Overview of LBD Research
Leah K. Forsberg, Ph.D.
Outline

• LBDA Centers of Excellence
• LBD Research and Biomarkers
• Current Research Studies at Mayo
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• LBDA Centers of Excellence
• LBD Research and Biomarkers
• Current Research Studies at Mayo
Research Centers of Excellence

• The LBDA created Research Centers of Excellence (RCOE)

• Primary Goals of the program:
  1). Improve LBD Clinical Care
  2). Develop a clinical trials-networks and the associated infrastructure

• Currently 25 centers around the United States have been designated Centers of Excellence
LBDA RCOE Program

25 centers

https://www.lbda.org/rcoe
RCOE Objectives

Improving Clinical Care

1) identify the optimal tools for clinical diagnosis

2) define the standards of care for management throughout the course of the disorder

3) promote continuing medical education to health care providers

4) operate and maintain LBD-specific resources, support groups and programs

Developing Clinical Trial Ready Network

1) review the landscape of clinical measures and biomarkers pertinent to LBD trial methodology

2) determine the optimal core and supplemental battery of measures for clinical trials, and develop new measures when needed

3) expand relationships with industry partners

4) determine core principles for LBD trials
   - (ie, minimize pt/family burden, master trial agreements, data/sample/scan sharing, etc.)
LBDA RCOE Investigators and Staff

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Todd Graham
Ian Richards
Angela Taylor
Mark Wall
Outline

• LBDA Centers of Excellence
• LBD Research and Biomarkers
• Current Research Opportunities at Mayo
Lewy Bodies and Alpha-synuclein

Alpha-synuclein protein is a major component of Lewy Bodies

Lewy bodies affect different parts of the brain:

- Brainstem—important for regulating sleep and maintaining alertness
- Limbic—regulates emotion and behavior
- Cerebral cortex—controls many functions like information processing, perception, thought, and language
- Hippocampus—essential to forming new memories
- Midbrain and basal ganglia—involved in movement

Photomicrographs courtesy Dennis Dickson, MD
## Clinical Features of DLB

<table>
<thead>
<tr>
<th>Symptom/sign</th>
<th>Manifestation</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>Attention, visual spatial &gt; memory</td>
<td>100</td>
</tr>
<tr>
<td>Core features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluctuations</td>
<td>Altered levels of attention</td>
<td>60</td>
</tr>
<tr>
<td>Visual hallucinations</td>
<td>Recurrent, fully formed</td>
<td>50-75</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Action &gt; rest tremor</td>
<td>75</td>
</tr>
<tr>
<td>REM sleep behavior disorder</td>
<td>Act out dreams</td>
<td>79</td>
</tr>
</tbody>
</table>

Slide courtesy of Dr. Jon Graff-Radford
Research Biomarkers

What is a Biomarker?

A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.—NCI

A measurable substance in an organism whose presence is indicative of some phenomenon such as disease, infection, or environmental exposure.—Dictionary.com
Theoretical Biomarker Framework

Biomarker Measure  Clinical Measure

<table>
<thead>
<tr>
<th>Age/Time</th>
<th>Clinical Measure</th>
<th>Biomarker Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewy Body Dementia</td>
<td>Abnormal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>“MCI”</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal (presymptomatic)</td>
<td>Normal</td>
<td>Normal</td>
</tr>
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</table>
Research Biomarkers for LBD

• Neuropsychology
• Sleep studies
• Blood
• CSF
• Skin/salivary gland biopsy
• MRI
• DaTscan
• Glucose (FDG) PET
• Amyloid (PiB, other) PET
• Tau (AV1451, other) PET
• Brain donation
Neuropsychology as a Biomarker

Impaired on:
- Memory measures
  - AD
  - DLB

Impaired on:
- Attention/executive and visuospatial measures
  - AD
  - DLB

Ferman et al, Neurology 1999
Ferman et al, Clin Neuropsych 2006
Neuropsychology as a Biomarker

Impaired on:
Memory measures

AD

DLB

Ferman et al, Neurology 1999
Ferman et al, Clin Neuropsych 2006
Bloodwork

- Rule out other systemic cause for cognitive changes
- Blood count, electrolytes, thyroid hormone, B12

Lumbar Puncture

- Sometimes done (particularly in atypical cases)
- Can assess whether there is an infectious, autoimmune, or inflammatory disorder present
- Can detect biomarkers for Alzheimer’s disease
Bloodwork

• Rule out other systemic cause for cognitive changes
• Blood count, electrolytes, thyroid hormone, B12

Lumbar Puncture

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• Can assess whether there is an infectious, autoimmune or inflammatory disorder present
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Currently we’re looking for proteins in the blood or cerebral spinal fluid that might be related to LBD or LBD progression
Dementia With Lewy Bodies
Radiologic Evaluation: MRI

Normal    AD    DLB

Slide courtesy of Dr. Jon Graff-Radford
Dementia With Lewy Bodies
Radiologic Evaluation: FDG PET

DLB

Normal

AD

Slide courtesy of Dr. Jon Graff-Radford
Dementia With Lewy Bodies
Radiologic Evaluation: Amyloid PET

Normal | DLB
Dementia With Lewy Bodies
Radiologic Evaluation: DaT Scan

Ioflupane binds presynaptically to the dopamine transporter receptors (DaT)

DLB

Normal
Importance of Biomarker Collection

A better understanding of changes in your body due to disease progression will:

• Improve diagnosis of DLB

• Identify biomarker changes that are linked to certain clinical symptoms

• Inform clinical trials
  • Tests that measure disease change can be used to understand if a therapeutic is working
Importance of Biomarker Collection

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- Improve diagnosis of DLB
- Identify biomarker changes that are linked to certain clinical symptoms
- Inform clinical trials
  - Tests that measure disease change can be used to understand if a therapeutic is working

But….How do we collect biomarkers? How often do we collect biomarkers? Who do we collect biomarkers on?
Outline

• LBDA Centers of Excellence
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Dementia with Lewy Body Related Research Opportunities

Lewy Body Disease

- Mayo Clinic Lewy Body Disease Functional Genomics Program
  - To understand the role genes, proteins, lipids, diet, microbiome, and other lifestyle factors relate to LBD.
  - 1-time visit for those with LBD
  - Clinical Exam, blood draw, stool sample, skin punch

REM Sleep Behavior Disorder (RBD)

- North American Prodromal Synucleinopathy Consortium (NAPS)
  - To collect information on RBD and help plan a future treatment study
  - 2 year study for those with RBD
  - Clinical Exam, Neuropsych Testing, Questionnaires, Blood Draw, LP
Dementia with Lewy Body Related Research Opportunities Continued

Dementia with Lewy Bodies (DLB)

- Longitudinal Imaging Biomarkers of Disease Progression in DLB (DLBU01)
  - See next series of slides

- Integrated Neurocognitive and Sleep-Behavior Profiler for the Endophenotypic Classification of Dementia Subtypes (INSPECDS)
  - Characterizing neuropsychological biomarkers for progression of neurodegenerative disease
  - Single visit with questionnaires, computerized tasks, sleep profiler device, clinical exam
Highlighted Research Study:
Longitudinal Imaging Biomarkers of Disease Progression in DLB Framework

Purpose: To determine the paths of change in imaging biomarkers of DLB and the associated rates of cognitive and functional decline.
Mayo Clinic DLB Research Consortium Cohort

Patients with probable dementia with Lewy bodies (n=90) with baseline and at least a six month and 2 annual follow-up assessments

Mayo Clinic Rochester (currently 46 participants)
Mayo Clinic Florida (currently 12 participants)
Assessments and Procedures
5 Year study, with 6 clinic visits

Visit 1
- Blood draw
- Neuropsych testing
- MRI
- TAU PET
- Amyloid PET
- DaTScan
- Clinical Assessments
- Lumbar puncture (Optional)

6 month Visit
- Blood draw
- Neuropsych testing (brief)
- Clinical Assessments

Annual Visits (years 2-5)
- Blood draw
- Neuropsych testing
- MRI
- Amyloid PET
- DaTScan
- Clinical Assessments
- Lumbar puncture (Optional)
Assessments and Procedures
5 Year study, with 6 clinic visits

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There are data repositories where many LBD research studies from across the United States send samples for storage. This allows LBD researchers access to the collected samples.
LBD Research at Mayo

• Thank you to everyone participating in research at any institution

• Interested in participating in research at the Mayo Clinic?
  • Call our research center at 507-293-5011

• Coming soon:
  • Phase II study with Neflamapimod (drug) for those with DLB
General LBD Research Resources

• LBDA has information on research studies
  • Find out more: https://www.lbda.org/rcoe

• Parkinson’s Disease Biomarker Program, supports many research studies (including the large Mayo DLB biomarker study)
  • Find out more: https://pdbp.ninds.nih.gov/
### Collaborations and Support

#### Behavioral Neurology
- Laura Allen, APRN, CNP
- Hugo Botha, MBChB
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- Bryan Woodruff, MD

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- Margaret Moutvic, MD

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- Jenny Evans
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- Leah Forsberg, PhD
- Jenny Hurt
- Ruth Kraft
- Paul Lewis
- Angela Lunde, MA
- Joel Miller
- Kevin Nelson
- Ryan Potaracke
- Josie Williams, MBA

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- Todd Graham
- Ian Richards
- Angela Taylor
- Mark Wall

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- Mike Silber, MBChB
- Erik St Louis, MD
- Maja Tippmann-Piekert, MD

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- Julie Steirwalt, PhD

#### Sleep Medicine
- Heather Clark, PhD
- Julie Steirwalt, PhD

#### PM&R
- Sarah Boyd, DPT
- Sarah Dahlhauser, OT
- Margaret Moutvic, MD

#### Neurogenic
- Numerous colleagues in US, Europe, Asia, Australia

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LBD Research

Functioning

Prodromal DLB/ RBD

MCI

Lewy Body Dementia

Age

Rx

Rx

Rx

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