Cognitive and Biological Markers of Dementia: A Review and Update

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Early Diagnosis

Onset of Pathology

Mean age of Front Men in Rock

Figure courtesy of C. Clark
Talk Objectives

- Summarize the molecular biology of AD;
- Define an ideal diagnostic marker of AD;
- Describe diagnostic statistical results for cerebrospinal fluid- and MRI- based biomarkers;
- Compare cognitive markers of AD with biological markers;
- Discuss the role of neuropsychology in the diagnostic evaluation of AD and mild cognitive impairment
Pathology of AD

- β- amyloid Plaque
- Neurofibrillary Tangles

Figure courtesy of C. Clark
Molecular Biology of AD

• β- amyloid is derived from a much larger protein, the amyloid beta precursor protein, or APP molecule.

• Cleavage of the APP protein takes place normally in all cells along the cell membrane.
Molecular Biology of AD

• Depending on the enzyme which cleaves APP, either β- amyloid or a soluble, harmless protein can be formed.

• There are two main types of β- amyloid, Aβ40 and Aβ42, depending on amino acid length.
  – The latter is less soluble and tends to aggregate, forming plaques which are toxic to neurons.
Molecular Biology of AD

- An illustration of APP enzymatic cleavage:
Molecular Biology of AD

• An illustration of APP enzymatic cleavage:
Neurofibrillary Tangles

• The second hallmark of AD is the presence of neurofibrillary tangles composed of the protein tau.

• Tau protein provides support for microtubules, cellular structures which are essential for transport of nutrients and other substances within the neuron.
Hyperphosphorylation of \textit{tau}

- Accumulation of β-amyloid may alter the activity of two enzymes
  
  – Kinases are responsible for adding phosphate groups to proteins
  
  – Phosphotases remove phosphate from the molecule
Neurofibrillary Tangles

Figure courtesy of C. Clark
Development of NFTs in AD

Fig. 3. Postulated sequence of spread of neurofibrillary pathology in AD, showing the medial aspect of the cerebral cortex. The depth of the red color is in proportion to the density of tangles (based on refs. 24 and 28). Several of the red areas showed atrophy in the study by Scahill et al. (6).

Amyloid Cascade Hypothesis

Shaw et al. (2007). Nature Reviews: Drug Discovery, 6, 295-303
Keep in Mind

• NFT-related pathology follows a predictable course
  – Tau is released into CSF

• Plaque pathology is more widely distributed
  – Amyloid Beta is sequestered in the CNS – the “amyloid or neuritic sink”

• Phosphorylated tau (epitopes) can be distinguished from tau in the CSF
The “Ideal” Biomarker

• Detect a fundamental component of the disease pathology
• Demonstrate sensitivity (detection of the disease) and specificity (ruling out of other diseases or good health) ≥ 80%.
• Reliable, reproducible, noninvasive, simple to perform, inexpensive
• Should change with a disease-modifying treatment (surrogate)

The “Ideal” Biomarker

- FDA requires efficacy on co-primary measures
- Showing very early change in cognition and function as co-primary measures is an elusive, insidious target
- Biomarkers may be adopted as “surrogate” end-points in Phase III clinical trials.

CSF Markers Predict Conversion

- Est. index sensitivity (85%) on independent AD vs. NC sample

- 750 MCI participants across 12 international centers

- Followed for at least 2 years or until AD.

- Multiple CSF biomarkers exceed a single marker

Baseline CSF Protein Concentration Predicts Incipient AD

MCI→AD using CSF

- Found that an a Aβ42:P Tauratio and Total Tau predicted conversion best (sensitivity 83%, specificity 88%)

MCI $\rightarrow$ AD using CSF

- 270 MCI Converters (56% percent conversion)
- 4% back conversion – MCI resolved
- Variable specificities, depending on reference group

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Specificity</th>
<th>Positive LR</th>
<th>Negative LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable MCI</td>
<td>420</td>
<td>72</td>
<td>3.0</td>
<td>0.24</td>
</tr>
<tr>
<td>Vascular</td>
<td>28</td>
<td>71</td>
<td>2.9</td>
<td>0.24</td>
</tr>
<tr>
<td>DLB</td>
<td>14</td>
<td>57</td>
<td>1.9</td>
<td>0.31</td>
</tr>
<tr>
<td>FTD</td>
<td>7</td>
<td>86</td>
<td>5.8</td>
<td>0.20</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>80</td>
<td>4.1</td>
<td>0.22</td>
</tr>
</tbody>
</table>

MCI ➔ AD using CSF & Pittsburgh Compound B

- People at very early stages of AD (CDR 0.5) show the same CSF biomarker signature as more advanced AD.

- CSF Aβ42 levels predict high levels of amyloid binding (PiB) in cortical and subcortical areas.

- Tau-Aβ42 ratios outperformed individual CSF markers and very high values predict very rapid decline.

Fagan et al. (2007). Archives of Neurology, 64, 343-349.
MCI→AD using CSF & Brain Volume

- CSF Aβ42 (but not T TAU) is related to brain volume in non-demented (CDR = 0) older adults
  - Aβ42 has + relationship whole brain volume \( r = 0.30 \)
  - T TAU is not related to whole brain volume \( r = 0.06 \)

- CSF tau (but not Aβ42) is related only after conversion to very mild AD (CDR = 0.5)
  - Aβ42 is not related to whole brain volume \( r = 0.05 \)
  - T TAU is negatively related to whole brain volume \( r = 0.44 \)

Early Diagnosis-Molecular Biology

Adopted from:
Craig-Schapiro et al. (2009). Neurobiology of Aging, 35, 128-140

Diagram showing the changes in neurons, amyloid, and tangles in the brain from normal to dementia stages with age.
MCI ➔ AD Summary

- Thus far, CSF-based neurochemical measures of protein degradation and MRI-based markers of brain atrophy have shown the most promise and have been studied most extensively.
  - Others: fMRI, FDG-PET, SPECT, PIB PET, etc.

MRI-based Biomarkers

- How should the structural integrity (volume) of the brain be assessed in early AD?
  - Globally
  - Medial Temporal/Hippocampal
  - Frontal
  - Pattern Classification
Is HC/ERC Volume “Enough”?

Davatzikos et al. (submitted). Integrating imaging and CSF biomarkers: Classification of AD, MCI via pattern analysis.
SPARE-AD BIOMARKER

- Atrophy patterns on MRI were assessed using a high-dimensional pattern classification approach to generate a SPARE-AD (Spatial Pattern of Abnormalities for Recognition of Early AD) score.

Regions in which AD participants showed greater brain atrophy compared to normal controls.

Davatzikos et al. (submitted). Integrating imaging and CSF biomarkers: Classification of AD, MCI via pattern analysis.
Desert Island Cognitive Tests

If you were the only health care professional on a desert island and you could have only one cognitive test to diagnose very early preclinical AD and to subsequently recommend a patient for a disease modifying treatment, which would you choose?
## Preclinical AD & Cognition

<table>
<thead>
<tr>
<th>Domains</th>
<th>% Sig.</th>
<th># Studies</th>
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</thead>
<tbody>
<tr>
<td>General Cognitive (ie, MMSE)</td>
<td>38</td>
<td>61</td>
</tr>
<tr>
<td>Attention</td>
<td>71*</td>
<td>7</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>43</td>
<td>28</td>
</tr>
<tr>
<td>Verbal Learning</td>
<td>57*</td>
<td>56</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Working Memory</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>Language</td>
<td>33</td>
<td>45</td>
</tr>
<tr>
<td>Executive Function</td>
<td>44</td>
<td>33</td>
</tr>
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</table>

Twamley et al., 2006, *JINS, 12, 707-735.*
MCI $\rightarrow$ AD using Cognition

- **Episodic Memory**
  - List learning free recall
  - List learning cued recall
  - Recognition discrimination
- **Executive Functioning**
  - WCST perseveration
  - Letter fluency
  - Trail Making A and B
- **Semantic Knowledge**
  - Category Fluency
  - Boston Naming Test

Mickes et al. (2008). *Neuropsychology*, 21, 696-705
# Cognitive Markers

Distinguishing MCI from Normal Aging

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Sensitivity</th>
<th>Specificity</th>
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</thead>
<tbody>
<tr>
<td>CWL with CA weighting</td>
<td>94</td>
<td>89</td>
</tr>
<tr>
<td>CWL delayed recall</td>
<td>82</td>
<td>91</td>
</tr>
<tr>
<td>Clock Drawing</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>MMSE</td>
<td>71</td>
<td>85</td>
</tr>
</tbody>
</table>

Shankle et al., 2005, *PNAS, 102, 4919-4924*
MCI → AD using Cognition

- Fleisher et al. (2007, Neurology, 68, 1588-1595)
  - aMCI to AD over 3 years (n = 212)
  - Regression formula for predicting progression
    - \[0.1889 + (0.782 \times \text{ADAS Cog 11 raw}) - (0.0246 \times \text{Symbol Digit Modalities raw}) - (0.0962 \times \text{Delayed Word Recall}) - 0.1321 \times \text{NYU Paragraph Delayed Recall}\]
    - = Composite Z score
MCI $\rightarrow$ AD using Cognition

- Fleisher et al. (2007, Neurology, 68, 1588-1595)

<table>
<thead>
<tr>
<th></th>
<th>Constant</th>
<th>Raw</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.1889</td>
<td>0.1889</td>
</tr>
<tr>
<td>ADAS Cog</td>
<td>0.0782</td>
<td>10</td>
</tr>
<tr>
<td>Symbol Digit</td>
<td>0.0246</td>
<td>50</td>
</tr>
<tr>
<td>Word Recall</td>
<td>0.0962</td>
<td>6</td>
</tr>
<tr>
<td>Story Recall</td>
<td>0.1321</td>
<td>8</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

Composite Z of $-1.89 = 10\text{-}15\%$ probability of progression from a MCI to AD in 36 months

(see Table 1)
Keep in Mind

• A variety of cognitive measures show adequate diagnostic characteristics for discriminating AD-MCI-healthy aging.

• Understanding of disease pathology is pushing the diagnosis of AD to more mild or pre-clinical stages

• Assessment of very subtle memory changes in combination with biomarker results is on the horizon (i.e., Dubois et al., 2007)
Christos Davatzikos, Deepthi Koka, Leslie M. Shaw, John Q. Trojanowski, Steven E. Arnold, Jason H. T. Karlawish, & Christopher M. Clark, Angela Schaffer
University of Pennsylvania School of Medicine

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www.cernd.org
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• Fleisher et al., 2007, Neurology, 68, 1588-1595
• Dubois et al., 2007, Lancet Neurol., 6 (8), 734-736.
• Nordlund et al. 2008 JINS, 14, 582.