Lewy Body Dementia: Diagnosis, Management and Future Directions

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Disclosures

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Off-label and/or Investigational Use

- Will discuss use of many medications which are not FDA-approved for the indications to be reviewed
Dementia with Lewy Bodies/Lewy Body Dementia Outline

• Nomenclature

• Diagnostic Features

• Management Options

• Future Directions
Dementia With Lewy Bodies
Nomenclature

The Syndrome

- Dementia with Lewy bodies (DLB)/Lewy body dementia (LBD)
  - Clinically probable DLB
  - Clinically possible DLB

The Disease

- Lewy body disease (LBD)
  - brainstem
  - limbic
  - neocortical
Dementia With Lewy Bodies
Clinical Features and Diagnostic Criteria

Core features
Dementia syndrome plus:
• Spontaneous parkinsonism (unrelated to drugs)
• Recurrent fully formed visual hallucinations
• Fluctuating arousal/cognition

2 or 3 of above = clinically probable DLB
1 of above = clinically possible DLB

McKeith et al, Neurology 1996
McKeith et al, Neurology 1999
McKeith et al, Neurology 2005
Dementia With Lewy Bodies
Clinical Features and Diagnostic Criteria

Suggestive features
(one or more present in addition to one or more core features is sufficient for a diagnosis of probable DLB, and in the absence of any core features is sufficient for possible DLB)

• REM sleep behavior disorder (which may precede onset of dementia by several years)

• Severe neuroleptic sensitivity

• Abnormal (low uptake) in basal ganglia on SPECT dopamine transporter scan

Boeve et al. Neurology 1998
McKeith et al. Neurology 2005
Core features

Dementia syndrome plus:

- Spontaneous parkinsonism (unrelated to drugs)
- Recurrent fully formed visual hallucinations
- Fluctuating arousal/cognition
- RBD

Any 2 of the following c/w DLB

RBD plus 1 of the other features - >90% accurate

Ferman et al, Neurology 2012
Dementia With Lewy Bodies
Video Example - RBD

70 year old male severe RBD
The data confirms subjective (ESS) and objective evidence of EDS (MSLT) is present in DLB and not in AD.
The most frequent neuropsychiatric features in DLB:

- Visual hallucinations
- Illusions
- Delusions (including Capgras syndrome)
- Depression
- Apathy
# Cognitive Domains

<table>
<thead>
<tr>
<th>Cognitive Domains</th>
<th>Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning &amp; Memory</td>
<td>0 to ++</td>
</tr>
<tr>
<td>Language</td>
<td>0 to +</td>
</tr>
<tr>
<td><strong>Executive Functions</strong></td>
<td>+ to +++</td>
</tr>
<tr>
<td><strong>Visuospatial Functions</strong></td>
<td>+ to +++</td>
</tr>
</tbody>
</table>

Ferman et al, Neurology 1999
Ferman et al, Clin Neuropsych 2006
Dementia With Lewy Bodies
Neuropsychological Features

Impaired on:
Memory measures
BNT and/or Cat Flu

Impaired on:
TMT, Dig Symbol
WAIS-BD, -PC
Rey-O CFT

Ferman et al, Neurology 1999
Ferman et al, Clin Neuropsych 2006
Dementia With Lewy Bodies
Neuropsychological Features

Please draw this figure:

Draw a clock showing the time of 11:10:

Please draw this figure:
Dementia With Lewy Bodies
Neuroimaging Features

MRI

Normal

AD

DLB

normal hippocampi

hippocampal atrophy

normal hippocampi
Dementia With Lewy Bodies
Neuroimaging Features

MRI VBM

Whitwell et al, Brain 2007
Dementia With Lewy Bodies
Neuroimaging Features – FDG-PET

Normal
Dementia With Lewy Bodies
Neuroimaging Features – FDG-PET

Kantarci et al, Neurobiol Aging 2011
Dementia With Lewy Bodies

Neuroimaging Features - DaTscan

Ioflupane

DaTscan - measures nigrostriatal uptake of dopamine transporter in the caudate and putamen

Normal
Dementia With Lewy Bodies
Neuroimaging Features - DaTscan

AD

DLB
Dementia With Lewy Bodies
Neuropathologic Features

Ach
DA
5-HT
HCT-1

? (RBD)
Dementia With Lewy Bodies
Neuropathologic Features

H&E

α-synuclein

Photomicrographs courtesy Dennis Dickson, M.D.
Dementia With Lewy Bodies
Clinical Tools - ESS

Epworth Sleepiness Scale

Name: ____________________________ Today’s date: ___________

Your age (Yrs): ____________ Your sex (Male = M, Female = F): ____________

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven’t done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:

0 = would never done
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

It is important that you answer each question as best you can.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of Dozing (0-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td></td>
</tr>
<tr>
<td>Watching TV</td>
<td></td>
</tr>
<tr>
<td>Sitting, inactive in a public place (e.g. a theatre or a meeting)</td>
<td></td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td></td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
<td></td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td></td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td></td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in the traffic</td>
<td></td>
</tr>
</tbody>
</table>

Dementia With Lewy Bodies
Clinical Tools - MSQ

1. Have you ever seen the patient appear to “act out your dreams” while sleeping? (punched or flailed arms in the air; shouted or screamed)

SN: 100%  SP: 97%  Olmsted County

Mayo Sleep Questionnaire-Informant

Do you live with the patient?  Yes  No  (If No, END FORM HERE)
Do you sleep in the same room as the patient?  Yes  No
If no, is it because of his/her sleep behavior (i.e. moans too loud, sets out dreams, etc.)?  Yes  No
Please mark “Yes” if the described event has occurred at least 3 times.

1. Have you ever seen the patient appear to “act out his/her dreams” while sleeping? (punched or flailed arms in the air, shouted or screamed)
   – 0 no
   – 1 yes
   • If Yes,
     a. How many months or years has this been going on?
        • year(s)  months
     b. Has the patient ever been injured from these behaviors (bruises, cuts, broken bones)?
        • No  Yes
     c. Has a bedpartner ever been injured from these behaviors (bruises, blows, pulled hair)?
        • No  Yes  No bedpartner
     d. Has the patient told you about dreams of being chased, attacked or that involve defending himself/herself?
        • No  Yes  Never told you about dreams

http://www.mayoclinic.org/pdfs/MSQ-copyrightfinal.pdf
Dementia With Lewy Bodies
Clinical Tools - MFS

DLB fluctuations
Specific features that reliably differentiate DLB from AD and normal aging

T.J. Ferman, PhD; G.E. Smith, PhD; B.F. Boeve, MD; R.J. Ivnik, PhD; R.C. Petersen, MD, PhD; D. Knopman, MD; N. Graff-Radford, MBBCh, MRCP; J. Parisi, MD; and D.W. Dickson, MD

Mayo Fluctuations Scale

Clinic #_________________ Patient Name ___________________________ Date________
Informant________________________ Relationship to patient________________________

Please mark the answer that best describes the patient within the past 6 months

1. Is the patient drowsy and lethargic during the day, despite getting enough sleep the night before? ..................................................... ___ No ___ Yes

2. Does the patient sleep 2 or more hours during the day (before 7 pm)? ___No ___ Yes

3. Are there times when the patient’s flow of ideas are disorganized, unclear or not logical? ..................................................... ___No ___ Yes

4. Does the patient tend to stare into space for long periods of time? ___No ___ Yes

Ferman et al, Neurology 2004
Dementia With Lewy Bodies
Clinical Tools - Friedman

Friedman Palate Position

Friedman Tonsil Grading

Friedman et al, Laryngoscope 2004;114:454–459
Dementia With Lewy Bodies
Management

Consider symptoms as they relate to:

• cognitive impairment
• neuropsychiatric features
• motor features
• sleep disorders
• autonomic dysfunction

Ask patient/family to prioritize the most troublesome issues they seek to change.
Dementia With Lewy Bodies
Management

Cognitive impairment

- Varying degrees of memory impairment
- Verbal blocking
- Executive dysfunction
- Bradyphrenia
- Spatial/geographic disorientation
- Visual misidentification
- Fluctuations

Management

Education and counseling

Therapies:
- Aricept, Razadyne, Exelon
- Sinemet, Mirapex
- Provigil, Nuvigil, methylphenidate, Adderall
Cognition issues

- Mainly due to reduced Ach
- Reductions in other brain chemicals contributes to cognitive impairment
- Some degree of neuron cell loss too

Dementia With Lewy Bodies
Brain-Behavior Relationships

Ach  DA  5-HT  HCT
Dementia With Lewy Bodies
Management

**Neuropsychiatric features**
- Visual hallucinations
- Illusions
- Delusions
- Capgras syndrome
- Depression
- Anxiety
- Agitation/aggressive behavior

**Management**

**Education and counseling**

**Therapies:**
- Aricept, Razadyne, Exelon
- SSRIs, melatonin
- Seroquel, Zyprexa
- Provigil, Nuvigil, methylphenidate, Adderall

**NO HALDOL**
Neuropsychiatric issues

- Hallucinations and delusions related to DA imbalance
- Depression related to low 5-HT
- Apathy – many causes
Dementia With Lewy Bodies
Management

Motor dysfunction
- Tremor
- Bradykinesia
- Rigidity
- Myoclonus
- Shuffling gait
- Stooped posture
- Difficulty with fine motor skills
- Masked facies
- Sialorrhea

Management

Education and counseling

Therapies:
- Sinemet
- Mirapex, Requip,
  Neupro patch (when available)
- Clonazepam, Neurontin
Motor issues

- The Parkinson’s disease-like features (parkinsonism) primarily relate to the reduction in DA
Dementia With Lewy Bodies
Management

**Sleep disorders**
- REM sleep behavior disorder
- Excessive daytime somnolence
- Insomnia
- Obstructive sleep apnea
- Central sleep apnea
- Restless legs syndrome
- Periodic limb movement in sleep

**Management**

**Education and counseling**

**Therapies:**
- Clonazepam, Melatonin
- Provigil, Nuvigil,
  methylphenidate, Adderall
- Trazodone, Ambien,
  chloral hydrate
- nasal CPAP
- oxygen, temazepam
- Mirapex, Sinemet
Sleep issues

- Daytime sleepiness, insomnia, and fragmented sleep relate in part to the loss in HCT.
- Acting out dreams (RBD) relates to changes in the dorsal pons.
- Reduced DA and 5-HT also affects sleep.
Dementia With Lewy Bodies
Management

**Autonomic dysfunction**
- Orthostatic hypotension
- Impotence
- Urinary incontinence
- Constipation

**Management**
- Education and counseling
- **Therapies:**
  - Midodrine, Florinef, salt
  - Viagra, etc.
  - Enablex, Gelnique, Sanctura
  - Senokot, MiraLAX
Autonomic issues

- Many autonomic changes related to changes in the spinal cord and peripheral nerves in and around the:
  - heart
  - stomach
  - intestines
  - bladder
  - sex organs
Dementia With Lewy Bodies
Management

Initial evaluation

MMSE: 21
ESS: 14

donepezil
levodopa
CPAP

Follow-up evaluation

MMSE: 28
ESS: 4

Boeve BF. AAN Continuum 2004
Dementia With Lewy Bodies

Management

Initial evaluation
- MMSE: 7/30
- STMS: 21/38
- DRS: 52/144
- ESS: 15

Follow-up evaluation
- donepezil
- levodopa
- modafinil
- MMSE: 25/30
- STMS: 31/38
- DRS: 129/144
- ESS: 6
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

Brain 2010: 133; 540–556
Dementia With Lewy Bodies
Future Directions

Temporal Evolution of α-Synuclein Pathology Could Explain the Onset of RBD Before Parkinsonism and/or Dementia

Braak et al, Cell Tiss Res 2004
Boeve BF. Ann NY Acad Sci 2010
Dementia With Lewy Bodies
Future Directions

Assessment Tools

RBD onset

Functioning

Age

MCI MPS

DLB PD

PD

onset
Probable REM Sleep Behavior Disorder Increases Risk for Mild Cognitive Impairment and Parkinson’s Disease: A Population-Based Study

Brendon P. Boot¹ MBBS, Bradley F. Boeve¹,5 MD, Rosebud O. Roberts² MBChB, Tanis J. Ferman³ PhD, Yonas E. Geda²,³ MD MSc, V. Shane Pankratz² PhD, Robert J. Ivnik³ PhD, Glenn E. Smith³ PhD, Eric McDade¹a DO, Teresa J.H. Christianson² BSc, David S. Knopman¹ MD, Eric G. Tangalos⁴ MD, Michael H. Silber¹,5 MBChB, and Ronald C. Petersen¹,² PhD MD.

Departments of Neurology¹, Health Sciences Research², Psychiatry and Psychology³, Internal Medicine⁴, and Center for Sleep Medicine⁵, Mayo Clinic College of Medicine, Rochester, Minnesota, and Jacksonville, Florida.

Boot et al, Ann Neurol 2012
15/44 subjects developed MCI/PD (14 MCI, 1 PD) – HR 2.2

Boot et al, Ann Neurol 2012
Serial dopamine transporter imaging of nigrostriatal function in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study

Alex Iranzo, Francesc Valldeoriola, Francisco Lomeña, José Luis Molinuevo, Mónica Serradell, Manel Salamero, Albert Cot, Domèneç Ros, Javier Pavía, Joan Santamaria, Eduardo Tolosa
Dementia With Lewy Bodies
Future Directions

Normal  RBD  RBD  RBD

Boeve et al, unpublished data
Dementia With Lewy Bodies
Future Directions

Delay the onset and slow the course of symptoms

Assessment Tools

Rx
Dementia With Lewy Bodies

Resources

Lewy Body Dementia Association

http://www.lbda.org/

Please access this website and check it at least monthly, review the newsletter
Dementia With Lewy Bodies

Resources

Living With Lewy’s
Empowering Today’s Dementia Caregiver
A Revolutionary New Survival Guide For All Caregivers
Especially For Caregivers Of Patients With: Dementia With Lewy Bodies, Alzheimer’s And Other Dementias

Written By Family Caregivers For Caregivers
Amy J. Throop and Gerald S. Throop

Foreword by Carol F. Lippa, M.D., Professor of Neurology, Director, Memory Disorders Program and Dementia Research Laboratory at Drexel University College of Medicine

The Parkinson’s Disease Treatment Book
Partnering with Your Doctor to Get the Most from Your Medications

Effective medication and nutrition strategies
Advice on treating anxiety, depression, sleep problems, dementia, and sexual dysfunction

Helen Buell Whitworth
James Whitworth

Lewy Body Dementia

A Caregiver’s Guide To
Dementia With Lewy Bodies

Resources

In addition to the seminars for families, please consider attending Meeting of the Minds Dementia Conference. To register for this conference go to: www.alz.org/mind/

The Meeting of the Minds Dementia Conference is the premier dementia conference for persons with MCI or early dementia, families, friends and professionals. The conference is co-sponsored by the Alzheimer’s Association Minnesota-North Dakota Chapter and Mayo Clinic, who work together to create a day designed to inform, equip and support persons with dementia, family caregivers and professionals. The historically sold-out conference will be held at the RiverCentre in St. Paul, Minnesota on Saturday, March 17, 2012.
Collaborators/Support

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Maja Tippmann-Peikert  
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Joseph Parisi, MD  
Dennis Dickson, MD

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