Neuroimaging: an Early Diagnostic Marker

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Disclosures

Consultant for: Eli Lilly, AVID, Merck, Grifols, Quintiles

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Neuroimaging in AD

- New AD Diagnostic criteria
- Biomarkers in AD
  - CSF, MRI, PET
- Amyloid Imaging in disease progression and risk
- Value of amyloid imaging in the clinic
- Current recommendations for use
- Access to Imaging – who pays for it
Diagnostic Criteria for Alzheimer’s Disease: IWG and NIA-AA criteria

- Preclinical AD
  - Three stages
    - Asymptomatic cerebral amyloidosis
    - Asymptomatic amyloidosis plus neurodegeneration
    - Asymptomatic amyloidosis plus neurodegeneration and cognitive/behavioral change

- Prodromal AD (Mild Cognitive Impairment due to AD)
  - Core clinical criteria
  - + Biomarkers: intermediate or high likelihood with Aβ and/or Neuronal injury

- AD dementia
  - Probable/Possible based on clinical criteria
  - + Biomarkers: intermediate or high likelihood with Aβ and/or Neuronal injury

MCI = mild cognitive impairment.
McKhann G et al, JALZ April, 2011; Albert M et al, JALZ April, 2011; Sperling R et al, JALZ April, 2011
Syndromal Definitions
Diagnostic and Statistical Manual - 5

• Minor Neurocognitive Disorder (MCI)
  - Cognitive decline 1-2 SD from normal on formal cognitive testing
  - Do not interfere with independence
  - Not due to delerium
  - Not attributed to another mental disorder (eg, major depression, schizophrenia)

• Major Neurocognitive Disorder (Dementia)
  - Cognitive decline ≥2 SD from normal on formal cognitive testing
  - Interferes with independence
  - Not due to delerium
  - Not attributed to another mental disorder (eg, major depression, schizophrenia)

MCI = mild cognitive impairment.
Aβ peptide → App

p-tau → Synaptic dysfunction

NFT → Cell injury

Cell-to-cell propagation

Transmitter deficits

Cell death/atrophy

Neuritic plaque

β + γ-secretase inhibitors

Immunotherapies

Aggregation inhibitors

Neuroprotective agents

Antioxidants

Antiinflammatories

Neurotransmitter replacement

Antibody therapies

ß + γ-secretase inhibitors

Spread of AD Pathology

Braak and Braak, NBA, 1997
Alzheimer’s Disease

AD More Likely:
- Age
- Female sex
- E4 genotype
- Hypertension
- Diabetes
- Homocysteine
- Cholesterol
- Head trauma
- Family history

AD Less Likely:
- Education
- Exercise
- Brain fitness
- Antioxidant diet
- Heart health
Biomarkers of AD

Any identifiable marker that accurately represents underlying pathology associated with disease

• Blood or CSF
• Imaging
Alzheimer’s Disease Progression

- CSF abeta42
- Amyloid imaging
- FDG-PET
- CSF tau
- MRI Hippocampal volume
- Cognitive performance

Abnormal

Normal

Pre-Symptomatic | eMCI | LMCI | Dementia

CSF Aβ42

Amyloid imaging

FDG-PET

MRI hipp

Cog

Fx

CSF abeta42

Amyloid imaging

CSF tau

FDG-PET Function (ADL)

MRI Hippocampal volume

Cognitive performance

eMCI = early MCI; LMCI = late MCI.
Biomarker changes in relation to the estimated age at clinical onset: ADAD studies


Fleisher AS, AAIC, 2013
Biomarker changes in relation to age of dementia diagnosis: Australian Imaging Biomarker and Lifestyle study

NL, MCI, AD = 200
3-5 year f/u

Amyloid 17 years prior

Hipp Atrophy 4 years prior

Using imaging as a biomarker of brain pathophysiology of AD

R Buckner, J Neuroscience, 2005
Hippocampal volumes predict progression from MCI to AD

Smaller hippocampal volumes associated with increased progression to dementia over time

Annual risk of progression to AD in one year based on hippocampal volumes

L.K. McEvoy, Radiology, 2011
Alzheimer’s Disease neuroImaging Initiative
Use of Volumetrics in the Clinic

NeuroQuant™
Age-Related Atrophy Report

PATIENT INFORMATION

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<tr>
<th>Patient ID:</th>
<th>Patient Name:</th>
<th>Sex:</th>
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MORPHOMETRY RESULTS

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<tr>
<th>Brain Structure</th>
<th>Volume (cm³)</th>
<th>% of ICV 25%-75% Normative Percentile</th>
<th>Normative Percentile</th>
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<tbody>
<tr>
<td>Hippocampi</td>
<td>6.77</td>
<td>0.47 (0.41-0.58)</td>
<td>35.81</td>
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<tr>
<td>Lateral Ventricles</td>
<td>38.99</td>
<td>2.73 (1.13-4.21)</td>
<td>68.07</td>
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<tr>
<td>Inferior Lateral Ventricle</td>
<td>3.03</td>
<td>0.21 (0.12-0.30)</td>
<td>73.50</td>
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</table>

AGE-MATCHED REFERENCE CHARTS

- L & R Hippocampus
- L & R Inferior Lateral Ventricle
Voxel by voxel assessments
Normal Aging Versus AD

Normal aging is distinguishable from AD with more generalized atrophy.
Reduction in cortical thickness is associated with disease stage and predicts decline in Normal controls.
Functional MRI in Alzheimer’s Disease

- Indirect measure of neuronal activity
- fMRI can be acquired during cognitive tasks comparing one condition to a control or to a resting state
- Increased prefrontal cortical activity in MCI may be compensatory mechanism for hippocampal failure

FDG PET to distinguish Dementias and genetic risk

- AD-Dementia
- Cog NL APOE4 carriers

Empirically pre-defined statistical ROI for the assessment of 12-Month CMRglI declines in AD patients

Defined using data from 27 training-set patients using bootstrap with replacement

Number of AD patients per group needed in a 12-month multi-center RCT to detect a 25% treatment effect with power=80%, p=0.05 & no need to correct for multiple comparisons

<table>
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<tr>
<th>FDG PET</th>
<th>ADAS-COG11</th>
<th>MMSE</th>
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<tr>
<td>61</td>
<td>612</td>
<td>493</td>
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</table>

Characterized in 29 test-set patients (excluding HiRez & HRRT scanners)

K. Chen, et al, Neuroimage, in press

Banner Alzheimer Institute
Amyloid Imaging Correlates With Amyloid Pathology

59 AUTOPSIES: Compared to Pathologic diagnosis

**SUVR**, cut point of ≥ 1.1,
sensitivity of 97%
specificity of 100%


<table>
<thead>
<tr>
<th>18F-AV-45 PET</th>
<th>Visual Read</th>
<th>AV45 SUVr</th>
<th>Amyloid Staining (4G8 antibody)</th>
<th>Amyloid Burden (Quant IHC) (%)</th>
<th>Neuropathologic Diagnosis</th>
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<tr>
<td>MCI</td>
<td>1</td>
<td>1.08</td>
<td></td>
<td>0.0</td>
<td>Normal brain</td>
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<tr>
<td>AD</td>
<td>0</td>
<td>0.87</td>
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<td>0.2</td>
<td>Tangle only</td>
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<td>PDD</td>
<td>3</td>
<td>1.15</td>
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<td>AD with cortical Lewy bodies</td>
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<td>1.42</td>
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<td>1.67</td>
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</table>

Amyloid PET Measurements of Fibrillar A\textsubscript{β} Burden: AD spectrum

CC Rowe, NBA 2007

APOE4, Age and Amyloid PET


Percent florbetapir positivity for mean cortical SUVR cutoff >1.08 for diagnostic groups, split by APOE carriers (E4+) and Non-Carriers (E4-).
Aging, APOE4 and Amyloid PET

Cortical Amyloid predicts 36 month cognitive decline with and without Fibrillar amyloid

ADAS-cog

CDR-SOB

MMSE

NL 67, MCI 47, dAD 28

Doraiswamy et al, Submitted, 2013
**Aβ related cognitive decline - Retrospective ADNI Normal Subjects (N=72)**

Longitudinal ADAS-Cog Scores

Florbetapir +
N=23

Florbetapir –
N=49

Aβ+ 0.5 pt/year greater decline compared to Aβ- normals (p<0.001)

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

Figure 1. Individuals with greater cognitive engagement show reduced amyloid burden. Carbon 11–labeled Pittsburgh Compound B ([11C]PIB) in cognitively normal older participants (x-axis) is inversely associated with past cognitive activity (y-axis) (linear regression, $\beta=-1.73 \pm 0.47; P<.001$). Both variables are residual values after correcting for age, sex, and years of education.

Cortical amyloid is associated with increased annual rate of global atrophy in cognitively normal individuals.
Australian ADNI (AIBL)
3 year risk of progression:
Positive versus Negative Amyloid PET scan

<table>
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<tr>
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<th>Positive (n=60)</th>
<th>Negative (n=27)</th>
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<tr>
<td>MCI</td>
<td>77% (47/60)</td>
<td>29% (8/27)</td>
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<tr>
<td>HC</td>
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<td></td>
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<tr>
<td>HC</td>
<td>25% to MCI/AD</td>
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<tr>
<td>Odds Ratio</td>
<td>14</td>
<td>4.8</td>
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</table>

C Rowe, AAIC 2013
Australian ADNI (AIBL)
HC to MCI over 3 years (n=183; 13% progressed)

<table>
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<tr>
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<th>Odds Ratio</th>
<th>PPV</th>
<th>NPV</th>
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<tr>
<td>HV</td>
<td>2.2</td>
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<td>ApoE ε4</td>
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<td>composite cog</td>
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<td>PiB PET</td>
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<td>PiB+composite</td>
<td>16</td>
<td>0.50</td>
<td>0.94</td>
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C Rowe, AAIC 2013
Australian ADNI (AIBL)
MCI to AD over 3 years (n=87; 59% progressed)

<table>
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<tr>
<th></th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td>HV</td>
<td>4</td>
<td>0.67</td>
<td>0.65</td>
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<tr>
<td>ApoE ε4</td>
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<td>0.74</td>
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<td>CVLT&lt; -1.5</td>
<td>11</td>
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<td>PiB PET</td>
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<td>PiB+ε4</td>
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<td>PiB+HV</td>
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<td>PiB+CVLT</td>
<td>NA</td>
<td>0.86</td>
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Strongly positive amyloid PET scans more predictive than mildly positive (PPV 82% vs 44%)

C Rowe, AAIC 2013
What we now know

Amyloid on PET is:
- Associated with fibrillar amyloid on pathology
- It distinguishes clinical stages of AD
- Influenced by age and APOE gene
- Associated with degree of lifetime cognitive activity
- Associated with increased rate of memory decline in “cognitively intact” elderly.
- Associated with increased rate of brain atrophy and brain metabolism
- It is associated with progression to MCI and Dementia
- More is worse
Amyloid PET use impacts Clinician decision making

Objective: To determine whether amyloid imaging could influence the diagnosis and management of patients undergoing evaluation for cognitive decline.

Methods:
• 229 patients with progressive cognitive decline and an uncertain diagnosis.
• Provisional diagnosis given, diagnostic confidence estimated, and a plan for diagnostic evaluation and management both before and immediately following receipt of the florbetapir F18 PET results.

Results: After amyloid PET physicians changed their diagnosis in 54.6% (125/229) of cases.
• 62% (53/86) who had a pre-scan diagnosis of AD prior to the scan were amyloid positive.
• 57% (12/21) with a non-AD diagnosis pre-scan were also amyloid positive.
• 39% (48/122) with “MCI/ dementia of unclear etiology” pre-scan were amyloid positive.
• Diagnostic confidence increased by an average of 21.6%.
• 86.9% (199/229) of cases had at least one change in their management plan.

Cholinesterase inhibitor or memantine use increased by 17.7% among amyloid positive cases and decreased by 23.3% among those with negative scans.
• Planned brain structural imaging (CTs/MRIs) decreased by 24.4%
• Planned neuropsychological testing decreased by 32.8%.

Conclusions: florbetapir F18 PET altered physician diagnostic thinking and intended testing and management plans in patients undergoing evaluation for cognitive decline.

Amyloid PET use impacts Clinician decision making

Use of AD meds in MCI over 36 months

Doraiswamy et al, Submitted, 2013
"The Role of Amyloid imaging” in the Clinic
FDA Indication for Amyloid imaging

Amyvid PET

Indication

• 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.

Amyvid [prescribing information]. Indianapolis, MN; Eli Lilly and Company; 2012.
Suggested Use of Amyloid Imaging

Amyloid Imaging Taskforce: Appropriate USE Criteria

Amyloid imaging is appropriate in the following situations:

1. A cognitive complaint with objectively confirmed impairment
2. Performed only after full standard w/u is completed:
   • Structured clinical evaluation with objective neurocognitive testing
   • Structural brain imaging
   • Relevant laboratory tests
3. AD as a possible diagnosis, but uncertain
4. Knowledge of Aβ pathology would increase diagnostic certainty and alter management
5. Should only be ordered by dementia experts:
   • Specialty training, ≥25% dementia care practice
   • Geriatric/behavioral Psychiatry and Neurology

Who Pays for Amyloid Imaging

- Amyloid Imaging is now available in the clinic
  - Jan 30th, 2013:
    - Medicare Evidence Development Coverage Advisory Committee (MEDCAC)
      - “not sufficient evidence to support current Medicare reimbursement at this time”
  - July 3, 2013
    - Centers for Medicare & Medicaid Services (CMS)
      - Draft decision- “Coverage with Evidence Development”
  - Therefore: Amyloid imaging is only available to those who can afford it ($3-4k)
Value of Biomarkers in the clinic

- Earlier diagnosis
  - Care planning
  - Reduced hospitalization
  - Reduced cost of lifetime care

- Improve accuracy of diagnosis
  - Near 50% of patients with clinically diagnosed MCI, and 20% of Dementia are miss diagnosed with Alzheimer’s Disease
    - Leads to excess diagnostic testing
    - Inappropriate treatments given
    - Inappropriate long term planning and use of resources
    - Missing true diagnosis
      - Untreated underlying disease – leading to future complications and cost of care
      - INCREASED COST

- MRI, FDG PET, and CSF are available and variably covered by third party payers
- Amyloid PET may have the greatest value of current available biomarkers for early diagnosis and prediction of decline.
Summary

- New Diagnostic criteria are recently established for clinical diagnosis and incorporation of biomarkers for improved earlier diagnosis
- Several biomarkers are available for clinical use
- Amyloid imaging is now playing a large role in
  - Understanding the natural history of AD
  - Associations with other pathophysiology
  - In treatment development –
    - symptomatic and pre-symptomatic
- How widely used amyloid PET will be is yet to be seen
- Value may be linked to emerging anti-amyloid therapy development
Questions?