



Mild Cognitive Impairment +/- Subsequent Dementia Associated With Underlying Lewy Body Disease

Jennifer R. Molano MD, Bradley F. Boeve MD, Tanis J. Ferman, PhD, Glenn E. Smith PhD, Joseph E. Parisi MD, Dennis W. Dickson MD, David S. Knopman MD, Neill R. Graff-Radford MBChB, Yonas E. Geda MD, John A. Lucas PhD, Robert J. Ivnik PhD, and Ronald C. Petersen PhD, MD

Departments of Neurology, Laboratory Medicine and Pathology, and Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota; Department of Neurology, Neuropathology Laboratory and Neurogenetics Laboratory, Mayo Clinic, Jacksonville, Florida; and Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program of the Mayo Foundation Supported by the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program of the Mayo Foundation, and grants AG15866, AG06786, and AG16574

OBJECTIVE

To characterize the clinical, neuropsychological, and neuropathological findings in subjects diagnosed with mild cognitive impairment (MCI), prospectively followed, and who had autopsy-proven Lewy body disease (LBD).

BACKGROUND

- Patients with amnesic MCI (a-MCI) often develop the dementia syndrome and neuropathologic findings of Alzheimer's disease (AD).
- Other subtypes include multiple-domain amnesic MCI (md-MCI-a), single-domain non-amnesic MCI (sd-MCI-na) and multiple-domain non-amnesic MCI (md-MCI-na), but their pathological substrates are not well-characterized.
- There also is little data on the relationship between LBD and MCI syndromes.

METHODS

- The Mayo Clinic Rochester and Jacksonville Alzheimer's Disease Patient Registry/Alzheimer's Disease Research Center database was queried for cases classified as MCI from 1/96-4/08, prospectively followed, and who had autopsy-proven LBD.
- The presence of REM sleep behavior disorder (RBD) was assessed.
- MCI subtypes were determined by clinical impression and neuropsychological profiles, and the diagnosis of clinically probable dementia with Lewy bodies (DLB) was based on the 2005 McKeith criteria.

Table 1. Clinical Features of MCI +/- Subsequent Dementia Associated with LBD Pathology

Case	Sex	Education Level	Age of RBD Onset	Age of Cognitive Symptom Onset	Age of MCI Dx	Age of Park Onset	Age of VH Onset	Age of Fluctuation Onset	MCI Subtype and Cognitive Domain Affected	Age of Conversion from MCI to Dementia	Age of Death
1	M	16	61	66	70	71	NA	No	md-MCI-na Attn/Visuospatial	NA	71
2	M	10	83	85	86	84	88	Yes - 90	sd-MCI-na Attention	90	90
3	F	13	91 PSG+	89	91	92	90	Yes - 92	md-MCI-na Attn/Visuospatial	92	94
4	M	16	27 PSG+	74	75	74	NA	Yes - 78	md-MCI-na Attn/Visuospatial	77	81
5	M	14	57 PSG+	69	70	69	72	Yes - 74	sd-MCI-na Attention	75	76
6	M	14	60 PSG+	69	71	71	72	Yes - 72	md-MCI-a Memory/Visuospatial/Language	73	76
7	M	12	51	62	66	66	66	Yes - 68	md-MCI-a Memory/Attention/Visuospatial	67	71
8	F	12	No	67	67	69	64	No	md-MCI-a Memory/Visuospatial/Language	69	73

Table 2. Neuropathological Findings of MCI +/- Subsequent Dementia Associated with LBD Pathology

Case	LBD Pathology Type	CERAD Neuritic Plaque Score	Braak Stage of NFT Pathology	NIA-Reagan Likelihood of AD	CDLB Criteria Likelihood of DLB	Other Findings	Final Neuropathological Diagnosis
1	Neocortical/ Diffuse	Sparse	III	Low	High	Diffuse plaques	Neocortical LBD and Path. Aging
2	Neocortical/ Diffuse	Frequent	IV	High	Intermediate		Neocortical LBD and AD (high)
3	Limbic/ Transitional	Possible	III	Low	High	Diffuse plaques and old infarcts	Limbic LBD, Path. Aging, and Mild Cerebrovascular Disease
4	Neocortical/ Diffuse	Sparse	III	Low	High	Diffuse plaques	Neocortical LBD and Path. Aging
5	Limbic/ Transitional	Sparse	II	Low	High		Limbic LBD
6	Neocortical/ Diffuse	NA	I	Low	High		Neocortical LBD
7	Neocortical/ Diffuse	Sparse	V	Low	High		Neocortical LBD
8	Neocortical/ Diffuse	Frequent	I	Low	High	Argyrophilic grains	Neocortical LBD and AGD

RESULTS

- Eight patients were identified (6M, 2F). The clinical features are shown in **Table 1**.
- Seven developed DLB prior to death; one died characterized as MCI
- Median age of onset (range) for specific features were:
 - RBD – 60 years (27-91) in 7 patients
 - Cognitive symptom onset – 69 years (62-89)
 - MCI – 70.5 years (66-91)
 - Dementia – 75 years (67-92) in 7 patients
 - Fluctuations – 76 years (68-92) in 6 patients
 - Death – 76 years (71-94)
- RBD preceded cognitive symptom onset in six cases by a median of 10 years (2-47) and MCI by a median of 12 years (3-48).
- Both amnesic and non-amnesic MCI subtypes were represented. The most frequent domains affected were attention/executive function and visuospatial skills.
- The neuropathological features are seen in **Table 2**. Six had neocortical-predominant LBD and 2 had limbic-predominant LBD; only 1 had coexisting high-likelihood AD.

CONCLUSIONS

- LBD passes through an MCI transitional state
- Both amnesic and non-amnesic MCI subtypes potentially can evolve into DLB.
- All cases with RBD and MCI eventually were shown to have autopsy-proven LBD, indicating that RBD plus MCI likely reflects brainstem and cerebral LBD