Nonamnestic mild cognitive impairment progresses to dementia with Lewy bodies

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ABSTRACT

Objective: To determine the rate of progression of mild cognitive impairment (MCI) to dementia with Lewy bodies (DLB).

Methods: We followed 337 patients with MCI in the Mayo Alzheimer's Disease Research Center (range 2–12 years). Competing risks survival models were used to examine the rates of progression to clinically probable DLB and Alzheimer disease (AD). A subset of patients underwent neuropathologic examination.

Results: In this clinical cohort, 116 remained as MCI, while 49 progressed to probable DLB, 162 progressed to clinically probable AD, and 10 progressed to other dementias. Among nonamnestic MCI, progression rate to probable DLB was 20 events per 100 person-years and to probable AD was 1.6 per 100 person-years. Among amnestic MCI, progression rate to probable AD was 17 events per 100 person-years, and to DLB was 1.5 events per 100 person-years. In 88% of those who developed probable DLB, the baseline MCI diagnosis included attention and/or visuospatial deficits. Those who developed probable DLB were more likely to have baseline daytime sleepiness and subtle parkinsonism. In 99% of the clinically probable AD group, the baseline MCI diagnosis included memory impairment. Neuropathologic confirmation was obtained in 24 of 30 of those with clinically probable AD, and in 14 of 18 of those with clinically probable DLB.

Conclusion: In a clinical sample, patients with nonamnestic MCI were more likely to develop DLB, and those with amnestic MCI were more likely to develop probable AD. *Neurology*® 2013;81:2032–2038

GLOSSARY

AD = Alzheimer disease; **ALB** = amygdala-predominant Lewy bodies; **CI** = confidence interval; **DLB** = dementia with Lewy bodies; **DLBD** = diffuse Lewy body disease; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **NFT** = neurofibrillary tangle; **RBD** = REM sleep behavior disorder; **TLBD** = transitional Lewy body disease; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Neurodegenerative conditions can evolve for many years before a threshold of neuronal loss is reached that triggers the emergence of clinical signs. Our ability to detect the earliest stage of these conditions is critical for purposes of intervening while neuronal viability is still present. Mild cognitive impairment (MCI) was initially characterized by isolated memory impairment and preserved activities of daily living. It is now well established that amnestic MCI most often represents an early stage of Alzheimer disease (AD),^{1,2} with an annual rate of transition in clinical samples ranging from 10% to 17%.^{3–5} Although much work has been done to examine the predictive value of MCI as it relates to AD, very little is known about the prodementia MCI stage of dementia with Lewy bodies (DLB).^{6–8} The purpose of this study was to determine the clinical characteristics of patients with MCI at increased risk of DLB, and to quantify the annual rate of progression from MCI to probable DLB in a clinical referral sample.

When dementia severity is mild or mild to moderate, cognitive comparisons reveal a consistent dissociation between clinically probable AD and DLB. This is characterized by early memory and naming deficits with relatively preserved attention and visuospatial skills in AD, and impaired attention and visuospatial skills with better memory and naming in DLB.^{9–11} We

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hypothesized that nonamnesic MCI would predict a greater risk of the development of DLB but not AD.

METHODS Clinical assessment. Consecutive patients who were followed longitudinally, seen at least twice, and who had a baseline diagnosis of MCI were categorized into 4 subtypes (amnesic, nonamnesic, multidomain amnesic, multidomain nonamnesic).³ Patients were recruited from the Mayo Clinic Alzheimer's Disease Research Center, and were excluded if cognitive difficulties could be explained by nonneurodegenerative conditions (e.g., stroke, neoplasm, head injury, hydrocephalus, or medical conditions).

The Mini-Mental State Examination (MMSE),¹² and the Clinical Dementia Rating Scale¹³ were administered to obtain a general measure of dementia severity. All participants underwent an annual neurocognitive evaluation to establish the presence or absence of formal cognitive impairment in one or more cognitive domains.^{1,3} This included 10 tests to assess the following domains using Mayo age-adjusted norms^{14–18}: 1) memory (delayed recall from the logical memory subtest from the Wechsler Memory Scale–Revised, delayed recall from the Auditory Verbal Learning Test); 2) attention/executive (Trail Making Test A and B, Stroop Color Word Test); 3) visual spatial/perceptual skills (Rey Complex Figure Copy, Block Design subtest from the Wechsler Adult Intelligence Scale–Revised, Judgment of Line Orientation); and 4) language (Boston Naming Test, Controlled Oral Word Association, Semantic Fluency). Performance was considered impaired if scores were 1.5 SDs below the mean in at least one cognitive test within a domain.

Each patient had an annual neurologic examination that typically occurred the same week as the neurocognitive evaluation, and included the Unified Parkinson's Disease Rating Scale (UPDRS).¹⁹ Estimated onset of cognitive symptoms was based on informant report. The patient's ability to manage functional activities of daily living was assessed through a clinical interview and by informant report using the Record of Independent Living²⁰ (used from 2000 to 2005) or the Functional Activities Questionnaire²¹ (used since 2005). Other standardized informant questionnaires obtained annually included the Mayo Sleep Questionnaire,²² the Epworth Sleepiness Scale,²³ and the Mayo Fluctuations Scale.²⁴

Designation of MCI and its subtypes was based on cognitive test performance and assessment of the patient's capacity to manage complex activities of daily living, but not on the MMSE or Clinical Dementia Rating score. A clinical diagnosis was determined annually by a consensus of neurologists and neuropsychologists, including quarterly dual-site consensus conferences (the Mayo Alzheimer's Disease Research Center sites in Rochester, MN, and Jacksonville, FL). The diagnosis of probable DLB was made according to the Third Report of the DLB Consortium Criteria for DLB, and required dementia plus 2 of 4 clinical features (visual hallucinations, fluctuations, parkinsonism, and REM sleep behavior disorder [RBD]).^{25,26} Established diagnostic criteria for clinically probable AD, frontotemporal dementia, and MCI were used.^{3,27–29}

Standard protocol approvals, registrations, and patient consents. This study was approved by the Mayo Clinic Institutional Review Board, and informed consent for participation was obtained from every subject and a surrogate.

Neuropathology. A subset of patients was followed to autopsy with standardized neuropathologic assessment, including macroscopic and microscopic evaluation, with assignment of a pathologic diagnosis using current criteria. Braak neurofibrillary tangle (NFT) stage was identified using thioflavin-S microscopy

or Bielschowsky silver stain. Neuritic and diffuse plaques were classified according to the National Institute on Aging–Reagan criteria.³⁰ The subtypes of Lewy body pathology (diffuse vs transitional) were determined on the basis of Lewy body counts using a polyclonal antibody to α -synuclein. Those with diffuse Lewy body pathology in the neocortex, limbic, and brainstem are referred to as DLBD, and those with limbic and brainstem Lewy body pathology as TLBD. Individuals who met criteria for AD and who had Lewy bodies restricted to the amygdala were classified as AD with amygdala-predominant Lewy bodies (ALB).³¹

Statistical analysis. We compared the MCI groups who remained as MCI with those who progressed to dementia (AD and DLB) using χ^2 tests for qualitative variables. One-way analysis of variance with post hoc analysis was performed for comparison of the 3 groups, and repeated-measures analysis of variance for comparisons at 2 points in time. A survival model that allowed for competing risks was used to estimate the cumulative incidence of either clinically probable DLB or AD among the amnesic and nonamnesic MCI groups. Incidence density methods were used to estimate rate of progression as the expected number of events per 100 person-years of follow-up, and proportional hazards models were used to test for differences in dementia risks by MCI type. In all of these survival analyses, when we estimated quantities for a dementia outcome, we used the other dementia outcome as a competing risk.³²

RESULTS Demographic and clinical features. Of 337 patients with MCI, 10 developed either frontotemporal dementia or sustained a cerebrovascular accident, and these patients were excluded from subsequent analyses.

At the baseline evaluation, none of the patients met criteria for Parkinson disease, which requires at least 2 of 4 cardinal features (bradykinesia, rigidity, tremor, postural instability). Of 327 patients, 278 had amnesic MCI and 49 had nonamnesic MCI (see table 1), and patients were followed annually for up to 12 years, with a mean $\pm$ SD follow-up of 4.6 ± 2.7 years (see table 2). A subset of patients remained as MCI, and although MCI subtype may vary, this group is referred to as stable MCI.

At least 1 year before the estimated onset of cognitive difficulty, 22 of 49 of those who developed probable DLB had one singular DLB core feature, typically RBD (see table 3). Only 4 individuals who later developed DLB had 2 of the core features of parkinsonism, visual hallucinations, or RBD before cognitive onset.

Demographic data are presented in table 2. Those with MCI who transitioned to DLB were disproportionately male. There was no difference in baseline age, minority status, or dementia severity compared with those who developed clinically probable AD. Not surprisingly, the MCI groups who developed dementia showed a decline in MMSE score from the initial evaluation to dementia diagnosis (baseline MMSE mean 26 ± 2 vs dementia diagnosis MMSE mean 23 ± 3 , $F = 151$, $p < 0.001$). The stable MCI group showed a mild decline in MMSE scores between baseline and the last evaluation (baseline MMSE mean 27 ± 2 vs last MMSE mean 26.7 ± 3 , $F = 4.9$, $p < 0.03$). Only the DLB group showed an increase in motor signs over time

Table 1 Breakdown of MCI subtypes and diagnosis at time of transition to dementia or last clinical evaluation

	327 MCI			
	278 Amnestic MCI		49 Nonamnestic MCI	
	245 Single-domain amnestic MCI	33 Multidomain amnestic MCI	38 Single-domain nonamnestic MCI	11 Multidomain nonamnestic MCI
Probable DLB	2	14	25	8
Probable AD	145	14	2	1
Stable MCI	98	5	11	2

Abbreviations: AD = Alzheimer disease; DLB = dementia with Lewy bodies; MCI = mild cognitive impairment.

(baseline UPDRS mean 4.9 ± 4 vs dementia diagnosis UPDRS mean 9.6 ± 6 , $F = 130.2$, $p < 0.001$).

At baseline, a history of probable RBD was found in 80% of those with MCI who developed probable DLB compared with 8% in those who developed clinically probable AD. The patients with MCI who developed DLB were also more likely to have baseline fluctuations, daytime sleepiness, and subtle, but measurable, extrapyramidal signs (see table 2).

During the longitudinal follow-up, 21 patients (6%) showed instability in their diagnosis and reverted from dementia back to MCI, or from MCI back to normal. In this group, the mean follow-up was 6 ± 3 years, and 10 of these patients progressed to the MCI or dementia stage.

Rates of progression to DLB or AD. The mean time to develop dementia from the MCI baseline evaluation was

3.1 ± 2 years for clinically probable AD, and 2.6 ± 2 years for DLB ($p = 0.096$). Single and multidomain MCI were pooled into the classifications of amnestic and nonamnestic MCI. Survival curves reflecting the cumulative incidence of transitions from the amnestic and nonamnestic MCI groups to clinically probable DLB or AD, with each outcome serving as a competing risk for the other, are illustrated in figure 1. Incidence density estimate of the annualized competing risk of transitioning from nonamnestic MCI to probable DLB was 20% (20 per 100 person-years, 95% confidence interval [CI] 15.3–27.5) compared with 1.6% to probable AD (1.6 per 100 person-years, 95% CI 0.61–4.3). In contrast, the annual relative competing risk of amnestic MCI to DLB was 1.5% (1.5 per 100 person-years, 95% CI 1.0–2.2) compared with 17% to clinically probable AD (17 per 100 person-years, 95% CI 14.9–19.4). Thus, in a clinical sample, it is 10 times more likely for amnestic MCI to progress to clinically probable AD

Table 2 Demographic and clinical variables

	MCI to DLB	MCI to AD	MCI stable	F/χ^2	p
No.	49	162	116		
Males, %	84	52	55	16.1	0.000
Minority, %	6	7	7	0.04	0.98
Age at baseline, y, mean $\pm$ SD	72 ± 7	74 ± 7	74 ± 8	1.5	0.22
Education, y, mean $\pm$ SD	16.0 ± 3^a	15.1 ± 3^b	14.6 ± 3^b	4.16	0.02
Years follow-up, mean $\pm$ SD	4.5 ± 3^a	5.5 ± 2^b	3.4 ± 2^c	21.3	0.000
CDR baseline score ≤ 0.5 , %	100	95	98	12.3	0.06
MMSE, baseline mean $\pm$ SD	26 ± 2^a	26 ± 2^a	27 ± 2^b	4.5	0.01
UPDRS, baseline mean $\pm$ SD	4.9 ± 4^a	0.7 ± 2^b	1.4 ± 3^b	32.9	0.000
Probable RBD, %	80	8	11	112.2	0.000
Mayo Fluctuations Score ≥ 3 at baseline, %	41.3	7	9	33.6	0.000
Epworth Sleepiness Scale, baseline mean $\pm$ SD	11 ± 5^a	5.8 ± 4^b	7.3 ± 4^b	17.0	0.000
Deceased during follow-up, %	49	31	28	7.8	0.02
Death age, y, mean $\pm$ SD	79 ± 7^a	84 ± 7^b	84 ± 7^b	5.8	0.00

Abbreviations: AD = Alzheimer disease; CDR = Clinical Dementia Rating; DLB = dementia with Lewy bodies; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; RBD = REM sleep behavior disorder; UPDRS = Unified Parkinson's Disease Rating Scale. The different superscript letters represent least significant difference post hoc comparisons at <0.05 level.

Table 3 Core DLB features present at least 1 year before estimated cognitive onset

Present at least 1 year before estimated cognitive onset	MCI to DLB (n = 49)	MCI to AD (n = 162)	MCI stable (n = 116)
RBD only	18	2	3
VH only	0	0	0
Parkinsonism only	4	1	1
RBD + parkinsonism	3	0	1
VH + parkinsonism	1	0	0
Total, n (%)	26/49 (53)	3/162 (2)	5/116 (4)

Abbreviations: AD = Alzheimer disease; DLB = dementia with Lewy bodies; MCI = mild cognitive impairment; RBD = REM sleep behavior disorder; VH = visual hallucinations.

than DLB, and the risk is 10 times greater for non-amnesic MCI to progress to clinically probable DLB than AD. Although nonamnesic MCI transitioned to DLB at a rate that was 1.21 times faster than that of amnesic MCI transitioning to clinically probable AD, this difference is not statistically significant (95% CI 0.88–1.66, $p = 0.25$).

The cumulative proportion of patients with non-amnesic MCI who developed probable DLB by 4-year follow-up was 45% and by 10-year follow-up was 59%; 2% developed clinically probable AD by 4-year follow-up and 5% by 10-year follow-up. In contrast, the cumulative proportion of clinically probable AD among amnesic MCI was 40% at 4-year follow-up and 56% at 10-year follow-up; 5% developed probable DLB by 4-year follow-up and 6% by 10-year follow-up.

MCI subtypes: Progression to DLB and AD. Almost 75% of this clinical sample had single-domain

amnesic MCI, and in accordance, more patients transitioned to clinically probable AD (see table 2). Of those who progressed from MCI to clinically probable AD, 99% had memory involvement at their baseline MCI diagnosis (see figure 2). Of that 99%, 90% presented with single-domain amnesic MCI at their initial evaluation. In contrast, 88% of those who developed DLB had a baseline MCI diagnosis comprising attention and/or visuospatial impairment (see figure 2). Of that 88%, 63.5% had attention or visuospatial deficits without a memory problem, and about a quarter of those (24.5%) had memory plus an attention or visual processing deficit at initial MCI diagnosis.

Neuropathology of MCI and dementia. The percentages of deaths are presented in table 2. Those who met clinical criteria for probable DLB had a younger age at death compared with clinically probable AD and with stable MCI. In the clinically probable DLB group, 18 of 24 came to autopsy, and pathologic examination revealed 10 with DLBD, 4 with TLBD, 1 with multiple system atrophy, 2 AD with ALB, and 1 with AD plus subcortical lacunar infarcts. The patient with AD and subcortical lacunar infarcts had single-domain non-amnesic MCI in the language domain at baseline, and the 2 AD with ALB had multidomain amnesic MCI at baseline. Of the 14 patients with autopsy-confirmed DLBD or TLBD, 53% had a Braak NFT stage $\leq$ IV and all had attention or visuospatial deficits (4 had concomitant memory involvement at baseline).

In the group of patients with MCI who progressed to a clinical diagnosis of clinically probable AD, there were 50 deaths and 30 of those came to autopsy. Of these 30, 20 had pure AD, 4 had AD with ALB, 5 had DLBD, and 1 had TLBD. In those with DLBD and TLBD, 3 had a single core DLB feature (1 had parkinsonism, 2 had probable RBD), and each had a Braak NFT stage $>$ IV. In those with AD or AD with ALB, 83% had a Braak NFT stage $>$ IV.

In the stable MCI group, 32 died at follow-up with a diagnosis of MCI, and 7 came to autopsy (all had single-domain amnesic MCI). Pathologic diagnoses included 1 with hippocampal sclerosis/vascular disease (Braak NFT stage III), 5 with pure AD (Braak NFT stage V), and 1 with AD and argyrophilic grain disease (Braak NFT stage V).

DISCUSSION In a clinical sample of patients with MCI followed longitudinally, those with nonamnesic MCI were 10 times more likely to develop clinically probable DLB compared with clinically probable AD, whereas those with amnesic MCI were 10 times more likely to develop clinically probable AD. The annual rate of transition from nonamnesic MCI was 20% to probable DLB and 1.6% to

Figure 1 Competing risks: AD and DLB

Survival curves for transitions from amnesic and nonamnesic MCI to DLB and clinically probable AD. AD = Alzheimer disease; DLB = dementia with Lewy bodies; MCI = mild cognitive impairment.

Figure 2 Mild cognitive impairment subtypes and progression to clinically probable Alzheimer disease (A) and probable dementia with Lewy bodies (B)

clinically probable AD, and from amnesic MCI was 17% to clinically probable AD and 1.5% to probable DLB. These data imply that those who present to a clinical referral center with nonamnesic MCI are at a substantially higher risk of developing DLB than clinically probable AD. Of those who progressed to clinically probable AD, 90% had single-domain amnesic MCI, 9% had multidomain amnesic MCI, and only 1% had nonamnesic MCI. This is consistent with other studies indicating that amnesic MCI typically represents early-stage AD.^{2,33}

Of those who progressed to clinically probable DLB, 88% presented initially with attention and/or visuospatial impairment, and 24.5% of that group had concomitant memory difficulty. These data are consistent with prior reports indicating a more mixed representation of MCI subtypes that predict transition to non-AD dementia.^{6,7,34,35} Despite the heterogeneity, these findings indicate that the well-established pattern of attention and visuospatial deficits in mild to moderate DLB¹¹ are also present in the MCI stage of DLB. Although single-domain amnesic MCI rarely progressed to probable DLB, memory impairment did occur in the context of multidomain MCI progressing to probable DLB. The degree to which memory deficits in DLB are attributable to Alzheimer-type pathology, or to attention-related deficits in encoding and retrieval, needs to be investigated.

Approximately 6% of the clinical sample reverted back to either an MCI or normal diagnosis at some point during longitudinal follow-up. While instability of the MCI diagnosis occurs, many evolve back to MCI or progress to dementia.³⁶ By 4 years of follow-up, a little less than half the sample developed some type of dementia and by 10 years of follow-up, the cumulative proportion of the MCI sample that developed dementia was 63% (deaths during the MCI stage accounting for 28%). Thus, even though MCI predicts dementia, patients are not certain to develop dementia even 10 years after their initial MCI diagnosis. Nonetheless, of those who underwent autopsy, individuals who died during the single-domain amnesic MCI stage tended to have pathology consistent with AD.

During the MCI stage of DLB, patients were more likely to have a history of RBD, greater overall daytime sleepiness, and greater likelihood of fluctuations. At the initial MCI diagnosis, none of the patients met criteria for Parkinson disease (2 of 4 cardinal parkinsonian features), but baseline and follow-up UPDRS scores were higher in those who developed DLB compared with clinically probable AD or stable MCI groups. Subtle parkinsonism has also been reported in “idiopathic” RBD, which is associated with elevated predictive risk of DLB and PD.^{26,37} This suggests that some core DLB clinical features may emerge before the cognitive and functional impairment constitutes a dementia syndrome.

Neuropathologic examination revealed that 14 of 18 of those who progressed to clinically probable DLB had autopsy-confirmed Lewy body disease, and 24 of 30 of those who developed clinically probable AD had autopsy-confirmed AD or AD with ALB. Of the false-positive AD diagnoses, 6 had TLBD or DLBD (3 had one core DLB clinical feature). Clearly, further study is needed to improve diagnostic accuracy. Conversely, in those with autopsy-confirmed Lewy body disease, 47% had co-occurring AD pathology. How AD pathology contributes to the DLB clinical presentation is not yet known, but voxel-based morphometry and functional imaging during life may be useful in identifying antemortem AD pathology and its relationship to DLB subtypes.³⁸

In the clinically probable AD group, 8% had a history of probable RBD without evidence of other core DLB features. Two of these patients had postmortem studies and both had DLBD. Because idiopathic RBD can precede the onset of DLB by many years,³⁹ this raises the question of whether a history of probable RBD in the context of dementia should be diagnosed as DLB in the absence of other core features, even in the presence of memory impairment. With the current DLB criteria, patients with RBD and dementia may incorrectly be designated as clinically probable AD.

This study has several limitations, most apparent of which are the modest sample size and the greater proportion of amnesic MCI cases. This may reflect the greater prevalence of clinically probable AD compared with DLB, but may be indicative of an unintended ascertainment bias because this sample largely reflects referrals to behavioral neurology clinics. It would be helpful to broaden the nonamnesic MCI sample representation and determine whether the predictive relationship between nonamnesic MCI and probable DLB in a clinical setting is reliably confirmed. Also, because rates of progression are typically lower in community samples,⁴⁰ epidemiologic studies that examine the transition from MCI to DLB are needed. In addition, the clinical diagnosis of clinically probable AD is heavily influenced by cognitive MCI subtype, and although formal criteria were used to diagnose dementia, it is important to be transparent about the strong relationship between memory impairment and a diagnosis of clinically probable AD. As such, pathologic confirmation is critical to clarify the relationship between MCI and evolving dementia.

AUTHOR CONTRIBUTIONS

Dr. Ferman: study concept and design, acquisition of data, analysis and interpretation of the data, drafting and revising the manuscript. Dr. Smith: acquisition of data, analysis and interpretation of the data, critical revision of the manuscript. Dr. Kantarci: study concept and design, critical revision of the manuscript. Dr. Boeve: acquisition of data, critical revision of the manuscript. Dr. Pankratz: statistical analysis and interpretation of the data, critical revision of the manuscript. Dr. Dickson: acquisition of data, analysis and interpretation of the data, critical revision of the manuscript. Dr. Graff-Radford, Dr. Wszolek, Dr. Van Gerpen, Dr. Uitti, Dr. Pedraza, and Dr. Murray: acquisition of data, critical revision of the manuscript. Mr. Aakre: statistical analysis. Dr. Parisi, Dr. Knopman, and Dr. Petersen: acquisition of data, critical revision of the manuscript.

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DISCLOSURE

T. Ferman reports no disclosures. G. Smith serves on the external advisory board of the University of Wisconsin Alzheimer's Disease Center (nonprofit) and is an editorial board member of *The Clinical Neuropsychologist* and *Journal of the International Neuropsychological Society*. K. Kantarci serves on the data safety monitoring board for Pfizer Inc., Janssen Alzheimer Immunotherapy, and Takeda Global Research & Development Center, Inc. B. Boeve has served as an investigator for clinical trials sponsored by Cephalon, Inc., Allon Pharmaceuticals, and GE Healthcare. He receives royalties from the publication of a book titled *Behavioral Neurology of Dementia* (Cambridge Medicine, 2009). He has

received honoraria from the American Academy of Neurology. He serves on the scientific advisory board of the Tau Consortium. V. Pankratz reports no disclosures. D. Dickson is an editorial board member of the *American Journal of Pathology*, *Annals of Neurology*, *Parkinsonism and Related Disorders*, *Journal of Neuropathology and Experimental Neurology*, and *Brain Pathology*. He is editor-in-chief of *American Journal of Neurodegenerative Disease*, and *International Journal of Clinical and Experimental Pathology*. N. Graff-Radford serves on a scientific advisory board for Codman; serves on the editorial boards of *The Neurologist* and *Alzheimer's Research & Therapy*; has received publishing royalties from UpToDate, Inc.; and receives research support from Allon Therapeutics, Inc. and TauRx. He has consulted for Sanofi and lectured for the Alzheimer Association. Z. Wszolek receives funding from the Mayo Clinic Center for Regenerative Medicine, Dystonia Medical Research Foundation, The Michael J. Fox Foundation for Parkinson's Research, and the gift from Carl Edward Bolch, Jr., and Susan Bass Bolch. J. Van Gerpen reports no disclosures. R. Uitti serves as an associate editor for *Neurology*. O. Pedraza, M. Murray, and J. Aakre report no disclosures. J. Parisi receives publishing royalties for *Principles & Practice of Neuropathology*, 2nd ed. D. Knopman serves as deputy editor for *Neurology*; served on a data safety monitoring board for Lilly Pharmaceuticals; served as a consultant to TauRx Pharmaceuticals, was an investigator in clinical trials sponsored by Baxter, Elan Pharmaceuticals, and Forest Pharmaceuticals in the past 2 years; and receives research support from the NIH. R. Petersen serves on scientific advisory boards for Elan Pharmaceuticals, Wyeth Pharmaceuticals, and GE Healthcare, and receives royalties from publishing *Mild Cognitive Impairment* (Oxford University Press, 2003). Go to Neurology.org for full disclosures.

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REFERENCES

- Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–308.
- Morris JC, Storandt M, Miller JP, et al. Mild cognitive impairment represents early-stage Alzheimer disease. *Arch Neurol* 2001;58:397–405.
- Petersen RC, Roberts RO, Knopman DS, et al. Mild cognitive impairment: ten years later. *Arch Neurol* 2009;66:1447–1455.
- Landau S, Harvey D, Madison C, et al. Comparing predictors of conversion and decline in mild cognitive impairment. *Neurology* 2010;75:230–238.
- Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia: meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand* 2009;119:252–265.
- Molano J, Boeve B, Ferman T, et al. Mild cognitive impairment associated with limbic and neocortical Lewy body disease: a clinicopathological study. *Brain* 2010;133:540–556.
- Fischer P, Jungwirth S, Zehetmayer S, et al. Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology* 2007;68:288–291.
- Jicha G, Schmitt F, Abner E, et al. Prodromal clinical manifestations of neuropathologically confirmed Lewy body disease. *Neurobiol Aging* 2010;31:1805–1813.
- Calderon J, Perry R, Erzinclioglu S, Berrios G, Denning T, Hodges J. Perception, attention, and working memory are disproportionately impaired in dementia with Lewy bodies compared with Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2001;70:157–164.
- Ferman TJ, Boeve BF, Smith GE, et al. Dementia with Lewy bodies may present as dementia and REM sleep behavior disorder without parkinsonism or hallucinations. *J Int Neuropsychol Soc* 2002;8:907–914.

11. Ferman TJ, Smith GE, Boeve BF, et al. Neuropsychological differentiation of dementia with Lewy bodies from normal aging and Alzheimer's disease. *Clin Neuropsychol* 2006;20:623–636.
12. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198.
13. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993;43:2412–2414.
14. Ivnik R, Malec J, Smith G, et al. Mayo older Americans normative studies: WMS-R norms for ages 56 to 94. *Clin Neuropsychol* 1992;6:49–82.
15. Ivnik R, Malec J, Smith G, et al. Updated AVLT norms for ages 56 to 97. *Clin Neuropsychol* 1992;6:83–104.
16. Ivnik RJ, Malec JF, Smith GE, Tangalos EG, Petersen RC. Neuropsychological tests' norms above age 55: COWAT, BNT, MAE token, WRAT-R reading, AMNART, STROOP, TMT, and JLO. *Clin Neuropsychol* 1996;10:262–278.
17. Machulda MM, Ivnik RJ, Smith GE, et al. Mayo's Older Americans Normative Studies: visual form discrimination and copy trial of the Rey-Osterrieth complex figure. *J Clin Exp Neuropsychol* 2007;29:377–384.
18. Lucas JA, Ivnik RJ, Willis FB, et al. Mayo's Older African Americans Normative Studies: normative data for commonly used clinical neuropsychological measures. *Clin Neuropsychol* 2005;19:162–183.
19. Fahn S, Elton RL; UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. *Recent Developments in Parkinson's Disease*. Florham Park, NJ: Macmillan Healthcare Information; 1987:153–163.
20. Weintraub S. The record of independent living: an informant-completed measure of activities of daily living and behavior in elderly patients with cognitive impairment. *Am J Alzheimers Dis Other Dement* 1986;1:35–39.
21. Teng E, Becker BW, Woo E, Knopman DS, Cummings JL, Lu PH. Utility of the Functional Activities Questionnaire for distinguishing mild cognitive impairment from very mild Alzheimer's disease. *Alzheimer Dis Assoc Disord* 2010;24:348–353.
22. Boeve BF, Molano JR, Ferman TJ, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. *Sleep Med* 2011;12:445–453.
23. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;14:540–545.
24. Ferman TJ, Smith GE, Boeve BF, et al. DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. *Neurology* 2004;62:181–187.
25. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005;65:1863–1872.
26. Ferman T, Boeve B, Smith G, et al. Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. *Neurology* 2011;77:875–882.
27. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Washington, DC: American Psychiatric Association; 1994.
28. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998;51:1546–1554.
29. Rascofsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011;134:2456–2477.
30. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD): part II: standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* 1991;41:479–486.
31. Uchikado H, Lin WL, DeLucia MW, Dickson DW. Alzheimer disease with amygdala Lewy bodies: a distinct form of alpha-synucleinopathy. *J Neuropathol Exp Neurol* 2006;65:685–697.
32. Klein JP, Moeschberger ML. *Survival Analysis: Techniques for Censored and Truncated Data*. New York: Springer; 2003.
33. Storandt M, Grant EA, Miller JP, Morris JC. Longitudinal course and neuropathologic outcomes in original vs revised MCI and in pre-MCI. *Neurology* 2006;67:467–473.
34. Busse A, Hensel A, Gühne U, Angermeyer M, Riedel-Heller S. Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology* 2006;67:2176–2185.
35. Schneider J, Arvanitakis Z, Leurgans S, Bennett D. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann Neurol* 2009;66:200–208.
36. Ganguli M, Snitz BE, Saxton JA, et al. Outcomes of mild cognitive impairment by definition: a population study. *Arch Neurol* 2011;68:761.
37. Postuma R, Gagnon J, Vendette M, Fantini M, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. *Neurology* 2009;72:1296–1300.
38. Kantarci K, Ferman TJ, Boeve BF, et al. Focal atrophy on MRI and neuropathologic classification of dementia with Lewy bodies. *Neurology* 2012;79:553–560.
39. Boeve B, Silber M, Ferman T, et al. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. *Sleep Med* 2013;14:754–762.
40. Farias ST, Mungas D, Reed BR, Harvey D, DeCarli C. Progression of mild cognitive impairment to dementia in clinic vs. community-based cohorts. *Arch Neurol* 2009;66:1151–1157.