Improving diagnosis of Alzheimer’s disease and lewy body dementia

Brain TLC
October 2018
Plan for this discussion:

- Introduction to AD and LBD
- Why do we need to improve diagnosis?
- What progress has been made?
- What research is currently under way at OHSU?
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- **Parkinson’s disease** = A disease of movement With dementia occurring Years after diagnosis.
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- **Amyloid plaques**

- **Neurofibrillary tangles**

- **Cerebral atrophy**
Parkinson’s disease

- Tremor
- Rigidity
- Bradykinesia
- Gait disorder
Cognitive Impairment in PD

- Dementia
  - 20% of PD have mild cognitive impairment (MCI) at time of PD diagnosis
  - 30-40% of all PD have dementia
  - Up to 80% by 15 years into disease
  - 4-6x greater than elderly without PD
Alzheimer’s vs Parkinson’s:

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<th>PD Dementia</th>
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<td>Attention</td>
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<td>Memory</td>
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<td>Executive</td>
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What is “Lewy body dementia”?

• A dementia characterized by:
  – Parkinsonism
  – Hallucinations
  – Sensitivity to anti-psychotic medications
  – Fluctuations
  – Brain autopsy shows lewy bodies in the brain
What is “Lewy body dementia”?

- “Sensitivity to antipsychotic medications” is part of Lewy body dementia.
  - Patients can become “frozen” from low doses of these medications
- Fluctuations in level of consciousness are also common in Lewy body dementia.
What is “Lewy body dementia”? 

- The “cognitive profile” looks like Parkinson’s dementia
- Brain autopsy shows Lewy bodies in the “thinking parts” of the brain
- (Lewy bodies confined to “movement parts” of the brain in Parkinson’s)
How is Lewy body dementia different from Parkinson’s disease?

- In Parkinson’s disease, the dementia appears several years after diagnosis of movement problems.
- In Lewy body dementia, the movement problems and the dementia come on together.
How is Lewy body dementia different from Parkinson’s disease?

- Tremor is less common
- Slowness and stiffness are more symmetric
- Motor symptoms are less responsive to medication in Lewy body dementia than in Parkinson’s disease
How is Lewy body dementia different from Parkinson’s disease?

• In Parkinson’s disease, hallucinations are promoted by the drugs used to treat Parkinson’s disease.
• In Lewy body dementia, hallucinations appear without being triggered by any drugs.
Why is it important to recognize Lewy body dementia?

• Need to be careful with Parkinson’s medicines, because they will increase hallucinations.
• Need to be careful with medicine for hallucinations, because it worsens parkinsonian motor symptoms.
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Why do we need to improve diagnosis?

• Until recently, the only way to diagnose AD or DLB was at brain autopsy
• We need precise diagnosis in order to identify appropriate patients for testing new treatments.
• We also need diagnostic markers that we can monitor during testing of new treatments.
Example of treatment target requiring precise diagnosis: Lewy body:

• Aimed at underlying pathology: Lewy bodies, the chief component of which is alpha synuclein:
Example of disease process requiring precise diagnosis: spread of lewy bodies:

Braak stages 1 and 2
Autonomic and olfactory disturbances

Braak stages 3 and 4
Sleep and motor disturbances

Braak stages 5 and 6
Emotional and cognitive disturbances

Via olfactory bulb
Premotor symptoms
Via vagus nerve
Motor symptoms

Brainstem Lewy body
Cortical Lewy body
Example of treatment requiring precise diagnosis: antibody therapy:

(A) Neuronal uptake and Microglial activation lead to Neurodegeneration.

(B) Neuronal uptake and Microglial degradation lead to Neuroprotection.
Designing a clinical trial

• selecting the patients: want to be sure that the patients have lewy bodies in their brain before enrolling them in a clinical trial targeting lewy bodies/alpha-synuclein

• Determining if the treatment works: want to be sure that the treatment actually lowers brain levels of lewy bodies/alpha-synuclein
Why do we need to improve diagnosis?

- Antibody therapies now in development:
  - Anti-amyloid (plaques)
  - Anti-tau (neurofibrillary tangles)
  - Anti-synuclein (alpha synuclein)
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What progress has been made?

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First PET scans for amyloid:

Amyloid imaging permits identification of MCI subjects who have brain amyloid:

Use of Florbetapir-PET for Imaging β-Amyloid Pathology

Christopher M. Clark, MD
Julie A. Schneider, MD
Barry J. Bedell, MD, PhD
Thomas G. Beach, MD, PhD

**Context** The ability to identify and quantify brain β-amyloid could increase the accuracy of a clinical diagnosis of Alzheimer disease.

**Objective** To determine if florbetapir F 18 positron emission tomographic (PET) imaging performed during life accurately predicts the presence of β-amyloid in the brain at autopsy.

![Image](image-url)

**A** Participant age at death, 82 y

Mean cortical SUV = 0.87, PET score = 0

β-Amyloid burden = 0.16%
Low likelihood of Alzheimer disease

![Image](image-url)

**B** Participant age at death, 78 y

Mean cortical SUV = 1.17, PET score = 2

β-Amyloid burden = 1.53%
High likelihood of Alzheimer disease

![Image](image-url)

**C** Participant age at death, 79 y

Mean cortical SUV = 1.66, PET score = 4

β-Amyloid burden = 7.92%
High likelihood of Alzheimer disease

![Image](image-url)
Using amyloid PET scans to monitor treatment outcomes:

53 assessed for eligibility

25 failed screening
23 did not meet inclusion criteria
1 withdrew consent
1 other reasons*

28 randomised

20 assigned to receive bapineuzumab (safety population)

7 to 0.5 mg/kg
7 to 1.0 mg/kg
6 to 2.0 mg/kg

1 had no post-baseline PET data

2 withdrew
2 had adverse events

19 included in PiB PET analysis (modified intention-to-treat population)†

8 assigned to receive placebo (safety population)

3 to 0.5 mg/kg
3 to 1.0 mg/kg
2 to 2.0 mg/kg

1 had no post-baseline PET data

2 withdrew
1 had adverse events
1 owing to loss of caregiver

7 included in PiB PET analysis (modified intention-to-treat population)‡
Using amyloid PET scans to monitor treatment outcomes:

Figure 2: Estimated change from baseline over time in mean $^{11}$C-PiB PET
Data are least squares means and 95% CIs. * Difference between patients in the placebo group and those in the bapineuzumab group at week 78 = -0.24 (p = 0.003). PiB = Pittsburgh compound B.
Amyloid PET scans to monitor experimental treatments:

Amyloid-β 11C-PiB-PET imaging results from 2 randomized bapineuzumab phase 3 AD trials

Use of white matter reference regions for detection of change in florbetapir positron emission tomography from completed phase 3 solanezumab trials

Impact of Reference/Target Region Selection on Amyloid PET Standard Uptake Value Ratios In the Phase 1b PRIME Study of Aducanumab

Neurology® 2015;85:692-700

Alzheimer’s & Dementia 13 (2017) 1117-1124

doi:10.2967/jnumed.118.209130
PET scans for tau are in development.
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Problems with PET scans:

• Only available for amyloid at present

• Very expensive:
  – $8000 per clinical scan
  – $2500 per research scan
Alternatives to PET scans:

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Spinal fluid tests

- Marker of plaque: beta amyloid 1-42
- Marker of tangle: tau, p-tau
Reduction of $\beta$-Amyloid Peptide$_{42}$ in the Cerebrospinal Fluid of Patients with Alzheimer’s Disease

R. Motter, MPH,* C. Vigo-Pelfrey, PhD,* D. Kholodenko, MS,* R. Barbour, BS,* K. Johnson-Wood, BA,* D. Galasko, MD,† L. Chang, MD,‡ B. Miller, MD,‡ C. Clark, MD,§ R. Green, MD,‖ D. Olson, MD,‖ P. Southwick, PhD,‖ R. Wolfert, PhD,‖ B. Munroe, PhD,‖ I. Lieberburg, MD, PhD,* P. Seubert, PhD,* and D. Schenk, PhD*

Ann Neurol 1995;38:643–648
Ann Neurol 1995;38:643–648
Using spinal fluid tests to monitor treatment:

A phase 2 randomized trial of ELND005, scyllo-inositol, in mild to moderate Alzheimer disease

*Neurology® 2011;77:1253-1262*
Spinal fluid tests

• Marker of plaque: beta amyloid 1-42
• Marker of tangle: tau, p-tau
• Marker of lewy body: alpha synuclein
CSF synuclein in Parkinson’s disease:
Efforts to measure these things in blood:

Plasma exosomal α-synuclein is likely CNS-derived and increased in Parkinson’s disease

Min Shi · Changqin Liu · Travis J. Cook · Kristin M. Bullock · Yanchun Zhao · Carmen Ginghina · Yanfei Li · Patrick Aro · Romel Dator · Chunmei He · Michael J. Hipp · Cyrus P. Zabetian · Elaine R. Peskind · Shu-Ching Hu · Joseph F. Quinn · Douglas R. Galasko · William A. Banks · Jing Zhang
Continuing challenges with spinal fluid and blood biomarkers:

• Technology for blood biomarkers is too complex for clinical use
• Would like to have a broader range of biomarkers to tell us more about mechanisms of disease.
• Reproducibility of CSF biomarkers across different institutions has inhibited research applications
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• Brain imaging: Alzheimer’s Disease Neuroimaging Initiative (ADNI)

• Spinal fluid and blood: “microRNA” studies in AD and PD

• Spinal fluid and blood: expanding the numbers of biomarkers, solving the problem of reproducibility across sites
Alzheimer’s Disease Neuroimaging Initiative: lessons about biomarkers:

Jack CR et al, Lancet Neurology 2010
MicroRNAs in Human Cerebrospinal Fluid as Biomarkers for Alzheimer’s Disease

Theresa A. Lusardi, Jay I. Phillips, Jack T. Wiedrick, Christina A. Harrington, Babett Lind, Jodi A. Lapidus, Joseph F. Quinn, and Julie A. Saugstad

Lusardi et al.
What research is currently under way at OHSU?

• R01 Saugstad: 12/01/2018 -11/30/2023

• “Establishing MicroRNA Biomarkers for Diagnosing Alzheimer's Disease & Predicting Progression”
  – Aim 1. Establish the utility and short-term stability of miRNAs as AD biomarkers in plasma.
  – Aim 2. Establish the predictive values of plasma miRNAs for AD.
  – Aim 3. Examine the specificity of AD miRNA biomarkers vs. other dementias.
What research is currently under way at OHSU?

- R01 Zhang: 8/15/17-4/30/22
- “Peptide Biomarkers for Alzheimer Disease”
  - Aim 1: Discovery and confirmation of CSF and LEEP peptide markers in large cohorts.
  - Aim 2: Independent validation and identification of peptide biomarkers for disease progression.
  - Aim 3. Discovery of peptide biomarkers for very early prodromal AD.
What research is currently under way at OHSU?

- Galasko multi-center NIA-funded supplement:
  - Multi-center prospective CSF standardization protocol across (16) AD centers

- will do the following:
  - collect CSF using a standard pre-analytical protocol
  - analyze A-beta42 tau and P-tau using Roche Elecsys assays in a central lab
  - bank CSF and plasma centrally

- Some questions we can look at are:
  - reassess cutoffs for A-beta42, tau and P-tau in AD and ADRD
  - examine cognitive decline using the UDS battery in subjects with CSF analyses
  - assess genetic variation that may contribute to CSF A-beta42, tau and P-tau
  - measure additional analytes of interest in future in CSF and plasma
Who volunteers for spinal taps?

- Patients participating in clinical trials
- Patients who want to contribute to biomarker research
- Healthy subjects who want to contribute to biomarker research
We are looking for volunteers to donate CSF:

• Healthy “control” subjects
• Alzheimer’s disease
• Mild cognitive impairment
• Lewy body dementia
• Parkinson’s disease
• Frontotemporal dementia
requirements

- Clear-cut diagnosis in one of these categories
- No coumadin or other blood thinners
- No low back abnormality
If you’re interested...

• Please provide us with your contact information tonight,

• or email zhje@ohsu.edu
Thank you for your attention...
Questions?