Sleep Disorders Pertinent to Dementia Research: REM Sleep Behavior Disorder and Obstructive Sleep Apnea

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Disclosures

Financial/Other

- Investigator for a clinical trial sponsored by GE Healthcare
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- Advisor for the Tau Consortium
- Honoraria from the American Academy of Neurology
- Research support from the NIA, NINDS, Alzheimer's Association, Mangurian Foundation

Off-label and/or Investigational Use

- May discuss use of some medications and/or devices not FDA-approved for the indications to be reviewed
REM Sleep Behavior Disorder (RBD)
• To review the clinical features and pathophysiology of RBD
• To review the relevance of RBD to dementia research

Obstructive Sleep Apnea (OSA)
• To review the clinical features and pathophysiology of OSA
• To review the relevance of OSA to dementia research

ADC Program/NACC
• To underscore the importance of recording sleep-related issues in UDS 3.0
REM Sleep Behavior Disorder
States of Being

- Wakefulness

- Non-REM Sleep
  - Stage N1
  - Stage N2
  - Stage N3

- REM sleep (Stage R)
Normal REM Sleep
Normal REM Sleep
REM Sleep Behavior Disorder
Clinical Features

• Simple or complex limb movements and/or vocalizations during rapid eye movement (REM) sleep

• Behaviors typically mirror the content of the dream when a patient is awakened and questioned

• Dream content often involves animals and/or people with chasing or attacking theme

• Behaviors can be violent, and patient and bedpartner injuries can occur
Normal REM Sleep vs REM Sleep Without Atonia

A
Normal REM Sleep

B
REM Sleep Without Atonia (RSWA)
REM Sleep Behavior Disorder

70 year old male severe RBD
RBD Pathophysiology

Adapted from Boeve BF, Lancet Neurol 2013
RBD Pathophysiology

Adapted from Boeve BF, Lancet Neurol 2013
Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder

B.F. Boeve\textsuperscript{a,b,*}, M.H. Silber\textsuperscript{a,b}, T.J. Ferman\textsuperscript{g}, S.C. Lin\textsuperscript{d,g}, E.E. Benarroch\textsuperscript{a}, A.M. Schmeichel\textsuperscript{a}, J.E. Ahlskog\textsuperscript{a}, R.J. Caselli\textsuperscript{h}, S. Jacobson\textsuperscript{i}, M. Sabbagh\textsuperscript{j}, C. Adler\textsuperscript{h}, B. Woodruff\textsuperscript{h}, T.G. Beach\textsuperscript{i}, A. Iranzo\textsuperscript{l}, E. Gelpi\textsuperscript{l}, J. Santamaria\textsuperscript{l}, E. Tolosa\textsuperscript{l}, C. Singer\textsuperscript{k}, D.C. Mash\textsuperscript{k}, C. Luca\textsuperscript{k}, I. Arnulf\textsuperscript{m}, C. Duyckaerts\textsuperscript{m}, C.H. Schenck\textsuperscript{j}, M.W. Mahowald\textsuperscript{j}, Y. Dauvilliers\textsuperscript{n}, N.R. Graff-Radford\textsuperscript{c}, Z.K. Wszolek\textsuperscript{c}, J.E. Parisi\textsuperscript{a,e}, B. Dugger\textsuperscript{i}, M.E. Murray\textsuperscript{f}, D.W. Dickson\textsuperscript{f}
RBD is Associated with the Synucleinopathies – Which is Typically Lewy Body Disease

<table>
<thead>
<tr>
<th>Primary Neuropathologic Diagnosis</th>
<th>PSG-confirmed n=82 (%)</th>
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<tbody>
<tr>
<td>Neurodegenerative/Prion</td>
<td></td>
</tr>
<tr>
<td>Lewy body disease +/- Alzheimer’s disease</td>
<td>59 (72)</td>
</tr>
<tr>
<td>Lewy body disease*</td>
<td>34 (41)</td>
</tr>
<tr>
<td>Combined LBD and AD</td>
<td>25 (30)</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>16 (20)</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>1 (1)</td>
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<tr>
<td>Other</td>
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<tr>
<td>Combined LBD and MSA</td>
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<tr>
<td>Combined LBD and ALS</td>
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<tr>
<td>NBI-1 + LBD + tauopathy</td>
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</tr>
<tr>
<td>CJD and ALS</td>
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</table>

**Synucleinopathy among neurodegenerative diseases**

78/80 = 98%

Boeve BF et al, Sleep Med 2013
## RBD Associated with Neurodegenerative Disease

<table>
<thead>
<tr>
<th>Synucleinopathy</th>
<th>Tauopathy</th>
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<tbody>
<tr>
<td>Lewy Body Disease</td>
<td>Pick’s disease</td>
</tr>
<tr>
<td>Parkinson’s disease (PD)</td>
<td>Corticobasal degeneration (CBD)</td>
</tr>
<tr>
<td>Dementia with Lewy bodies (DLB)</td>
<td>Progressive supranuclear palsy (PSP)</td>
</tr>
<tr>
<td>Pure autonomic failure (PAF)</td>
<td>Argyrophilic grain disease (AGD)</td>
</tr>
<tr>
<td>Multiple system atrophy (MSA)</td>
<td>Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17MAPT)</td>
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<table>
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<tr>
<th>Trinucleotide Repeat Disorders</th>
<th>TDP-43opathy</th>
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<tr>
<td>Spinocerebellar Atrophy-3 (SCA-3)</td>
<td>Frontotemporal lobar degeneration (FTLD) with TDP-43-positive inclusions</td>
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<tr>
<td>Huntington’s Disease (HD)</td>
<td>FTLD with motor neuron disease (FTLD-MND)</td>
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<table>
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<tr>
<th>Prionopathy</th>
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<tbody>
<tr>
<td>Creutzfeldt-Jakob disease (CJD)</td>
<td></td>
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<tr>
<td>Fatal familial insomnia (FFI)</td>
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<tr>
<td>Gerstmann-Straussler-Scheinker (GSS)</td>
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</table>

<table>
<thead>
<tr>
<th>Amyloidopathy</th>
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<tbody>
<tr>
<td>Alzheimer’s disease (AD)</td>
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</table>

<table>
<thead>
<tr>
<th>Amyotrophic lateral sclerosis (ALS)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17PGRN)</td>
<td></td>
</tr>
</tbody>
</table>
Diagnosis and management of dementia with Lewy bodies

Third report of the DLB consortium

I.G. McKeith, MD, FMedSci; D.W. Dickson, MD; J. Lowe, DM; M. Emre, MD; J.T. O'Brien, DM; H. Feldman, MDCM; J. Cummings, MD; J.E. Duda, MD; C. Lippa, MD; E.K. Perry, DSc; D. Aarsland, MD; H. Arai, MD; C.G. Ballard, MD; B. Boeve, MD; D.J. Burn, FRCP; D. Costa, MD; T. Del Ser, MD, PhD; B. Dubois, MD; D. Galasko, MD; S. Gauthier, MD, FRCP; C.G. Goetz, MD; E. Gomez-Tortosa, MD, PhD; G. Halliday, PhD; L.A. Hansen, MD; J. Hardy, PhD; T. Iwatsubo, MD; R.N. Kalaria, FRCP; D. Kaufer, MD; R.A. Kenny, MD; A. Korczyn, MD; K. Kosaka, MD; V.M.-Y. Lee, PhD, MBA; A. Lees, MD; I. Litvan, MD; E. Londoño, MD, PhD; O.L. Lopez, MD; S. Minoshima, MD, PhD; Y. Mizuno, MD; J.A. Molina, MD; E.B. Mukaetova-Ladinska, MD, PhD; F. Pasquier, MD, PhD; R.H. Perry, DSc; J.B. Schulz, MD; J.Q. Trojanowski, MD, PhD; and M. Yamada, MD, PhD, for the Consortium on DLB*

McKeith et al, Neurology 2005
**Table 1 Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)**

1. **Central feature** (essential for a diagnosis of possible or probable DLB)
   - Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent.

2. **Core features** (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB)
   - Fluctuating cognition, with pronounced variations in attention and alertness
   - Recurrent visual hallucinations that are typically well formed and detailed
   - Spontaneous features of parkinsonism

3. **Suggestive features** (If one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.)
   - REM sleep behavior disorder
   - Severe neuroleptic sensitivity
   - Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging
RBD and the Association With Lewy Body Disease/Dementia With Lewy Bodies

Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies

T.J. Ferman, PhD
B.F. Boeve, MD
G.E. Smith, PhD
S.-C. Lin, MD
M.H. Silber, MBChB
O. Pedraza, PhD
Z. Wszolek, MD
N.R. Graff-Radford, MBBCh, FRCP (London)
R. Uitti, MD
J. Van Gerpen, MD
W. Pao, MD
D. Knopman, MD
V.S. Pankratz, PhD
K. Kantarcı, MD
B. Boot, MBBS
J.E. Parisi, MD
B.N. Dugger
H. Fujishiro, MD
R.C. Petersen, MD
D.W. Dickson, MD

Results: Each of the 3 core features increased the odds of autopsy-confirmed DLB up to 2-fold, and RBD increased the odds by 6-fold. When clinically probable DLB reflected dementia and 2 or more of the 3 core features, sensitivity was 85%, and specificity was 73%. When RBD was added and clinically probable DLB reflected 2 or more of 4 features, sensitivity improved to 88%. When dementia and RBD were also designated as probable DLB, sensitivity increased to 90% while specificity remained at 73%. The VH, parkinsonism, RBD model lowered sensitivity to 83%, but improved specificity to 85%.

Conclusions: Inclusion of RBD as a core clinical feature improves the diagnostic accuracy of autopsy-confirmed DLB. Neurology® 2011;77:875-882

Ferman et al, Neurology 2011
RBD Tends to Precede Cognitive Impairment and/or Parkinsonism by Years or Decades

REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century

RBD onset

Cognitive impairment and/or parkinsonism onset

Idiopathic RBD

Claassen et al, Neurology 2011
RBD Tends to Precede Cognitive Impairment and/or Parkinsonism by Years or Decades
RBD Tends to Precede Cognitive Impairment and/or Parkinsonism by Years or Decades

- PD/PDD
  - Mean = 27 years
  - Range = 15-50 years

- MCI/DLB

- MSA

20 30 40 50 60 70 80
RBD and the Association With Lewy Body Disease/Dementia With Lewy Bodies

- Prodromal RBD
- Early Symptomatic MCI
- Neurodegenerative Syndrome Cognitive Impairment
- DLB
REM Sleep Behavior Disorder and Relevance To Dementia/Neurodegenerative Disease

Salient Points:

• RBD is often associated with the synucleinopathies, and usually precedes the other “classic” features of DLB, PD or MSA by years

• RBD associated with cognitive impairment/dementia almost always reflects underlying Lewy body disease (ie, DLB)

• Treatment directed toward LBD pathophysiology in those with RBD could delay the onset or prevent the development of DLB
Obstructive Sleep Apnea
Obstructive Sleep Apnea
Clinical Features

• loud and disruptive snoring
• witnessed snorts, gasps, and apnea
• snort arousals
• daytime hypersomnolence
• cognitive impairment
• depression, irritability
• reduced quality of life
Obstructive Sleep Apnea
Polysomnographic Features

EEG

EMG

O₂
Obstructive Sleep Apnea
Etiology/Pathophysiology

- Repetitive episodes of reduced or ceased airflow due to obstruction in the oropharynx during sleep

- Often associated with:
  - obesity
  - excessive neck tissue (collar size >17 ½)
  - large tonsils
  - retrognathia
Obstructive Sleep Apnea
Office Tasks

Friedman Palate Position

Grade III and IV – associated with increased frequency of OSA

Friedman et al, Laryngoscope 2004;114:454–459
Obstructive Sleep Apnea Management

• nasal continuous positive airway pressure (CPAP)

• positional OSA - “tennis balls in a T-shirt” technique

• oral appliance

• uvulopalatopharyngoplasty (UPPP)
Obstructive Sleep Apnea
Nasal CPAP
Obstructive Sleep Apnea

- Untreated OSA in the nondemented population causes cognitive impairment, excessive daytime somnolence (EDS), and diminished mood and quality of life.

- Treatment of OSA with nasal continuous positive airway pressure (CPAP) improves cognitive performance, EDS, mood and quality of life.

- Neuropsychological analyses have revealed that in patients with OSA, cognitive flexibility, attention, processing speed, and memory all improve with CPAP therapy.
Obstructive Sleep Apnea

*OSA should be considered one of the reversible causes of cognitive impairment/delirium/dementia*
Obstructive Sleep Apnea
Relevance to MCI/AD

Cognitive Effects of Treating Obstructive Sleep Apnea in Alzheimer’s Disease: A Randomized Controlled Study

Sonia Ancoli-Israel, PhD,* † Barton W. Palmer, PhD,* † Jana R. Cooke, MD, ‡ Jody Corey-Bloom, MD, PhD, † ‡ Lavinia Fiorentino, PhD, ‡ ‡ Loki Natarajan, PhD, # Lianqi Liu, MD, * † Liat Ayalon, PhD, * Feng He, MS, # and Jose S. Loredo, MD ‡ ‡

JAGS 2008

Sustained Use of CPAP Slows Deterioration of Cognition, Sleep, and Mood in Patients with Alzheimer’s Disease and Obstructive Sleep Apnea: A Preliminary Study

Jana R. Cooke, M.D. ‡ ‡; Liat Ayalon, Ph.D. ‡; Barton W. Palmer, Ph.D. ‡; Jose S. Loredo, M.D. ‡ ‡; Jody Corey-Bloom, M.D., Ph.D. ‡ ‡, ‡ ‡; Loki Natarajan, Ph.D. ‡; Lianqi Liu, M.D. ‡; Sonia Ancoli-Israel, Ph.D. ‡

JCSM 2009
Obstructive Sleep Apnea
Relevance to MCI/AD

Sleep-Disordered Breathing, Hypoxia, and Risk of Mild Cognitive Impairment and Dementia in Older Women

Kristine Yaffe, MD
Alison M. Laffan, PhD
Stephanie Litwack Harrison, MPH
Susan Redline, MD, MPH
Adam P. Spira, PhD
Kristine E. Ensrud, MD
Sonia Ancoli-Israel, PhD
Katie L. Stone, PhD

Conclusion Among older women, those with sleep-disordered breathing compared with those without sleep-disordered breathing had an increased risk of developing cognitive impairment.

JAMA. 2011;306(6):613-619

Adjusted odds ratio of 1.85
Obstructive Sleep Apnea
Relevance to MCI/AD

Amyloid-β Dynamics Are Regulated by Orexin and the Sleep-Wake Cycle

Jae-Eun Kang,1 Miranda M. Lim,1 Randall J. Bateman,1,2,3 James J. Lee,1 Liam P. Smyth,1 John R. Cirrito,1,2 Nobuhiro Fujiki,4 Seiji Nishino,4 David M. Holtzman1,2,3,5*

Kang et al., Science Express 2009
Obstructive Sleep Apnea
Relevance to MCI/AD

Sleep and Alzheimer disease pathology—a bidirectional relationship

Figure 1: The bidirectional relationship between sleep and AD. Potential positive-feedback mechanisms exist between the accumulation of Aβ, impaired sleep quality and effects on cognitive function. Abbreviations: Aβ, amyloid-β; AD, Alzheimer disease.

Ju et al., Nature Rev Neurosci 2014
Obstructive Sleep Apnea
Relevance to MCI/AD

Sleep-disordered breathing advances cognitive decline in the elderly

Ricardo S. Osorio, MD
Tyler Gumb, BA
Elizabeth Pirraglia, MA
Andrew W. Varga, PhD, MD
Shou-en Lu, PhD
Jason Lim, BA
Margaret E. Wohleber, BA
Emma L. Ducca, BA
Viacheslav Koushyk, MD
Lidia Glodzik, MD
Lisa Mosconi, PhD
Indu Ayappa, PhD
David M. Rapoport, MD
Mony J. de Leon, EdD
For the Alzheimer’s Disease Neuroimaging Initiative

Osario et al., Neurology 2015
Obstructive Sleep Apnea
Relevance to MCI/AD

OSA ~ sleep disordered breathing (SDB)

+SDB compared to no SDB was associated with earlier age of onset of MCI (and AD)

Osario et al., Neurology 2015
Obstructive Sleep Apnea
Relevance to MCI/AD

Among those with SDB:

CPAP use associated with delayed age of onset of MCI
Obstructive Sleep Apnea and Relevance To Dementia/Neurodegenerative Disease

Salient Points:

• OSA is associated with cognitive impairment, MCI and AD

• Evidence suggests:
  • OSA increases risk of MCI/AD
  • OSA decreases age of onset of MCI +/- AD
  • CPAP improves cognition in those with MCI/AD
  • CPAP delays development of MCI +/- AD

• OSA may alter intracranial amyloid physiology
Sleep-Related Topics of Interest in the ADC Program/NACC
### Form A5: Subject Health History

<table>
<thead>
<tr>
<th>5. Medical conditions (cont.)</th>
<th>Absent</th>
<th>Recent/active</th>
<th>Remote/inactive</th>
<th>Unknown</th>
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<tbody>
<tr>
<td>5g. Incontinence — urinary</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>9</td>
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<tr>
<td>5h. Incontinence — bowel</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>5i. Sleep apnea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>9</td>
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<tr>
<td>5j. REM sleep behavior disorder (RBD)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>9</td>
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<tr>
<td>5k. Hyposomnia/insomnia</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>9</td>
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<tr>
<td>5l. Other sleep disorder (SPECIFY):</td>
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<td>1</td>
<td>2</td>
<td>9</td>
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</table>
### Sleep-Related Topics of Interest in the ADC Program/NACC

#### Form B9: Clinician Judgment of Symptoms

<table>
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<tr>
<th>Question</th>
<th>No</th>
<th>Yes</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>9g. Personality change Does the subject exhibit bizarre behavior or behavior uncharacteristic of the subject, such as unusual collecting, suspiciousness (without delusions), unusual dress, or dietary changes? Does the subject fail to take others’ feelings into account?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9h. REM sleep behavior disorder While sleeping, does the subject appear to act out his/her dreams (e.g., punch or flail their arms, shout, or scream)?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9h1. If yes, at what age did the REM sleep behavior disorder begin?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(The clinician must use his/her best judgment to estimate an age of onset.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9i. Anxiety For example, does s/he show signs of nervousness (e.g., frequent sighing, anxious facial expressions, or hand-wringer) and/or excessive worrying?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sleep-Related Topics of Interest in the ADC Program/NACC

Reminder: RBD is recorded under the “behavior” domain, and when present, usually precedes changes in cognition and motor functioning – this box should be checked in such instances.
Sleep-Related Topics of Interest in the ADC Program/NACC

**Form D2: Clinician-assessed Medical Conditions**

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<td>14. Sleep apnea</td>
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<tr>
<td>15. REM sleep behavior disorder (RBD)</td>
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<tr>
<td>16. Hyposomnia/insomnia</td>
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<tr>
<td>17. Other sleep disorder (SPECIFY):</td>
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<td></td>
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</table>
Collaborators/Support

Rick Caselli, MD  
Daniel Drubach, MD  
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Neill Graff-Radford, MBChB  
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Mayo ADRC Staff

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International Dementia with Lewy Bodies Conference

December 1-4, 2015

Marriott Harbor Beach Resort & Spa
Fort Lauderdale, Florida
Abstract Deadline – June 2015

Diagnosis
Epidemiology
Clinical aspects
Neuropsychology
Neuroimaging
Therapeutics

Genetics
Biofluid markers
Neuropathology
Molecular biology
Animal models
Controversies
Mild cognitive impairment associated with limbic and neocortical Lewy body disease: a clinicopathological study

Jennifer Molano, Bradley Boeve, Tanis Ferman, Glenn Smith, Joseph Parisi, Dennis Dickson, David Knopman, Neill Graff-Radford, Yonas Geda, John Lucas, Kejal Kantarci, Maria Shiung, Clifford Jack, Michael Silber, V. Shane Pankratz and Ronald Petersen

Table 1 Clinical features of eight patients with mild cognitive impairment± subsequent dementia associated with Lewy body disease pathology

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Educational level in years</th>
<th>Age of RBD onset in years</th>
<th>Age of cognitive symptom onset in years</th>
<th>Age of MCI diagnosis in years</th>
<th>Age of parkinsonism onset in years</th>
<th>Age of VH onset in years</th>
<th>Fluctuations based on MFS, and onset in years</th>
<th>MCI subtype and specific cognitive domains of impairment</th>
<th>Age at conversion from MCI to dementia in years</th>
<th>Age of death in years</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>16</td>
<td>61</td>
<td>66</td>
<td>70</td>
<td>71</td>
<td>--</td>
<td>No</td>
<td>md-MCI-na Attention/visuospatial</td>
<td>--</td>
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<td>2</td>
<td>M</td>
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<td>83</td>
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<td>88</td>
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<td>sd-MCI-na Attention</td>
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<td>90</td>
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<td>14</td>
<td>57 PSG+</td>
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<td>Yes 78</td>
<td>md-MCI-na Attention/visuospatial</td>
<td>77</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>12</td>
<td>51</td>
<td>62</td>
<td>66</td>
<td>66</td>
<td>66</td>
<td>Yes 68</td>
<td>md-MCI+a Memory/attention/visuospatial</td>
<td>67</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>14</td>
<td>60 PSG+</td>
<td>69</td>
<td>71</td>
<td>71</td>
<td>72</td>
<td>Yes 72</td>
<td>md-MCI+a Memory/language/visuospatial</td>
<td>73</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>12</td>
<td>--</td>
<td>67</td>
<td>67</td>
<td>69</td>
<td>64</td>
<td>No (no MFS)</td>
<td>md-MCI+a Memory/language/visuospatial</td>
<td>69</td>
<td>73</td>
</tr>
</tbody>
</table>

M = male; F = female; RBD = REM sleep behaviour disorder; PSG+ = polysomnogram-proven RBD; MCI = mild cognitive impairment (a = amnestic; na = nonamnestic; sd = single domain; md = multiple domain); VH = visual hallucinations; MFS = Mayo Fluctuations Scale.
RBD-LBD Association
RBD Precedes Cognitive Impairment/Parkinsonism

Molano et al, Brain 2010
RBD-LBD Association
RBD Precedes Cognitive Impairment/Parkinsonism

Age

General Timeline of Features

RBD Precedes Cognitive Impairment/Parkinsonism

Adapted from Molano et al, 2010 and Fields et al, 2011
RBD-LBD Association
RBD Precedes Cognitive Impairment/Parkinsonism

Early Symptomatic

Prodromal

RBD

MCI

Neurodegenerative Syndrome

DLB

Function

Age
Obstructive Sleep Apnea

Consider screening for OSA with overnight oximetry in appropriate patients

Normal

OSA
67 yr old woman with 2 year history of cognitive decline
- Forgetful, errors in arranging family activities, multi-tasking difficult
- Rare errors balancing checkbook, but living independently, driving OK

- MMSE 27/30
- General neurologic exam normal
- Crowded oropharynx
Obstructive Sleep Apnea
Case Example

Neuropsychologic Profile

MOANS (Mean 10, SD 3)

Cognitive Measures and Domains

Global, Memory, Language, Attention, Executive, Visuospatial
Obstructive Sleep Apnea
Case Example

• Labs normal, MRI head normal
• Dx: mild cognitive impairment
• Overnight oximetry:
Case example (cont)

- PSG – moderately severe OSA (AHI >30)
- Commenced on nasal CPAP
- Excellent response, tolerated CPAP well
- Within 1-2 months cognitive problems resolved

- Returned 1 year later
Obstructive Sleep Apnea
Case Example

Neuropsychologic Profile

Cognitive Measures and Domains

Global
Memory
Language
AttentionExecutive
Visuospatial

DRS-2
WMS-R LM % R
WMS-R VR % R
AVLT Delay
BNT
Letter Flu
Categ Flu
TMT A
TMT B
Stroop CW
Rey O
WAIS-BD
JLO

MOANS (Mean 10, SD 3)
Dementia with Lewy Bodies
Many Sleep Issues in DLB

Polysomnographic Findings in Dementia With Lewy Bodies

Winnie C. Pao, MD,* † Bradley F. Boeve, MD,* † Tanis J. Ferman, PhD,‡ Sioung-Chi Lin, MD, †
Glenn E. Smith, PhD, † David S. Knopman, MD,* Neill R. Graff-Radford, MBChB,*
Ronald C. Petersen, PhD, MD,* Joseph E. Parisi, MD,* ‡ Dennis W. Dickson, MD, ||
and Michael H. Silber, MBCbB* †

Pao et al, The Neurologist 2013
Dementia with Lewy Bodies
Many Sleep Issues in DLB

Main points

- RBD is common (83%)
- PLM arousals are common
  - 45% had >5 arousals/hr
- AFNARs are very common
  - 76% had >5 arousals/hr
- Sleep efficiency is poor
  - 72% had <80%
  - 49% had <70%

Pao et al, The Neurologist 2013
Dementia with Lewy Bodies
DLB Patients Are Hypersomnolent

The data confirms subjective (ESS) and objective evidence of EDS (MSLT) is present in DLB and not in AD.

Ferman et al, Alz Res Therapy 2014
The data suggests that hypersomnia is present in DLB and not in AD.

Ferman et al, Alz Res Therapy 2014
Dementia with Lewy Bodies
DLB Patients Struggle to Maintain Wakefulness

Boeve et al, AAN 2012
Dementia with Lewy Bodies
DLB Patients Struggle to Maintain Wakefulness

Open label pilot study of armodafinil for treatment of hypersomnia associated with DLB

**Maintenance of Wakefulness Test Results**

- Baseline
- Armodafinil 250 mg

**Epworth Sleepiness Scale Results**

- Baseline
- Armodafinil 250 mg

Both results show a significant improvement with armodafinil compared to baseline, with p-values of 0.003 and 0.0001 respectively.
### REM Sleep Behavior Disorder and Relevance to Neurodegenerative Disease

**Salient Points:**

- RBD is common in MCI/DLB and usually precedes the cognitive features by years or decades.
- Many other sleep issues in DLB, including hypersomnia.
REM Sleep Behavior Disorder and Relevance To Neurodegenerative Disease

Parkinson’s Disease/Dementia With Lewy Bodies/
Lewy Body Disease Phenomenology:

LBD Phenomenology
Lewy Body Disease

Lewy body
Lewy Body Disease

Ach
DA
5-HT
NE
Glu
HCT
Lewy Body Disease

- anosmia
- dysrythmia
- constipation
- erectile dysfunction
- urinary dyscontrol
- cognitive impairment
- visual hallucinations
- hypersomnia
- parkinsonism
- sleep fragmentation
- depression
- anxiety
- orthostatic hypotension
- RBD
Lewy Body Disease

Cognitive

Neuropsychiatric

Motor

Smell

Sleep

Autonomic

LBD
REM Sleep Behavior Disorder and Relevance To Neurodegenerative Disease

Parkinson’s Disease/Dementia With Lewy Bodies/
Lewy Body Disease Phenomenology:

The PD-Predominant Phenotype

The DLB-Predominant Phenotype
Lewy Body Disease
Major Clinical Phenotypes

**Motor**

<table>
<thead>
<tr>
<th>Normal</th>
<th>Mild Parkinsonian Signs</th>
<th>Parkinson’s Disease</th>
<th>Parkinson’s Disease + Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>NI</td>
<td>MPS</td>
<td>PD</td>
</tr>
<tr>
<td>MCI</td>
<td>PD + MCI</td>
<td>PDD</td>
<td></td>
</tr>
</tbody>
</table>

**Cognitive**

<table>
<thead>
<tr>
<th>Normal</th>
<th>Mild Cognitive Impairment</th>
<th>Dementia with Lewy Bodies</th>
</tr>
</thead>
</table>
Lewy Body Disease

Functioning

MCI MPS

Dementia Parkinsonism

Time
Lewy Body Disease
Parkinson’s Disease-Predominant Phenotype

MPS PD PD+MCI PDD
Lewy Body Disease
Dementia with Lewy Bodies-Predominant Phenotype

Functioning vs. Time

MCI  DLB
Lewy Body Disease

Functioning

Time

RBD onset

RBD

MCI

MPS

Dementia

Parkinsonism
REM Sleep Behavior Disorder and Relevance To Neurodegenerative Disease

Idiopathic RBD Analyses

Retrospective Analyses
Idiopathic RBD

**Definition**
- Presence of RBD in the absence of any other obvious neurologic signs/symptoms or disorders

**Prevalence**
- 0.5% to 9% (depending on population studied)
RBD preceded neurodegenerative syndrome (n=170):

- >50% of cases
- mean – 10 years
- range – 1-61 years

Pathology in PSG proven cases (n=82):

- LBD +/- AD
- MSA
- AD
- PSP
- Other

Boeve BF et al, Sleep Med 2013
Analyses have repeatedly shown that when RBD is associated with a neurodegenerative disease:

- The neurodegenerative syndrome is almost always (>95%) within the presumed synucleinopathy spectrum (eg, PD, DLB, MSA, PAF)

- RBD usually precedes the onset of cognitive impairment, parkinsonism or autonomic dysfunction by years or decades
REM Sleep Behavior Disorder and Relevance To Neurodegenerative Disease

Idiopathic RBD Analyses

Cross-Sectional Correlative Analyses
Idiopathic RBD
Correlative Analyses

Abnormalities demonstrated on measures of:

- Olfaction
- Color vision
- Motor functioning
- Mood
- Anxiety
- Apathy
- Neuropsychological functioning
- Autonomic testing
- EEG
- MRI/MRS/fMRI/DTI
- MIBG
- Perfusion SPECT
- DaTscan
- FDG-PET
- FD-PET

Numerous investigators
DaTscan
Correlative Analyses

AD
mPOR
2.41

RBD + DLB
mPOR
1.01
DaTscan Correlative Analyses

- AD
  - mPOR: 2.41

- aMCI
  - mPOR: 2.31

- RBD+ naMCI
  - mPOR: 2.1

- RBD + DLB
  - mPOR: 1.01

Boeve et al, AAN 2013
DaTscan Correlative Analyses

AD mPOR 2.41
aMCI mPOR 2.31
iRBD mPOR 2.49
RBD+naMCI mPOR 2.1
RBD+DLB mPOR 1.01
Idiopathic RBD
Correlative Analyses

Salient Points

• A significant proportion of iRBD patients have demonstrable abnormalities on 1 or more measures

• Abnormalities on these measures are most consistent with early/evolving Lewy body disease
Theoretical Evolution of Clinical Manifestations According to Braak Stage in the Prototypical DLB Phenotype of Lewy Body Disease

<table>
<thead>
<tr>
<th>Clinical Phase</th>
<th>Prodromal</th>
<th>Cognitive Impairment</th>
<th>Cognitive Impairment + Parkinsonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braak Stage</td>
<td>1 2 3 4 5 6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Degree of Abnormality

- 80%
- 50%
- 20%

Time

- Autonomic
- Smell
- RBD
- Mood
- Cognitive
- Motor
- Visual hallucinations and delusions
**Parkinson’s Disease/Lewy Body Disease**

**Braak Staging Scheme**

<table>
<thead>
<tr>
<th>Braak stage</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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</thead>
<tbody>
<tr>
<td>RBD</td>
<td>NI</td>
<td>+/-</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Smell tests</td>
<td>↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Autonomic tests</td>
<td>↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Motor tests</td>
<td>NI</td>
<td>NI</td>
<td>+/-</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Neuropsych tests</td>
<td>NI</td>
<td>NI</td>
<td>+/-</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Electrophysiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMG atonia during REM sleep</td>
<td>NI</td>
<td>↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
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<tr>
<td>EEG activity</td>
<td>NI</td>
<td>NI</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Imaging</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MIBG</td>
<td>↓</td>
<td>↓</td>
<td>↓down</td>
<td>↓down</td>
<td>↓down</td>
<td>↓down</td>
</tr>
<tr>
<td>DaTscan or FD-PET</td>
<td>NI</td>
<td>NI</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>MRI or MRS or TS changes</td>
<td>NI</td>
<td>NI</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>FDG-PET</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
</tbody>
</table>

Boeve BF. Lancet Neurology 2013
Framework of RBD Within Braak Staging Scheme

Key for degeneration of nuclei and axons:
- None
- Mild
- Moderate
- Severe

Braak 2
- Neocortex
- Limbic system
- Substantia nigra
- Sublaterodorsal nucleus
- Magnocellular reticular formation
- RSWA
- Muscle
- Spinal cord

Braak 3
- Neocortex
- Limbic system
- Substantia nigra
- Sublaterodorsal nucleus
- Magnocellular reticular formation
- RBD
- Muscle
- Spinal cord

Braak 4
- Neocortex
- Limbic system
- Substantia nigra
- Sublaterodorsal nucleus
- Magnocellular reticular formation
- RBD
- Muscle
- Spinal cord

Braak 5
- Neocortex
- Limbic system
- Substantia nigra
- Sublaterodorsal nucleus
- Magnocellular reticular formation
- RBD
- Muscle
- Spinal cord
Framework of RBD Within Braak Staging Scheme

Function

Age

- Normal
- iRBD
- MCI
- MPS
- DLB
- PD
Framework of RBD Within Braak Staging Scheme

<table>
<thead>
<tr>
<th>Braak 0</th>
<th>Braak 3</th>
<th>Braak 4</th>
<th>Braak 5/6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>iRBD</td>
<td>MCI MPS</td>
<td>DLB PD</td>
</tr>
</tbody>
</table>

Function

Age
Framework of RBD Within Braak Staging Scheme

- Normal
- Prodromal RBD
- iRBD
- MCI MPS
- DLB PD

Function vs Age
Framework of RBD Within Braak Staging Scheme

<table>
<thead>
<tr>
<th>Function</th>
<th>Age</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Braak 0</td>
</tr>
<tr>
<td>Prodromal RBD</td>
<td>Braak 2</td>
</tr>
<tr>
<td>iRBD</td>
<td>Braak 3</td>
</tr>
<tr>
<td>MCI MPS</td>
<td>Braak 4</td>
</tr>
<tr>
<td>DLB PD</td>
<td>Braak 5/6</td>
</tr>
</tbody>
</table>
REM Sleep Behavior Disorder and Relevance To Neurodegenerative Disease

Planning for Disease-Modifying Therapies in LBD:

“The RBD Window of Opportunity”
Planning for Disease-Modifying Therapies in LBD
Planning for Disease-Modifying Therapies in LBD

Assessment Measures

Functioning

Time

MCI
MPS

Dementia Parkinsonism
Planning for Disease-Modifying Therapies in LBD

Functioning

Assessment Measures

MCI
MPS

Dementia
Parkinsonism

Time

Rx
Planning for Disease-Modifying Therapies in LBD
Planning for Disease-Modifying Therapies in LBD

RBD onset

Assessment Measures

Functioning

MCI
MPS

Dementia Parkinsonism

Time
Rapid eye movement sleep behavior disorder: devising controlled active treatment studies for symptomatic and neuroprotective therapy—a consensus statement from the International Rapid Eye Movement Sleep Behavior Disorder Study Group


Sleep Medicine 2013
Assessment Measures

Clinical
Screening mental status exam (MMSE, MoCA)
Motor examination (UPDRS)
Olfactory, color vision

Neuropsychological
Measure each cognitive domain

Electrophysiologic
EEG, PSG, MSLT, MWT

Biofluid
Blood
CSF (amyloid, tau, TDP-43, α-synuclein)

Neuroimaging
MR – MRI, MRS, fMRI, DTI
PET – FDG, PiB
SPECT – DaTSCAN, MIBG
TCS
Planning for Disease-Modifying Therapies in LBD
Theoretical Considerations for RBD to MCI to DLB

Degree of Abnormality

Age

RBD
MCI
DLB

Red: DaTscan
Blue: FDG-PET
Orange: Cognition
Planning for Disease-Modifying Therapies in LBD
Theoretical Considerations for RBD to MCI to DLB

Degree of Abnormality

RBD  MCI  DLB

Age

DaTscan
FDG-PET
Cognition

Planning for Disease-Modifying Therapies in LBD
Theoretical Considerations for RBD to MCI to DLB

Degree of Abnormality

RBD  MCI  DLB

Age

DaTscan
FDG-PET
Cognition
Planning for Disease-Modifying Therapies in LBD
Theoretical Considerations for RBD to MCI to DLB
Planning for Disease-Modifying Therapies in LBD

Question 1: Idiopathic RBD

Question 2: Neurodegenerative disorder
- Parkinson's disease
- Dementia with Lewy bodies
- Multiple system atrophy
- Pure autonomic failure
- Incidental Lewy body disease

Question 3: Non-neurodegenerative disorder
- Synucleinopathy
- Non-synucleinopathy

Question 4: Test

Cognitive, motor or autonomic functioning:
- Onset of RBD
- A
- B
- C

Age
Planning for Disease-Modifying Therapies in LBD

- RBD onset
- Assessment Measures
- MCI
- MPS
- Dementia Parkinsonism

Functioning

Rx

Time
Planning for Disease-Modifying Therapies in LBD

Immunotherapy for neurodegenerative diseases: Focus on α-synucleinopathies
Elvira Valera, Eliezer Masliah

Pharm Ther 2013

α-Synuclein Immunotherapy Blocks Uptake and Templated Propagation of Misfolded α-Synuclein and Neurodegeneration
Hien T. Tran,1,2 Charlotte Hiu-Yan Chung,1 Michiyu Iba,1 Bin Zhang,1 John Q. Trojanowski,1 Kelvin C. Luk,1 and Virginia M.Y. Lee1,*

Tran et al, Cell Reports 2014
Planning for Disease-Modifying Therapies in LBD

Delay the onset and/or slow the course of parkinsonism and/or dementia

Assessment Measures

Functioning

RBD onsets

Rx

Time
Future Directions

• Advance our understanding of the pathophysiology of human RBD

  • Which specific nuclei/networks are involved?

  • Are networks involved in REM sleep control selectively vulnerable to neurodegeneration, particularly in the synucleinopathies? If so, why?
Future Directions

• Study the **natural history** of RBD, RBD+MCI, RBD+MPS to prepare for future disease modifying therapies
  • Identify which iRBD pts have an underlying **neurodegenerative disorder**
  • Identify which **proteinopathy** (ie, α-synuclein, tau, etc.) is causing RBD in those with an underlying neurodegenerative disorder
  • Identify which **phenotype** will evolve, and when
  • Identify those at **short-term risk** of developing parkinsonism and/or cognitive impairment for treatment trials
Future Directions

• Support or refute the **Braak staging scheme** as it relates to RBD, and to the MCI/DLB phenotype

• **Screen for RBD** to assess epidemiology of the parasomnia, and to detect those who could benefit from eventual therapy

• Characterize “prodromal RBD” by quantifying the degree of **RSWA** on PSGs for clinical and research purposes; characterize **REM behavioral events**

• Develop or refine more optimal **biomarkers** for the synucleinopathies
International Dementia with Lewy Bodies Conference

December 1-4, 2015

Marriott Harbor Beach Resort & Spa

Fort Lauderdale, Florida

Abstract Deadline – June 2015

Diagnosis
Epidemiology
Clinical aspects
Neuropsychology
Neuroimaging
Therapeutics

Genetics
Biofluid markers
Neuropathology
Molecular biology
Animal models
Controversies
Collaborators/Support

Mike Silber, MBChB  
Erik St. Louis, MD  
Suresh Kotagal, MD  
Siong-Chi Lin, MD  
Maja Tippmann-Peikert, MD  
Mithri Junna, MD  
Melissa Lipford, MD  
Tanis Ferman, PhD  
Glenn Smith, PhD  
Robert Ivnik, PhD  
John Lucas, PhD  
Rick Caselli, MD  
Daniel Drubach, MD  
Neill Graff-Radford, MBChB  
Keith Josephs, MD  
David Knopman, MD  
Ronald Petersen, PhD, MD  
Brendon Boot, MD  
Cliff Jack, Jr., MD  
Kejal Kantarci, MD  
Jennifer Whitwell, PhD  
Val Lowe, MD  

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