AMYLOID IMAGING IN EARLY DIAGNOSIS OF ALZHEIMER’S DISEASE

Adam Fleisher, MD, MAS
Director, Brain Imaging
Banner Alzheimer's Institute

Learning Objectives:
- Understand background on Amyloid imaging
- Determine appropriate clinical use in early diagnosis of Alzheimer's disease, using Amyloid imaging

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Eli Lilly/Arid
Amyloid Imaging in early diagnosis of Alzheimer’s Disease

Adam Fleisher, MD, MAS
Director of Brain Imaging
Banner Alzheimer’s Institute
Medical Director, Alzheimer’s Disease Cooperative Study
Associate Professor, Department of Neurosciences
University of California, San Diego
San Diego, California

Amyloid imaging in AD

- Amyloid Imaging Development
- Amyloid Imaging in disease progression and risk
- Amyloid imaging in treatment trials
- Use of Amyloid imaging in the clinic

Amyloid Initiates a Complex Cascade of Events

\[ \text{A} \beta \text{Initiates a Complex Cascade of Events} \]

- Tangles, oxidation, mitochondrial effects, inflammation, etc.
- Cell death
- Neurofibrillary tangles

\[ \text{A} \beta = \text{amyloid-} \beta; \; \text{CSF} = \text{cerebrospinal fluid}; \]
Hypothetical Course of Aging Brain and biomarker changes


Using imaging as a biomarker of brain pathophysiology of AD

R Buckner, J Neuroscience, 2005

Amyloid Imaging development
**Amyloid Imaging Compounds In Phase III trials**

**18F Amyloid Imaging Tracers**

<table>
<thead>
<tr>
<th></th>
<th>Flutemetamol</th>
<th>Florbetapir</th>
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<tbody>
<tr>
<td>AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**F18 Amyloid Imaging Tracers**

- **Florbetaben**
  - **18F Flutemetamol**
  - **Florbetapir**
  - **Navidea AZD4694**

**Amyloid Imaging Correlates With Amyloid Pathology**

<table>
<thead>
<tr>
<th></th>
<th>Visual</th>
<th>AU/45</th>
<th>Amyloid Staining</th>
<th>Amyloid Burden (Quarit H2O) (%)</th>
<th>Neuroradiologic Diagnosis</th>
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<tbody>
<tr>
<td></td>
<td>Read</td>
<td>SU/45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>1</td>
<td>1.06</td>
<td></td>
<td>0.0</td>
<td>Normal brain</td>
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<tr>
<td>DD</td>
<td>3</td>
<td>1.15</td>
<td></td>
<td>3.6</td>
<td>AD with periventricular leukoencephalopathy</td>
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<tr>
<td>AD</td>
<td>4</td>
<td>1.42</td>
<td></td>
<td>5.4</td>
<td>AD</td>
</tr>
<tr>
<td>AD</td>
<td>4</td>
<td>1.33</td>
<td></td>
<td>7.0</td>
<td>AD</td>
</tr>
<tr>
<td>AD</td>
<td>4</td>
<td>1.67</td>
<td></td>
<td>8.5</td>
<td>AD</td>
</tr>
</tbody>
</table>


**Amyloid Imaging Correlates With Amyloid Pathology**

### Correlation between Quantification, Visual reads, and pathology

<table>
<thead>
<tr>
<th>Region</th>
<th>PET Measure</th>
<th>Pathology Reference Standard</th>
<th>Correlation Coefficient (95% Confidence Interval)</th>
<th>P value (rho &gt;0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex (whole brain)</td>
<td>Visual</td>
<td>β-amyloid area</td>
<td>0.78 (0.58, 0.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cortex (whole brain)</td>
<td>SUV</td>
<td>β-amyloid area</td>
<td>0.75 (0.53, 0.88)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cortex (whole brain)</td>
<td>Visual</td>
<td>Neuritic plaque score</td>
<td>0.71 (0.47, 0.88)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Cortex (whole brain)</td>
<td>SUV</td>
<td>Neuritic plaque score</td>
<td>0.74 (0.51, 0.87)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cortex (whole brain)</td>
<td>SUV vs. Visual</td>
<td></td>
<td>0.82 (0.64, 0.93)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>


### Discrimination performance: Visual vs quantitative

**59 AUTOPSIES: Compared to Pathologic diagnosis**

SUVR, cut point of ≥ 1.1, sensitivity of 97%


### Amyloid Imaging in Alzheimer’s progression and risk
Amyloid accumulation begins approximately 15 years before dementia

Prevalence of PIB+ve PET in HC

Prevalence of plaques in HC

Prevalence of AD

(Davies, 1986, n=115)
(Shriberg, 1991, n=361)
(Coughlin, 1995, n=572)

Amyloid PET Measurements of Fibrillar Aβ Burden: AD spectrum

85.3% 46.7% 28.1%
N=68 N=82 N=60


APOE4, Age and Amyloid PET

Amyloid associations with cognition in “normal” individuals (“Pre-clinical AD?”)

<table>
<thead>
<tr>
<th></th>
<th>ADAS</th>
<th>WLM-M</th>
<th>WLM-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUVR</td>
<td>&lt;1.1</td>
<td>&gt;1.1</td>
<td>&gt;1.1</td>
</tr>
<tr>
<td>Mean ± StdErr</td>
<td>4.3±0.3</td>
<td>6.2±0.7</td>
<td>14.3±0.4</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0026</td>
<td>0.0013</td>
<td>0.0136</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>ADAS</th>
<th>WLM-M</th>
<th>WLM-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual rating</td>
<td>Aβ - (n=67)</td>
<td>Aβ + (n=11)</td>
<td>Aβ - (n=67)</td>
</tr>
<tr>
<td>Mean ± StdErr</td>
<td>4.5±0.3</td>
<td>6.0±0.8</td>
<td>14±0.4</td>
</tr>
<tr>
<td>P-value</td>
<td>p=0.0520</td>
<td>p=0.0401</td>
<td>p=0.0611</td>
</tr>
</tbody>
</table>

Doraiswamy et al, Neuro, in press 2012

Cortical Amyloid predicts 18 month cognitive decline in normal older controls, MCI, and dementia due to AD

NL 69, MCI 51, dAD 31

Doraiswamy et al, Neurol, in press 2012

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Self reported Lifetime Cognitive Engagement is associated with increased amyloid later in life


Cortical amyloid is associated with increased annual rate of global atrophy in cognitively normal individuals

Chetelat G, AIBL, Neurol, Feb 2012

Amyloid Imaging for clinical treatment development
Amyloid imaging in clinical trials

- All phase 3 and most phase 2b anti-amyloid therapy trials now incorporate amyloid imaging as study endpoints and/or for enrollment stratification.
- Prevention trials are now incorporating amyloid imaging as trial endpoints, or for enrollment stratification.
- Amyloid imaging may be particularly important in pre-clinical trials to identify target cohorts for anti-amyloid therapies.

Amyloid imaging in clinical trials

- Gantenerumab (Roche) phase 2 study – dose dependent decrease in amyloid 8-28 weeks of treatment

Amyloid Imaging in planned anti-amyloid prevention trials 2013

A4 (ADCS) – treatment trial in asymptomatic cognitively normal older adults. Biomarker evidence of disease used to enroll high risk individuals and follow treatment effects.

DIAN treatment trial – pre-symptomatic autosomal dominant AD. Multi-site, multi-mutation family, three different drugs. Biomarkers as primary endpoints. Leading to phase 3 clinical outcome trials.

API – Crenezumab trial – Autosomal dominant pre-symptomatic treatment in a single mutation family (90%), plus mixed mutation safety cohort (10%). Five year clinical outcomes.
Biomarker progression prior to expect age of disease onset:
Two Early Onset Autosomal Dominant biomarker studies


Cerebral pattern of fibrillar Aβ deposition in PS1 E280A mutation carriers

Amyloid Imaging use in the clinic
**DIAGNOSTIC CRITERIA FOR AD**

- New criteria published
  - National Institute on Aging/Alzheimer’s Association (NIA/AA)(2011)

- 3 phases of AD
  - Preclinical phase (no symptoms)
  - Prodromal/mild cognitive impairment (MCI) phase
  - AD dementia phase

Biomarkers can be used to increase diagnostic certainty

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**National Institute on Aging-Alzheimer’s Association Dementia Criteria**

<table>
<thead>
<tr>
<th>Biomarker Probability of AD Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJ (PET or CSF)</td>
</tr>
<tr>
<td>Neuronal Injury (CSF)</td>
</tr>
<tr>
<td>FDG-PET structural MRI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probable AD dementia based on clinical criteria</th>
<th>Intermediate</th>
<th>High</th>
<th>Probable AD dementia based on clinical criteria</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninformative</td>
<td>Unavailable, conflicting, or intermediate</td>
<td>Positive</td>
<td>Unavailable, conflicting, or intermediate</td>
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<tr>
<td>Intermediate</td>
<td>Unavailable, conflicting, or intermediate</td>
<td>Positive</td>
<td>Unavailable, conflicting, or intermediate</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Positive</td>
<td>Positive</td>
<td>Unavailable, conflicting, or intermediate</td>
<td>Positive</td>
<td></td>
</tr>
</tbody>
</table>

**“The Role of Amyloid imaging”**

**FDA Indication for Amyloid imaging**

**Amyvid Lilly**

- To estimate beta-amyloid neuritic plaque density
- In adult patients with cognitive impairment who are being evaluated for Alzheimer’s Disease and other causes of cognitive decline.
- A negative Amyvid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of Alzheimer's Disease at the time of image acquisition.
- A negative scan result reduces the likelihood that a patient’s cognitive impairment is due to Alzheimer’s Disease.
- A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques.
  - Neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with Alzheimer’s Disease, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition.
- Amyvid is an adjunct to other diagnostic evaluations.

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CASE 1

- 68-year-old right-handed man, retired mathematics professor presents with 5 years of insidious onset, gradually declining cognitive symptoms:
  - Decreased decision making
  - Geographic disorientation
  - Poor judgment while driving
  - Visual agnosias (eg, put brown touch-up paint on a white wall)
  - Word finding difficulty
  - “Difficulty making sense of the world”
  - Mild memory complaints – denies a significant problem
  - Financial management – “misplaced” $30,000. Difficulty with writing checks. Cannot present proper cash at the store or calculate tips
  - Losing items around the house
  - No behavioral problems

CASE 1 (CONT)

- ADLs:
  - Does not use washer/dryer properly – puts dirty clothes in the dryer
  - Has difficulty preparing meals
  - Needs prompting for showering
  - Very disorganized (big change for him)
- No evidence of depression/anxiety/apathy or personality change
- No hallucinations or delusions
- ROS: Night terrors and movements associated with REM sleep
- Physical and neurological exam: normal except positive glabellar sign
- Medications: statin, vitamins
- Family history: none relevant

CASE 1 (CONT)

- Bedside cognitive testing:
  - MMSE 24/30 – missing 2 points for orientation, 2 points for spelling “world” backwards, 1 for inability to copy intersecting pentagons, and missed 1/3 on delayed recall
  - Category fluency: 6 animals in 1 minute
  - Letter fluency (F words): 12 in 1 minute
  - Clock: abnormal number and hand placement
  - Visual figure recall 0/3
  - Naming intact
  - Could not do simple calculations
  - MoCA: 17/30 for errors in visuospatial, executive function, clock drawing, and 0/5 on word recall

ADLs = activities of daily living. ROS = Review of systems.

MMSE = Mini Mental State Examination. MoCA = Montreal Cognitive Assessment.
CASE 1: CLOCK DRAWING

CASE 1: MOCA CUBE

CASE 1: MOCA TRAILS B

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CASE 1 (CONT)

• Diagnostic workup
  - Labs – CBC, CMP, B12, TSH: normal
  - MRI of brain: mild-to-moderate periventricular white matter disease
  - Formal neurocognitive testing:
    • Prominent deficits in executive function, attention, calculations, and low-to-borderline scores on memory measures

CMP = Comprehensive metabolic panel; TSH = thyroid-stimulating hormone.

CASE 1: CHALLENGE OF A CLINICAL DIAGNOSIS (CONT)

• Initial clinical diagnostic assessment:
  - Meets DSM-IV dementia criteria
  - Differential diagnosis includes possible underlying Alzheimer’s disease with atypical presentation, dementia with Lewy bodies, comorbid vascular dementia (primary or mixed dementia) or other neurodegenerative disorders
  - NIA-AA diagnosis: Possible AD (atypical presentation) based on clinical criteria


CASE 1 (CONT)

• Biomarker-based diagnostic assessment:
  - FDG-PET (evidence of neuronal injury)
  - NIA-AA diagnosis: Probable AD, intermediate likelihood with biomarker evidence

FDG-PET = fluorodeoxyglucose positron emission tomography.
**CASE 1 (CONT)**

- Biomarker-based diagnostic assessment:
  - Amyloid PET (Positive)

**Summary**

- Amyloid imaging is now playing a large role in AD research
  - Understanding the natural history of AD
  - Associations with other pathophysiology
  - Playing a key clinical treatment trials –
    - symptomatic and pre-symptomatic

- Amyloid Imaging is now available in the clinic
  - Indications are defined
  - But guidelines for use require further experience
    - Who - at risk (not indicated), MCI, dementia
    - When – what step in diagnostic/prognosis

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**CASE 1 (CONT)**

- Biomarker-based diagnostic assessment:
  - Dementia: Amyloid and FDG PET evidence of AD
  - Final NIA-AA diagnosis:
    - Probable AD, high likelihood with biomarker evidence
  - Vascular/mixed dementia ruled out?
  - Lewy Body Dementia ruled out? DAT Scan?

**Influences on Management:**

- Patient motivated to start on ACHEI treatment
- Eligible and interested in treatment trials
Challenges for Amyloid PET Use in the Clinic

• For following over time?
  – Limited evidence of utility
  – Weakly associated with cognitive change in dementia
  – No anti-amyloid therapies available
• Prediction of clinical dementia
  – Not well understood who will become demented with asymptomatic cerebral amyloidosis
• Currently not recommended as a predictive tool
• How will clinicians use amyloid PET now that it is available?
• Significant risk of misuse and misinterpretation