preclinical disease course of DLB.

The presence of provoked (by medication or medical illness) psychiatric features was found in out of 9 MCI-DLB and none of the MCI-AD cases. Such episodes, regarded as delirium, are common in the elderly population and may relate more to cognitive reserve and severity of illness or stressors than to underlying disease process. Our conservative analysis showed

that the presence of these symptoms did not differ significantly between groups but that there was a trend for increased prevalence in MCI-DLB over MCI-AD. The absence of these symptoms in predementia disease states may reflect the true course of disease, or could merely represent the bias of the examining prospective clinician. One of the four cases meeting criteria for MCI-DLB in this series exhibited unprovoked hallucinations, which were concurrent with the diagnosis of dementia. Such symptoms are often so dramatic and exhibit such a profound effect on social functioning that we would anticipate a bias towards the clinical call of dementia for any subject exhibiting such symptoms in an unprovoked setting.

While early memory involvement is considered a hallmark of MCI-AD, the memory deficits seen almost one-half of the MCI-DLB subjects are intriguing. Early memory loss may lack specificity in the identification of the underlying neuropathologic process responsible for cognitive decline in MCI. The memory impairment noted in our MCI-DLB subjects could be attributed to the involvement of the basal forebrain (nucleus basalis of Meynert was involved in all MCI-DLB cases in this series) or to other limbic structures (hippocampus and cingulate gyrus) involved in the Papez circuitry.

Neuropathologically, the cases presented in this series represented relatively “pure” pathological entities. Cases with mixed pathology (significant AD/DLB or cases with significant coexistent vascular pathology) were excluded from the present analysis. While all subjects included as MCI-AD cases in this series met NIA-RI criteria for high-likelihood for AD, three cases classified as MCI-DLB met NIA-RI intermediate criteria for AD. The vast abundance of LBP and the low level of relative AD pathology support the diagnosis of MCI-DLB rather than as true mixed cases of disease. Further analysis attempting to define predictive variables for underlying pathological features in stringently clean or mixed disease states will require much larger sample sizes and possibly more detailed data analyzed in a prospective fashion.

The strengths of the current study lie in (1) the rigorous application and validation of a methodology for the retrospective application of the MCI diagnosis in subjects with prospectively collected clinical data; (2) extensive, detailed, and thorough analysis of confounding pathological features; and (3) the availability of a large group of autopsy subjects enrolled while cognitively normal and followed prospectively throughout the course of their cognitive decline.

The weaknesses of the current study lie in: (1) the retrospective application of the clinical diagnosis of MCI (despite the validation of this methodology presented in the current study); (2) the small sample size ($n = 21$); and (3) the relatively homogeneous baseline population (predominantly Caucasian, aged (mean > 88 years), highly educated (predominantly college degree)).

Despite these limitations, the present report clearly demonstrates an ability to accurately predict the underlying pathology (MCI-DLB vs. MCI-AD) responsible for early cognitive decline while subjects are in the predementia state of MCI. Further work in this area is essential as we begin to develop novel disease-specific therapeutics and disease-modifying strategies, and as we attempt to implement them as early in the disease course as possible to prevent further cognitive decline. Similar exploratory analyses should be done for other neuropathologically proven disease cases in other distinct but less common degenerative states.

Acknowledgments

This study was supported by NIH/NIA 1 P30 AG028383.

Contribution: Statistical analysis was performed by G.A. Jicha and E. Abner.

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Demographic, clinical, and neuropathological findings at autopsy.

Table 1

	Age (years)	Gender	Education (years)	ApoE status	Time followed while normal (days)	Time followed while MCI (days)	Clinical diagnosis at death	PMI (h)	Brain weight (g)	ADRDA	CERAD	Braak stage	NIA- Reagan	Lewy body pathology
DLB case #														
1	69	F	16	33	1143	329	MCI	2.08	1260	No	4	1	4	Neocortical
2	84	F	8	23	759	150	MCI	3.13	1250	Yes	4	1	4	Neocortical
3	85	F	16	23	2189	859	DLB	2.00	1080	Yes	1	2	3	Neocortical
4	94	M	19	–	2896	958	DLB	15.85	1250	Yes	2	3	2	Neocortical
5	95	F	13	23	2184	1056	MCI	11.25	1205	Yes	1	0	3	Neocortical
6	86	M	18	–	2790	1259	MCI	4.00	1180	Yes	2	2	3	Neocortical
7	90	F	16	33	829	435	DLB	2.50	1160	Yes	2	3	2	Neocortical
8	93	F	16	33	1170	712	DLB	10.75	1280	Yes	2	4	2	Neocortical
9	97	M	16	–	745	1135	DLB	3.50	1308	No	4	1	4	Neocortical
Mean	88.1	–	15.3	–	1634	766	–	6.12	1219	–	–	–	–	–
S.D.	8.6	–	3.2	–	880	386	–	5.12	71	–	–	–	–	–
AD case #														
1	83	F	18	34	2942	1057	MCI	2.25	1160	Yes	1	5	1	None
2	99	F	18	34	2532	1698	AD	13.25	1150	Yes	1	6	1	None
3	88	M	18	34	3284	1311	AD	3.75	1105	Yes	1	5	1	None
4	86	M	20	33	1444	570	MCI	3.75	1400	Yes	1	6	1	None
5	87	M	20	34	1471	112	AD	9.75	1190	Yes	1	5	1	None
6	97	F	16	–	2198	1911	MCI	3.50	1030	Yes	1	6	1	None
7	88	F	16	33	3635	753	AD	9.83	1080	Yes	1	5	1	None
8	88	F	18	23	2530	484	MCI	2.75	1240	Yes	1	6	1	None
9	96	F	12	23	1822	1409	MCI	1.58	1080	Yes	1	5	1	None
10	91	F	12	–	2194	1400	AD	4.75	1050	Yes	1	5	1	None
11	83	F	12	33	1108	380	AD	2.53	970	Yes	1	5	1	None
12	77	F	13	44	1140	197	AD	3.00	1190	Yes	1	5	1	None
Mean	88.6	–	16.1	–	2192	940	–	5.07	1137	–	–	–	–	–
S.D.	6.4	–	3.1	–	819	605	–	3.73	113	–	–	–	–	–
Two-tailed probability	0.89 ^a	1.00 ^b	0.59 ^a	0.12 ^b	0.15 ^a	0.46 ^a	1.00 ^b	0.59 ^a	0.07 ^a	0.34 ^b	0.0018 ^c	<0.0001 ^c	<0.0001 ^c	<0.0001 ^b

AD = Alzheimer’s disease; ADRDA = Alzheimer’s Disease and Related Disorders Association; CERAD = Consortium to Establish a Registry for Alzheimer’s Disease (1 = definite AD, 2 = probable AD, 3 = possible AD, 4 = incompatible with AD); DLB = dementia with Lewy bodies; MCI = mild cognitive impairment; NIA–Reagan = National Institute on Aging and Reagan Institute (1 = high likelihood of AD, 2 = intermediate likelihood of AD, 1 = low likelihood of AD, 4 = incompatible with AD); PMI = postmortem interval.

^aIndependent samples *t*-test.

^bFisher exact test.

^cMann–Whitney *U*-test.

Table 2

Global clinical features and noncognitive symptoms during the MCI stage of cognitive decline.

Variable	MCI-DLB (<i>n</i> = 9)	MCI-AD (<i>n</i> = 12)	Probability
MMSE mean (S.D.)	25.6 (3.3)	25.2 (5.3)	0.78 ^a
CDR (mode)	0.5	0.5	1.00 ^b
Onset of Parkinsonian features (<i>n</i> with symptoms during MCI diagnosis)	5	0	0.012 ^c
Onset of fluctuations (<i>n</i> with symptoms during MCI diagnosis)	3	0	0.13 ^c
Onset of provoked hallucinations/delirium (<i>n</i> with symptoms during MCI diagnosis)	4	0	0.042 ^c
Onset of any noncognitive symptom (<i>n</i> with symptoms during MCI diagnosis)	8	0	<0.0001 ^c

AD = Alzheimer's disease; CDR = Clinical Dementia Rating scale; DLB = dementia with Lewy bodies; MCI = mild cognitive impairment; MMSE = Mini Mental State Examination.

^aIndependent samples *t*-test.

^bMann-Whitney *U*-test.

^cFisher exact test.

Table 3

Cognitive test scores during the MCI stage of cognitive decline.

Cognitive test	MCI-DLB (<i>n</i> = 9)	MCI-AD (<i>n</i> = 12)	Probability (independent samples <i>t</i> -test)
Category fluency (animal naming), mean $\pm$ S.D.	13.8 $\pm$ 3.8	12.6 $\pm$ 3.3	0.23
Phonemic fluency (COWAT), mean $\pm$ S.D.	30.7 $\pm$ 12.5	38.8 $\pm$ 9.1	0.007
WMS I Immediate Recall, mean $\pm$ S.D.	11.8 $\pm$ 3.1	9.4 $\pm$ 4.1	0.019
Boston Naming Test (Short version, 15 words) mean $\pm$ S.D.	14.2 $\pm$ 1.0	13.4 $\pm$ 1.7	0.074
CERAD Word List Total Learned mean $\pm$ S.D.	16.3 $\pm$ 4.2	15.8 $\pm$ 3.4	0.56
CERAD Word List Delayed Recall mean $\pm$ S.D.	4.9 $\pm$ 2.2	3.9 $\pm$ 2.1	0.084
Trailmaking A Test (s) mean $\pm$ S.D.	93.5 $\pm$ 29.6	73.4 $\pm$ 28.4	0.027
Trailmaking B Test (s) mean $\pm$ S.D.	197.3 $\pm$ 98.0	180.0 $\pm$ 72.6	0.70

AD = Alzheimer's disease; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; COWAT = Controlled Oral Word Association Test; DLB = dementia with Lewy bodies; MCI = mild cognitive impairment; WMS = Wechsler Memory Scale.