

Hippocampal volumes predict risk of dementia with Lewy bodies in mild cognitive impairment

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ABSTRACT

Objective: To predict the risk of probable dementia with Lewy bodies (DLB) competing with Alzheimer disease (AD) dementia by hippocampal volume (HV) in patients with mild cognitive impairment (MCI) with impairments in amnesic or nonamnesic cognitive domains.

Methods: Patients with MCI ($n = 160$) from the Mayo Clinic Alzheimer's Disease Research Center, who participated in an MRI study at baseline from 2005 to 2014, were followed with approximately annual clinical evaluations. HVs were analyzed from 3T MRIs using FreeSurfer (5.3). Hippocampal atrophy was determined from the most normal 10th percentile of the measurement distributions in a separate cohort of clinically diagnosed patients with AD dementia. The subdistribution hazard ratios for progression to probable DLB and AD dementia were estimated by taking into account the competing risks.

Results: During a median (range) follow-up of 2.0 (0.7–8.1) years, 20 (13%) patients with MCI progressed to probable DLB, and 61 (38%) progressed to AD dementia. The estimated subdistribution hazard ratio (95% confidence interval) for normal HV relative to hippocampal atrophy for progression to AD dementia was 0.56 (0.34–0.91; $p = 0.02$) after taking into account the competing risks. The estimated hazard ratio for normal HV relative to hippocampal atrophy for progression to probable DLB was 4.22 (1.42–12.6; $p = 0.01$) after adjusting for age and after including the MCI subtype in the model.

Conclusions: Preserved hippocampal volumes are associated with increased risk of probable DLB competing with AD dementia in patients with MCI. Preservation of HV may support prodromal DLB over AD, particularly in patients with MCI with nonamnesic features.

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GLOSSARY

AD = Alzheimer disease; **DLB** = dementia with Lewy bodies; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **HVa** = hippocampal volume adjusted for total intracranial volume; **MCI** = mild cognitive impairment; **NIA** = National Institute on Aging; **RBD** = REM sleep behavior disorder.

Identifying patients with mild cognitive impairment (MCI) who are at risk for dementia with Lewy bodies (DLB) is critical for early interventions. Amnesic subtype of MCI has been established on clinical grounds in order to identify individuals who are at risk for Alzheimer disease (AD) dementia.^{1,2} Patients with MCI who have impairments in nonamnesic cognitive domains may be at an increased risk of DLB.^{3,4} We have previously demonstrated that the competing risk of progression to probable DLB vs AD is higher in patients with nonamnesic MCI compared to amnesic MCI.⁵

Hippocampal volumes on antemortem MRI are preserved in patients with DLB who have little or no additional AD pathology at autopsy.^{6–8} Hippocampal volumes are lower in patients with DLB with increasing Braak neurofibrillary tangle stage regardless of the severity of Lewy

Supplemental data
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From the Departments of Radiology (K.K., C.R.J.), Health Sciences Research (T.L., S.A.P., W.K.K.), and Neurology (B.F.B., D.S.K., R.C.P.), Mayo Clinic, Rochester, MN; Department of Psychology and Psychiatry (T.J.F.), Mayo Clinic Jacksonville; and Department of Psychology (G.E.S.), University of Florida, Gainesville.

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body disease pathology.⁷ Furthermore, while hippocampal phospho-tau burden is associated with hippocampal atrophy, α -synuclein burden does not appear to influence the global hippocampal volume in patients with Lewy body pathology.⁹ Therefore preserved hippocampal volumes may predict progression to DLB vs AD in MCI.

Our objectives were two fold: (1) To determine whether the risk of probable DLB accounting for progression to AD dementia is associated with hippocampal volume in patients with MCI, broadly defined with impairments in amnesic or nonamnesic cognitive domains; and (2) To determine whether MCI subtype and hippocampal volume would independently contribute to predicting the risk of probable DLB vs AD in MCI.

METHODS Participants. Consecutive patients with MCI ($n = 160$) from the Mayo Clinic Alzheimer's Disease Research Center participated in an MRI study during October 2005 to January 2014 and were followed approximately annually with clinical evaluations and neuropsychological testing. To be included, the patients had to have a diagnosis of MCI with at least one clinical follow-up evaluation by the end of January 2015. Diagnosis was determined by a consensus committee including the neurologist, neuropsychologist, and the nurse who evaluated each participant. Patients with known neurologic diseases such as epilepsy, brain tumors, or substance abuse that may impact cognitive function were excluded.

The operational definition of MCI was based on clinical judgment through a history from the patient and for the majority of patients from an informant. Published criteria were used for the diagnosis: cognitive complaint, cognitive function not normal for age, decline in cognition, essentially normal functional activities, no dementia.¹⁰ In addition, patients with MCI were classified into 1 of 4 MCI subtypes¹⁰: (1) amnesic MCI single-domain, if the impairment was only in the memory domain; (2) amnesic MCI multiple-domain, if the impairment was in the memory domain and one or more nonmemory domains such as language, attention/executive function, and visuospatial processing; (3) nonamnesic MCI single-domain, if the impairment was in one nonmemory domain and memory was relatively preserved; and (4) nonamnesic MCI multiple-domain, if the impairment was in more than one nonmemory domain with relative preservation of memory. We grouped patients with single and multiple-domain nonamnesic MCI because of the small number of patients with nonamnesic MCI multiple-domain ($n = 9$).

Diagnosis of dementia was based on DSM-IV criteria, diagnosis of probable AD dementia was based on National Institute on Aging (NIA)–Reagan criteria,¹¹ although all also fulfilled the NIA–Alzheimer's Association clinical criteria,¹² and diagnosis of probable DLB was based on the 3rd Consortium Criteria.¹³ Hippocampal preservation on MRI is not a core or supportive feature of these criteria, and therefore does not contribute to the diagnosis of probable DLB. The clinical characteristics of DLB were assessed in the following manner: presence of parkinsonism was assessed through the Unified Parkinson's Disease Rating Scale part III; visual hallucinations were characterized by being fully formed, not restricted to a single episode, and not related to another medical issue, treatment, or advanced dementia; fluctuations were considered

to be present if patients scored 3 to 4 on the Mayo Fluctuations Questionnaire¹⁴; and probable REM sleep behavior disorder (RBD) was diagnosed through The Mayo Sleep Questionnaire validated in a polysomnography-confirmed sample from the community, which revealed a sensitivity of 100% and specificity of 95%¹⁵ using published criteria for the diagnosis of RBD as the gold standard.¹⁶

MRI All participants underwent MRI examinations at 3T. A 3D high-resolution magnetization-prepared rapid gradient echo acquisition was performed for hippocampal volume measurements. Hippocampal volume was measured with FreeSurfer software (version 5.3) and adjusted for the total intracranial volume (HVa) by calculating the residual from a linear regression of hippocampal volume vs the total intracranial volume. Hippocampal atrophy was determined from the upper 10th percentile of the HVa measurement distributions in patients with clinically diagnosed AD dementia in a previous study from an independent cohort.¹⁷ In a secondary analysis, we derived the HVa cutoff for hippocampal atrophy using the upper 10th percentile of the HVa measurement from the AD converters in our sample.

Statistical analysis. We summarized baseline characteristics of the patients using median (interquartile range) for continuous variables and count (percent) for categorical variables. Because there are 2 competing outcomes of interest, AD dementia and probable DLB, standard survival methods would not be appropriate and would likely give biased results. We used a proportional subdistribution hazards regression survival model considering competing risks,¹⁸ implemented in the R package *cmprsk*. We estimated the cumulative incidence of either clinically probable DLB or AD dementia in 2 groups: those with and without hippocampal atrophy. Because age is a significant driver of progression to dementia, age was used as the time scale for tighter control of age effects. We summarized the results of the competing risk models using p values and subdistribution hazard ratios from product-limit methods to estimate the probability of a particular dementia outcome at a moment in time, given that the particular dementia has not occurred thus far. We plotted the cumulative probabilities of AD or probable DLB in the groups with and without hippocampal atrophy, using an age range covering the youngest (48.8) to oldest (90.5) ages with an event. A similar approach using a multivariate model was used to determine the contributions of hippocampal volume plus MCI subtype (MCI with nonamnesic impairments vs amnesic MCI single-domain) and contributions of hippocampal volume plus presence of clinical features (RBD, parkinsonism, visual hallucinations, and fluctuations) in predicting competing risks of probable DLB and AD dementia.

RESULTS Characteristics of the study cohort at baseline are listed in table 1. After a median (range) follow-up of 2.03 (0.69–8.10) years, patients with MCI progressed to AD dementia (n = 61; 38%), probable DLB (n = 20; 13%), or other dementias (n = 14; 9%) such as frontotemporal dementia (n = 4), multiple system atrophy (n = 1), progressive nonfluent aphasia (n = 3), semantic dementia (n = 2), logopenic progressive aphasia (n = 1), posterior cortical atrophy (n = 1), or corticobasal syndrome (n = 2), or died (n = 3; 2%). Because AD dementia and probable DLB were the 2 competing outcomes of interest, patients with MCI who died or progressed to other dementia were censored at the time of progression to dementia or death. The AD dementia progressor group had a higher frequency of women ($p = 0.005$) and *APOE* $\epsilon 4$ carriers than the probable DLB progressor group ($p = 0.004$). The AD dementia progressor group had lower median Dementia Rating Scale score at baseline compared to the probable DLB progressor group ($p = 0.02$), but the Mini-Mental State Examination scores were similar ($p = 0.53$).

Whereas a majority of the patients with MCI were diagnosed with amnesic MCI single-domain (n = 89; 56%), amnesic MCI multiple-domain (n = 34; 21%) and nonamnesic MCI (n = 37; 23%) were less frequent at baseline. Half of the patients with MCI who progressed to probable DLB were diagnosed with nonamnesic MCI (n = 10; 50%); on the contrary, a majority of patients with MCI who progressed to AD dementia were diagnosed with amnesic MCI single-domain (n = 42; 69%) at baseline. Clinical features of DLB were present in a majority of patients with MCI who progressed to probable DLB (n = 19; 95%) and some had 2 or more (n = 16; 80%) or 3 or more (n = 9; 45%) of these clinical features present at baseline. On the contrary, a few of the patients with MCI who progressed to AD dementia had 1 (n = 7; 11%) and none had 2 of the clinical features of DLB present at baseline. HVa were smaller in the AD dementia progressor group compared to the DLB progressor group at baseline ($p < 0.001$) (figure 1). Whereas a majority of the patients with MCI who progressed to probable DLB had normal

Table 1 Baseline characteristics of patients with mild cognitive impairment (MCI) who progressed to dementia with Lewy bodies (DLB) or Alzheimer disease (AD) dementia

	MCI stable ^a (n = 79)	DLB progressors (n = 20)	AD progressors (n = 61)	p Value ^b
Women	23 (29)	1 (5)	23 (38)	0.02
$\epsilon 4$ Carriers	43 (55)	8 (40)	46 (75)	0.006
Age, y	69 (63 to 76)	69 (66 to 72.5)	73 (68 to 77)	0.14
Education, y	16 (14 to 18)	15.5 (13 to 17)	16 (14 to 18)	0.38
MMSE	28 (26 to 29)	26 (23 to 28)	26 (24 to 27)	<0.001
DRS	135 (131 to 139)	135 (133 to 137)	132 (128 to 134)	0.001
UPDRS	0 (0 to 1)	8 (4.5 to 10.5)	0 (0 to 0)	<0.001
HVa	-1.71 (-2.37 to -0.95)	-1.33 (-1.88 to -0.59)	-2.70 (-3.66 to -1.94)	<0.001
Abnormal HVa	19 (24)	3 (15)	37 (61)	<0.001
Follow-up time	2.1 (1.1 to 3.8)	2.0 (1.1 to 2.1)	2.0 (1.0 to 2.3)	0.12
Time from first visit to MRI	0.00 (0.00 to 0.21)	0.00 (0.00 to 1.06)	0.02 (0.00 to 1.08)	0.13
Visual hallucinations	2 (3)	6 (30)	0 (0)	<0.001
Fluctuations	5 (6)	8 (40)	0 (0)	<0.001
Parkinsonism	16 (20)	17 (85)	3 (5)	<0.001
RBD	18 (23)	17 (85)	4 (7)	<0.001
MCI subtype				<0.001
aMCI single-domain	45 (57)	2 (10)	42 (69)	
aMCI multi-domain	11 (14)	8 (40)	15 (25)	
naMCI	23 (29)	10 (50)	4 (7)	

Abbreviations: aMCI = amnesic mild cognitive impairment; DRS = Dementia Rating Scale; HVa = hippocampal volume adjusted for total intracranial volume; MMSE = Mini-Mental State Examination; naMCI = nonamnesic mild cognitive impairment; RBD = REM sleep behavior disorder; UPDRS = Unified Parkinson's Disease Rating Scale part III.

Values represent median (interquartile range) or n (%).

^aPatients with MCI who remained stable or were censored at the time of death or progression to dementia syndromes other than DLB or AD dementia.

^bp Values are from a Kruskal-Wallis test or Wilcoxon rank sum test for the continuous variables or a χ^2 test of differences in proportions for the categorical variables among the clinical groups.

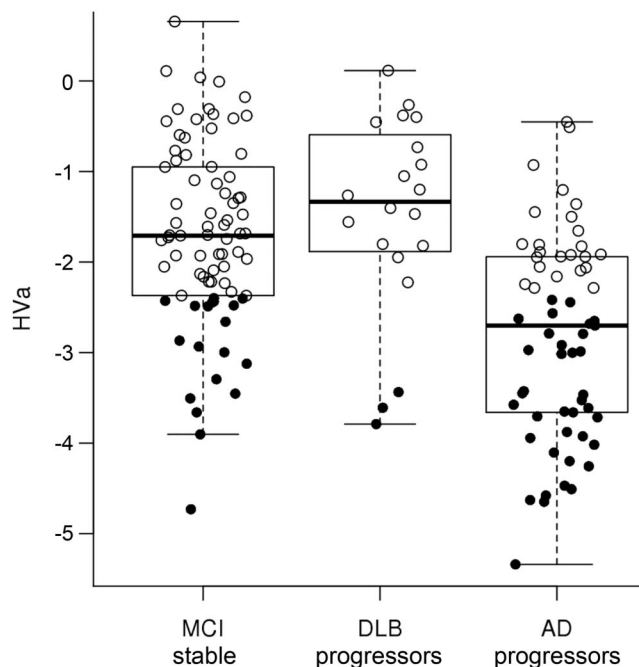
HVa (n = 17; 85%), a majority of patients with MCI who progressed to AD dementia had hippocampal atrophy (n = 37; 61%) using the previously published cutoff.¹⁷

Proportional hazards models for the HVa predicting competing risks of AD dementia vs probable DLB showed that patients with MCI with preserved HVa had a higher risk of progression to probable DLB (competing with AD dementia) relative to those with hippocampal atrophy with estimated subdistribution hazard ratio of 5.8 (1.86–18.0; $p = 0.002$). On the contrary, patients with MCI with preserved HVa had a lower risk of progression to AD dementia (competing with probable DLB) relative to those with hippocampal atrophy with estimated subdistribution hazard ratio of 0.56 (0.34–0.91; $p = 0.02$). Curves showing the probability of competing risk of progression to AD dementia and probable DLB are displayed in figure 2. We constructed multivariate models to determine whether hippocampal volumes provide information on probable DLB and AD risk when adjusting for MCI subtype. We investigated patients with MCI who had impairments in nonamnestic cognitive domains (i.e., nonamnestic MCI and amnestic MCI multiple-domain) compared to amnestic MCI single-domain, and normal HVa compared to atrophic HVa as predictors of probable DLB and AD dementia risk. In model 1, multidomain-amnestic

MCI ($p = 0.002$), and nonamnestic MCI ($p = 0.0003$) compared to single-domain amnestic MCI and normal HVa compared to atrophic HVa ($p = 0.02$) increased the risk of progressing to probable DLB, accounting for competing AD dementia. In model 2, we combined the multidomain-amnestic MCI and nonamnestic MCI groups into one group of patients with MCI having impairments in nonamnestic cognitive domains. MCI with impairments in nonamnestic cognitive domains ($p = 0.0003$) compared to single-domain amnestic MCI and normal HVa compared to atrophic HVa ($p = 0.01$) increased the risk of progressing to probable DLB accounting for competing AD dementia. The individual subdistribution hazard ratios for the 2 models are listed in table 2. In a secondary analysis, we used the HVa cutoff (upper 10th percentile) for hippocampal preservation or atrophy derived from the AD progressor MCIs in our cohort and the results did not change (table e-1 at Neurology.org).

Presence of core and suggestive clinical features of DLB as predictors was tested in a separate multivariate model to determine whether hippocampal volumes provide information on probable DLB and AD risk when adjusting for presence of these clinical features of DLB in patients with MCI. MCI with a clinical feature of DLB (RBD, parkinsonism, visual hallucinations, and fluctuations) compared to MCI without any one of these features ($p < 0.001$) and normal HVa compared to atrophic HVa ($p = 0.048$) increased the risk of progressing to probable DLB accounting for competing AD dementia (table e-2).

Figure 1 Hippocampal volumes adjusted for total intracranial volume (HVa) in patients with mild cognitive impairment (MCI)

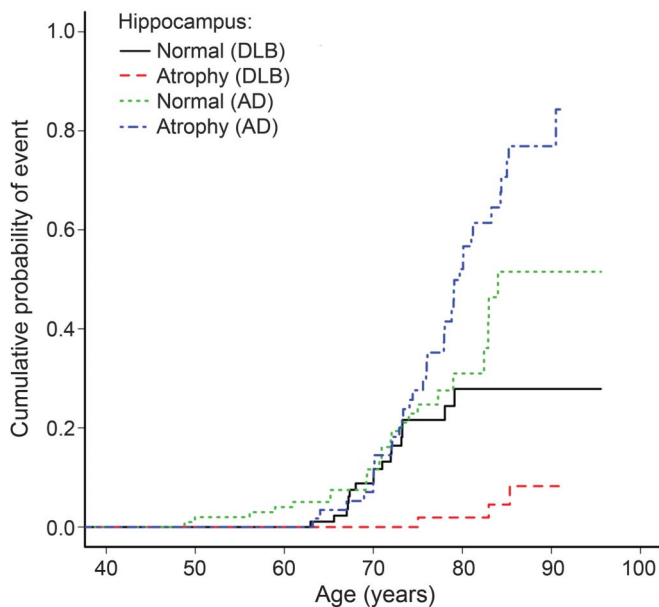


HVa in patients with MCI who did not progress to Alzheimer disease (AD) or dementia with Lewy bodies (DLB), patients with MCI who progressed to DLB, and patients with MCI who progressed to AD during follow-up. Dark circles indicate those labeled as having abnormal HVa for the survival analysis.

DISCUSSION In patients with MCI, preservation of hippocampal volumes was associated with a higher risk of progression to probable DLB, competing with the risk of progression to AD dementia. Competing risk analysis assumes that a patient with MCI who progresses to dementia will progress to either probable DLB or AD. Therefore the subdistribution hazard ratios for a dementia outcome are estimated by using the other dementia outcome as a competing risk. Patients with MCI with preserved hippocampal volumes had a hazard risk of progression to probable DLB 5.8 times that of those with hippocampal atrophy, when accounting for competing risk of progression to AD dementia. Furthermore, preserved hippocampal volumes predicted the hazard risk of progression to probable DLB along with the diagnosis of MCI with impairments in nonamnestic cognitive domains with or without memory impairment.

Hippocampal atrophy is associated with a higher risk of progression to AD dementia in patients with MCI.¹⁹ Based on these observations, hippocampal atrophy is included in the research criteria to support the diagnosis of MCI due to AD.² However, the

Figure 2 Cumulative incidences of progression to dementia with Lewy bodies (DLB) and Alzheimer disease (AD)



Cumulative incidences of progression to DLB and AD in patients with mild cognitive impairment by normal (preserved) hippocampus vs hippocampal atrophy. Hippocampal volumes are adjusted for total intracranial volume. Age is used as the timescale.

underlying etiologies of MCI, broadly defined with impairments in amnesic or nonamnesic cognitive domains, are heterogeneous.¹ Both vascular and Lewy body disease may contribute to the cognitive difficulties in patients with MCI.^{20,21} Furthermore, hippocampal volumes may be relatively preserved in patients with MCI, particularly in those with nonamnesic MCI.²²

In the current study, preserved hippocampal volumes predicted progression to DLB accounting for the competing risk for progression to AD dementia, even after considering nonamnesic MCI compared to amnesic MCI single-domain diagnosis. Impairment

in nonamnesic cognitive domains, particularly in the attention and visual-spatial processing domains, increases the risk for probable DLB in MCI.^{4,5,23} While nonamnesic MCI is characterized by relative preservation of hippocampal volumes, hippocampal atrophy may be present in some patients with nonamnesic MCI.²² Furthermore, hippocampal atrophy is common in patients with multiple-domain amnesic MCI, and these patients are at risk for both probable DLB and AD dementia.^{3,5,20,23} Thus, the distinction of patients with MCI who will progress to DLB vs AD dementia may not be clear only by the MCI subtype. Data from the current study suggest that hippocampal volumes predict progression to probable DLB along with the MCI subtype.

Relative preservation of medial temporal lobe structures is a supportive feature in the 3rd report of the DLB Consortium Criteria, categorized as a feature that is commonly present in DLB.¹³ However, as a supportive feature, preservation of hippocampal volume does not contribute to the diagnosis of probable DLB, which is made based on presence of 2 or more core and suggestive features.²⁴ In particular, hippocampal atrophy suggests additional AD-related neurofibrillary tangle pathology in probable DLB cases and may differentiate patients with mixed AD and Lewy body disease pathology from those with DLB.⁶⁻⁹ Preservation of hippocampal volumes is also observed in patients with hippocampal sparing AD,²⁵ therefore is not specific to DLB. We censored individuals who progressed to dementia syndromes other than AD dementia or probable DLB at the time of progression to dementia and several of these patients as well as those who received a clinical diagnosis of probable DLB or AD dementia may have had atypical AD pathology.^{26,27} Preservation of hippocampal volume in cases of atypical AD dementia may decrease the specificity of preserved hippocampal volumes in predicting progression to probable DLB in MCI. Furthermore, absence of hippocampal atrophy might have rather low positive predictive value in cognitively normal individuals; therefore the application would be limited to patients with MCI.

There are limitations to our study that need to be addressed. First, the study cohort was from an Alzheimer Disease Research Center-based dementia clinic sample, which was relatively small and is prone to ascertainment biases. Epidemiologic studies that examine the transition from MCI to probable DLB and the role of biomarkers in predicting this transition are needed. Furthermore, the outcomes of interest were clinical diagnosis of probable DLB or AD dementia. The clinical criteria for the diagnosis of DLB are criticized for having low sensitivity.^{28,29} Moreover, patients who fulfill the clinical criteria for probable DLB may have additional AD pathology and Lewy body disease pathology may be present in

Table 2 Multivariable model including hippocampal volume and mild cognitive impairment (MCI) subtype

Outcome	Predictors	Subdistribution HR (95% CI)	p Value
Model 1	Preserved HVa vs atrophic HVa	4.46 (1.27-15.67)	0.0200
	aMCI-MD vs aMCI-SD	12.84 (2.59-63.65)	0.0018
	naMCI vs aMCI-SD	11.21 (2.96-42.38)	0.0003
Model 2	Preserved HVa vs atrophic HVa	4.22 (1.42-12.6)	0.0098
	aMCI-MD plus naMCI ^a vs aMCI-SD	11.96 (3.08-46.46)	0.0003

Abbreviations: aMCI-MD = amnesic mild cognitive impairment-multiple-domain; aMCI-SD = amnesic mild cognitive impairment-single-domain; CI = confidence interval; HR = hazard ratio; HVa = total intracranial volume-adjusted hippocampal volume; naMCI = nonamnesic mild cognitive impairment.

Subdistribution hazard ratio is reported for dementia with Lewy bodies progression accounting for competing Alzheimer disease progression.

^a MCI with impairments in nonamnesic cognitive domains.

patients with AD dementia. Thus, many of our cases may have mixed AD and Lewy body disease pathologies. Pathologic confirmation of the diagnosis of DLB and AD is critical. Many of the patients with MCI had one or more of the core and suggestive features of probable DLB. We found that hippocampal volumes may be predictive of DLB vs AD diagnosis in addition to these clinical features. However, this finding should be interpreted with caution, because DLB competing with AD diagnosis was predicted based on the very features that are used for diagnosing probable DLB, and addition of the clinical features to the models introduced multicollinearity due to correlations among the predictors. An autopsy-confirmed and longitudinally followed cohort of patients with MCI is needed to determine the sensitivity and specificity of the core and suggestive clinical features of Lewy body disease at the stage of MCI.^{3,30} Finally, approximately 49% of the patients with MCI in our cohort were stable during follow-up. It is expected that there will be patients who progress to probable DLB or AD dementia from the MCI stable group in the future.

In a cohort of consecutive patients with MCI from a referral clinic, we demonstrated that those with preserved hippocampal volumes are at an increased risk for probable DLB, competing with the risk of progression to AD dementia, even after considering the MCI subtype. Therefore both nonamnestic features and hippocampal preservation may be considered for identifying patients with MCI at risk for probable DLB. Better response to cholinesterase inhibitors and neuroleptic sensitivity may need to be addressed in patients with MCI who are likely to progress to probable DLB.

AUTHOR CONTRIBUTIONS

Dr. Kantarci: study concept and design, acquisition of data, analysis and interpretation of the data, drafting the manuscript. T. Lesnick: study concept and design, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Dr. Ferman: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content. S.A. Przybelski: study concept and design, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Dr. Boeve: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Smith: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Kremers: study concept and design, analysis or interpretation of the data, critical revision of the manuscript for important intellectual content. Dr. Knopman: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Jack: acquisition of data, analysis and interpretation of the data, critical revision of the manuscript for important intellectual content. Dr. Petersen: acquisition of data, critical revision of the manuscript for important intellectual content.

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