2013 Webinar Series
State of the Science:
Dementia Evaluation and Management
Among Diverse Older Adults and Their Families

Sponsored by Stanford Geriatric Education Center in conjunction with
American Geriatrics Society, California Area Health Education Centers,
& Community Health Partnership

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NEW DIAGNOSTIC GUIDELINES
FOR ALZHEIMER’S DISEASE AND
RELATED DEMENTIAS

Michael D. Greicius, MD, MPH
Department of Neurology and Neurological Sciences
Medical Director, Stanford Center for Memory Disorders

Q & A

- We will save have some time at the end of the presentation to answer your questions. If you have any questions, please use the “Chat” feature located on the right side of your screen. Please send your chat to everyone if possible.

- At the conclusion of our webinar, please complete the short evaluation questionnaire.

Please complete our short survey. We appreciate your feedback.

NOTE: Continuing Education Participants must complete a final survey in order to receive CEU/CME credit.
“New Diagnostic Guidelines for Alzheimer’s Disease and Related Dementias”

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I have no financial relationships to disclose and I will not discuss off label use and/or investigational use in my presentation.

About the Presenters

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PI, Functional Imaging in Neuropsychiatric Disorders (FIND) Lab
Department of Neurology and Neurological Sciences
Stanford University School of Medicine
NINCDS-ADRDA Criteria for Probable AD

- dementia (decline from previous level, DSM mentions social/occupational decline)
- deficits in two or more areas
- progressive decline in memory and other realms
- no disturbance of consciousness (delirium)
- onset age 40-90 (mostly 65 and up)
- no other explanation

McKhann et al., *Neurology*, 1984

How Do the Clinical Criteria Fare?

- Good sensitivity (90-95%), few false -’s
- Poor specificity (60-70%), many false +’s
- diagnosis of AD is accurate about 90% of the time in specialty clinics (clinical criteria plus...)
What Goes on at These 4-hour Neuropsychological Evaluations?

Visuospatial Memory
AAN Recommendations for Work-Up of Dementia

- B12, TSH +/- RPR (if risk factors) remarkably low yield (about 9% partially reversible, 1-3% fully reversible)
- Imaging: routine CT or MRI
- Screen for depression
- Neuropsychological measures incorporated in NINCDS-ADRDA criteria for AD
- Recommended against volumetric MRI/PET/SPECT/APOE/CSF studies


Differential Diagnosis

- Mild cognitive impairment (MCI)
- Dementia with Lewy Bodies
- Frontotemporal Dementia/Corticobasal Degeneration/Progressive Supranuclear Palsy
- Vascular Dementia (or mixed AD/vascular)
- Mass lesion (screened out with imaging)
- Depression (tough to rule out in initial visit)
- Other (B12, thyroid, syphilis)
Mild Cognitive Impairment

- Petersen criteria (amnestic MCI)
  - Subjective memory complaints
  - Objective deficits limited to memory
  - Not demented/intact instrumental ADLs
- Conversion rate to AD of 12% per year (versus 1-2% in age-matched controls)
- General range across MCI studies is (6-25%)

Petersen et al., Arch Neurol, 1999

Clinical Spectrum of Disease

Research questions:
How do we predict who will convert?
How do we prevent them from converting?

Petersen, J Intern Med, 2004
The Ideal AD Biomarker

- Diagnostic
  - At or above 85% sensitivity/specificity
- Predictive
  - Which MCI patients will convert to AD
  - Which healthy older controls will convert to MCI
- Dynamic
  - Tracks course of disease
  - Measure of treatment efficacy
- +/- Surrogate
  - Becomes something to treat itself (like LDL)

Plaques and Tangles: Beta-Amyloid and Tau
Clinical Progression Tracks Tau > Fibrillar Amyloid

Clinically silent

Incipient AD

Fully-developed AD

Biomarker Candidates: FDG PET

Resting PET 34 healthy subjects versus 14 AD patients.

Single-Subject FDG PET

AAN recommended against PET as a diagnostic test in AD, but Medicare now pays for them

Biomarker Candidates: Amyloid Imaging PET

Klunk et al., Ann Neurol, 2004

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Amyloid Imaging: Achilles’ Heel(s)

- PIB positivity up to 51% in healthy older controls (Gomperts et al., Neurology, 2008)
- PIB binding may peak early in the course
- Oligomeric species of beta-amyloid, not plaques, may be the main culprit in memory loss (Lesne et al., Nature, 2006)

Engler et al., Brain, 2006
Jack et al., Brain 2009

Striatal Plaques in PS-1 Mutation Carriers

Klunk et al., J Neurosci, 2007
Amyloid Imaging with F\textsuperscript{18} Compounds

Wong et al., *J Nucl Med*, 2010

AV-45 Correlates Strongly with Plaques at Autopsy

Clark et al., *JAMA* 2011

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MCI Converters > Non-Converters (PIB)

17/31 MCI PIB+

14/17 PIB+ converted over 3 years

1/14 PIB- converted over 3 years

Okello A et al. *Neurology* 2009

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Spinal Fluid Markers: High p-Tau and t-Tau

- Sensitivity of 90.2%
- Specificity of 80.0%

Buerger et al., *Arch Neurol*, 2002

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Spinal Fluid Markers: Aβ42/Tau ratio

Figure 1: Combination of T-tau and Aβ42 (A), P-tau and Aβ42 (B), and T-tau and Aβ42/P-tau ratio (C) concentrations at baseline. Horizontal dotted lines represent the cut-off value for Aβ42 (A, B) or Aβ42/P-tau ratio (C). Vertical dotted lines represent the cut-off for T-tau (A, C) or P-tau (B).

Hansson et al., Lancet Neurol, 2006

Tau/Amyloid Ratio Predicts Conversion from Healthy Aging to Mild Dementia

Fagan et al., Arch Neurol 2007

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Biomarker Dynamics/March of the Biomarkers

Jack et al., Lancet Neurol, 2010

DIAN Study

Table 1. Characteristics of the Study Participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Carriers (N = 88)</th>
<th>Noncarriers (N = 40)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>39.1±10.3</td>
<td>39.5±8.9</td>
<td>0.92</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>36 (41)</td>
<td>17 (42)</td>
<td>0.85</td>
</tr>
<tr>
<td>Education level — yr</td>
<td>13.9±2.5</td>
<td>15.0±2.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Cognitive status — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>43 (49)</td>
<td>1 (2)</td>
<td>0.29</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>45 (51)</td>
<td>39 (98)</td>
<td></td>
</tr>
<tr>
<td>Positive for apolipoprotein E</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e4 allele — no. (%)</td>
<td>22 (25)</td>
<td>9 (22)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Bateman et al., NEJM, 2012

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March of the Biomarkers Confirmed

![Graph showing biomarkers and their progression]

Proposed New AD Criteria

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (CSF tau, FDG-PET, structural MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD-dementia</td>
<td>Uninformative</td>
<td>Unavailable, conflicting, or indeterminate</td>
<td>Unavailable, conflicting, or indeterminate</td>
</tr>
<tr>
<td>Based on clinical criteria</td>
<td></td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>With three levels of evidence of AD</td>
<td>Intermediate</td>
<td>Unavailable or indeterminate</td>
<td>Unavailable or indeterminate</td>
</tr>
<tr>
<td>Pathophysiological process</td>
<td>Intermediate</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Possible AD dementia (atypical clinical presentation)</td>
<td>High</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Based on clinical criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With evidence of AD</td>
<td>Uninformative</td>
<td>Unavailable, conflicting, or indeterminate</td>
<td>Unavailable, conflicting, or indeterminate</td>
</tr>
<tr>
<td>Pathophysiological process</td>
<td>High but does not rule out second etiology</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Dementia-unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; Aβ, amyloid beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, 18fluorodeoxyglucose; MRI, magnetic resonance imaging.

McKhann et al., Alzheimer’s & Dementia, 2011
Proposed New MCI Criteria

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (tau, FDG, sMRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI-core clinical criteria</td>
<td>Uninformative</td>
<td>Conflicting/indeterminant/untested</td>
<td>Conflicting/indeterminant/untested</td>
</tr>
<tr>
<td>MCI due to AD—intermediate likelihood</td>
<td>Intermediate</td>
<td>Positive</td>
<td>Untested</td>
</tr>
<tr>
<td>MCI due to AD—high likelihood</td>
<td>Highest</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>MCI—unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.

Albert et al., Alzheimer’s & Dementia, 2011

Clinical Skill

- 61 yo RH male with 2 years of worsening aphasia, 1 year of progressive memory loss
- Still working/paying bills/handling his meds
- MRI: mild generalized atrophy some left parietal focality
- Neuropsych: severe memory and language deficits
- Amyloid imaging: positive
- Dx: MCI due to AD intermediate likelihood
Conclusions

- Biomarkers will become increasingly common in clinical practice
- Judicious interpretation is critical
- Negative biomarker studies are as informative if not more informative (see Dr. Kerchner’s talk next week)

Q & A

- We now have some time to answer your questions. If you have any questions, please use the “Chat” feature located on the right side of your screen. Please send your chat to everyone if possible.
- After the Q and A, We would like to ask each of the participants to answer the short evaluation questionnaire.
Final Question
Thank You for Participating!

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