‘Typical’ and ‘Atypical’ Alzheimer’s Disease: Biomarkers and Clinical Phenotyping

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Objectives

The Diagnosis of MCI and Alzheimer’s Disease (AD)
  – Diagnostic criteria changes and conceptualization
  – When might biomarkers be useful and important?

Spotlight on Atypical Presentations with Likely Underlying AD Pathology
  – Logopenic, PCA, EOAD

Current Clinical Trials
Alzheimer’s Disease

DIAGNOSIS
Alzheimer’s Disease (AD)

Described by Alois Alzheimer in 1906

Presenile dementia with amnesia and psychosis

Microscopic level
  – amyloid plaque
  – neurofibrillary tangles
Accuracy of Clinical Diagnosis of AD
U.S. Alzheimer’s Disease Centers 2005-10

• Probable AD (Clinical Diagnosis) versus Neuropathology Findings
  – N=526
  – Sensitive and specificity: 71%

• Non-AD Dementia (Clinical Diagnosis) versus Neuropathology Findings (n=271)
  – N=271
  – 39% found to have primary neuropath evidence of AD
Why discuss ‘typical’ AD

• “More than 20% of patients diagnosed with AD based on clinical criteria were amyloid negative in the PET sub-studies of bapineuzumab and solanezumab, with higher proportions of Aβ- among APOE ε4 non-carriers and mild dementia.” –Salloway and Sperling

• 25% of individuals clinically diagnosed as having mild to moderate AD had no more than sparse neuritic amyloid plaques on postmortem examination. The percentage of individuals with low amyloid levels was much higher in ε4 noncarriers (37%) vs carriers (13%).-Monsell et al, JAMA Neurology 2015.
A Classic Case of AD

• 74 year-old man with high blood pressure, high cholesterol
  • “I can’t keep track of things anymore”
• Spouse reports that in last 18-24 months...
  • Forgets conversations, TV programs
  • Repeats questions, stories
  • Memory for events that happened in the distant past is spared
  • Last month he became lost on his way home from an appointment
“Normal” Aging
Decline with age:
- Processing speed
- Executive function
- Naming
- Memory

Improve with age:
- Vocabulary
- General knowledge

Mild Cognitive Impairment
- Decline in memory or other cognitive functions
- Beyond what is expected for age
- Does not interfere with daily function
- Multiple causes
- May or may not progress to AD

Alzheimer’s Dementia
- Decline in memory or other cognitive function
- Beyond what is expected for age
- Interferes with daily function

Adopted from: memory.ucsf.edu/Education
Brain Atrophy in ‘Typical’ AD

What’s the Typical Atrophy Pattern?:
Temporal and Parietal Cortices
• Episodic Memory, Language, Numerosity/Calculations, Visuospatial
Lateral frontal cortex
• Executive functions

What’s Typically Spared?
Medial frontal cortex
• Behavior, interpersonal social functioning

Teipel Et al, 2015, Lancet Neurology
Hypometabolism Alterations in ‘Typical’ AD: FDG-PET

Rabinovici et al, 2011, Neurology
Molecular Changes in Typical AD: Detecting AD Pathology in Cerebrospinal Fluid

- **What are the typical CSF alterations in AD?**
  - Decrease in \( A\beta_{1-42} \)
  - Increase in total and phospho tau

- **CSF Tau/A\( A\beta_{1-42} \) ratio**
  - ADNI Study: 85% accurate in discriminating neuropathology confirmed AD from controls
  - Predicted conversion from MCI->AD

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**Cerebrospinal Fluid Biomarker Signature in Alzheimer’s Disease Neuroimaging Initiative Subjects**

Leslie M. Shaw, PhD, Hugo Vanderstichele, PhD, Malgorzata Knapik-Czajka, PhD, Christopher M. Clark, MD, Paul S. Aisen, MD, Ronald C. Petersen, MD, Kaj Blennow, MD, PhD, Holly Soares, PhD, Adam Simon, PhD, Piotr Lewczuk, MD, PhD, Robert Dean, MD, Eric Siemers, MD, William Potter, MD, Virginia M-Y. Lee, PhD, John Q. Trojanowski, MD, PhD, and the Alzheimer’s Disease Neuroimaging Initiative
Molecular changes in ‘Typical’ AD: Imaging Amyloid Plaques (PIB-PET)

A. Participant age at death, 82 y
Mean cortical SUVR = 0.87, PET score = 0
β-Amyloid burden = 0.15%
Low likelihood of Alzheimer disease

B. Participant age at death, 78 y
Mean cortical SUVR = 1.17, PET score = 2
β-Amyloid burden = 1.63%
High likelihood of Alzheimer disease

C. Participant age at death, 79 y
Mean cortical SUVR = 1.68, PET score = 4
β-Amyloid burden = 7.92%
High likelihood of Alzheimer disease

Clark, C. M. et al. JAMA 2011;305:275-283
Amyloid PET in MCI

- 40%-75% of MCI patients are Aβ-PET+
- Aβ PET+ predicts conversion from MCI to AD dementia
- Aβ+ and FDG/MRI+ are more predictive than Aβ+ alone

Annapaola Prestia et al. Neurology 2013;80:1048-1056
Amyloid in “Healthy” Older Adults: Are we detecting a preclinical stage?

Sperling et al. Alzheimers Dement 2011
Amyloid in “Healthy” Older Adults: Amyloid+ Normals Show Accelerated Brain Atrophy

Chetelat et al. Neurology 2012
Amyloid in “Healthy” Older Adults: PIB Binding at Baseline Predicts Conversion From Normal to MCI/AD

Table 2. Cox Proportional Hazards Model Testing MCBP for PiB as a Predictor of Time to DAT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCBP</td>
<td>4.82 (1.22-19.01)</td>
<td>.02</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.14 (1.02-1.28)</td>
<td>.03</td>
</tr>
<tr>
<td>Education, y</td>
<td>0.91 (0.69-1.19)</td>
<td>.49</td>
</tr>
<tr>
<td>APOE ε4 carrier</td>
<td>0.98 (0.20-4.90)</td>
<td>.98</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.54 (0.10-2.90)</td>
<td>.48</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DAT, dementia of the Alzheimer type; HR, hazard ratio; MCBP, mean cortical binding potential; PiB, Pittsburgh Compound B.
“Although findings from both CSF and PET amyloid imaging studies are convergent that older CN with evidence of preclinical AD, particularly those with Aβ and ND markers, have a statistically greater risk of manifesting subsequent cognitive decline and progression to the symptomatic stages of AD at a group level, there are insufficient data at this time to make accurate predictions at an individual level.” –Sperling, 2014
What is the value of diagnosis given that we have no therapeutic treatment for AD?

- Diagnostic uncertainty can result in unexpected or ‘hidden’ costs
  - Second and third opinions
  - Unnecessary repeated imaging and lab testing
  - Unnecessary or ‘wrong’ treatments
    - e.g. cholinesterase inhibitors for FTD

- Knowledge may offer inherent value to patients and their families
  - Assists with future planning
  - Begin discussions earlier when patient still maintains capacity across most decisional domains
When Are Biomarkers Appropriate in a Clinical Setting?

• **MAY - Mild, Atypical, Young**
  - MCI
  - Early age-of-onset dementia, atypical syndromes
    • AD vs. FTD
  - “Rule out” AD in pts with co-morbid conditions
    • e.g. vascular disease, depression, substance abuse

• **Positive predictive value will be lower in older patients**

*Slide from Gil Rabinovici*
What AD Biomarkers Can’t Do

• Not a substitute for a careful H&P
• Should not screen cognitively normal individuals
  – Pre-clinical AD is a research concept only!
• Won’t differentiate AD from diseases that overlap pathologically
  – e.g. dementia with Lewy bodies; cerebral amyloid angiopathy

Slide from Gil Rabinovici
Model for Biomarker Cascade in AD

Clifford Jack Model

- Amyloid-PET
- CSF Aβ
- FDG-PET
- CSF Tau
- MRI atrophy
- Cognition

Clinical Disease Stage:
- Normal
- Preclinical
- Mild cognitive impairment
- Dementia
Introduction to the recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease

Clifford R. Jack Jr.\textsuperscript{a,*}, Marilyn S. Albert\textsuperscript{b}, David S. Knopman\textsuperscript{a}, Guy M. McKhann\textsuperscript{b}, Reisa A. Sperling\textsuperscript{c}, Maria C. Carrillo\textsuperscript{d}, Bill Thies\textsuperscript{d}, Creighton H. Phelps\textsuperscript{e}

Alzheimer’s & Dementia 7 (2011) 257–262

Preclinical AD  MCI-AD  AD Dementia

\( \text{Aβ deposition} \)  Neuronal Injury  Cognition/Function

CSF A\( \beta_{42} \)  Amyloid PET  CSF Tau  FDG PET  Structural MRI  Cognitive Test Performance

Adapted Slide from Gil Rabinovici
The diagnosis of mild cognitive impairment due to Alzheimer’s disease: Recommendations from the National Institute on Aging and Alzheimer’s Association workgroup

Marilyn S. Albert, Steven T. DeKosky, Dennis Dickson, Bruno Dubois, Howard H. Feldman, Nick C. Fox, Anthony Gamst, David M. Holtzman, William J. Jagust, Ronald C. Petersen, Peter J. Snyder, Maria C. Carrillo, Bill Thies, Creighton H. Phelps

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Biomarker Probability of AD Etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Markers of Neuronal Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI - Core Clinical Criteria</td>
<td>Uninformative</td>
<td>Conflicting/Untested</td>
<td>Conflicting/Untested</td>
</tr>
<tr>
<td>MCI due to AD - Intermediate Likelihood</td>
<td>Intermediate</td>
<td>Option 1: Positive</td>
<td>Option 1: Untested</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Option 2: Untested</td>
<td>Option 2: Positive</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>
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### The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease


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<th>Diagnostic Category</th>
<th>Biomarker Probability of AD Etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Markers of Neuronal Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD Dementia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on clinical criteria</td>
<td>Uninformative</td>
<td>Unavailable/Conflicting</td>
<td>Unavailable/Conflicting</td>
</tr>
<tr>
<td>Possible AD Dementia (Atypical presentation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on clinical criteria</td>
<td>Uninformative</td>
<td>Unavailable/Conflicting</td>
<td>Unavailable/Conflicting</td>
</tr>
<tr>
<td>+pathophysiology</td>
<td>High, doesn’t rule out 2nd etiology</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>
Atypical Language Case

57 year-old practicing physician with 2 years of progressive word-finding difficulties

• Struggles to come up with words that should be familiar. Results in reported embarrassment, both socially and professionally
• Feels less efficient at accomplishing tasks
• No other cognitive or physical symptoms
• Has not impacted daily function
Atypical Language Case

• **General physical and neurological exams**
  – Normal

• **Global Cognition:**
  – MMSE 30/30

• **Language Testing:**
  – Fluent speech with occasional pauses
  – Poor repetition
  – Mild difficulties with naming (Boston Naming Test: 12/15)
  – Comprehension/reading/writing intact

• **Other Cognitive Domains:**
  – Average to high average (including memory)
Atypical Language Case: Labs and Structural Imaging

- Basic laboratory work-up normal
- MRI: “age-appropriate global volume loss, mild periventricular white matter changes”
- Questions for the neurologist:
  - Is this normal aging?
  - If not, what is the diagnosis?
    - I’m worried about Alzheimer’s but my memory is fine
  - Can I keep working and if so for how long?
  - Should I take Aricept?
Case: At a Loss for Words: PET Results

- Diagnosis: MCI due to AD
- Treatment
  - Cholinesterase inhibitor
  - Referral to anti-Aβ clinical trial
AD-VARIANTS, OR ‘ATYPICAL’ AD
Logopenic Primary Progressive Aphasia: The ‘AD’ Version of PPA

Three variants of primary progressive aphasia (PPA):

– Non-fluent/agrammatic variant [FTD, often due to Tau]
– Semantic variant [FTD, TDP-43 Type C]
– Logopenic variant [AD]

## Logopenic Variant of PPA

<table>
<thead>
<tr>
<th>Speech-Language Core Characteristics</th>
<th>Supporting Speech-Language Characteristics</th>
<th>Neuroimaging Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IvPPA</strong></td>
<td><em>Both of the Following Must Be Present</em></td>
<td>1) Predominant left posterior perisylvian or parietal atrophy on MRI</td>
</tr>
<tr>
<td>1) Impaired single-world retrieval in spontaneous speech and naming</td>
<td>At Least Three of the Following Must be Present</td>
<td>2) Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET</td>
</tr>
<tr>
<td>2) Impaired repetition of sentences and phrases</td>
<td>1) Speech (phonologic) errors in spontaneous speech and naming</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2) Spared single-word comprehension and object knowledge</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3) Spared motor speech</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4) Absence of frank agrammatism</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1) Predominant left posterior perisylvian or parietal atrophy on MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET</td>
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</tbody>
</table>
Logopenic Variant of PPA

Clinically:
- Report early difficulties with word finding
- May report difficulties talking on the phone
- On Neuropsych Testing
  - Phonological processing and working memory impairment
  - Repetition impairment (e.g. Sentence Repetition)
  - Echoic/working memory impairment (Digit span)
  - Poor naming
  - Often will show acalculia
  - Intact single word comprehension, syntactic comprehension.
  - Intact motor speech.
MRI findings

Posterior perisylvian or parietal atrophy on MRI

Gorno-Tempini et al, 2004

Images courtesy of Maya Henry, PhD
### Posterior Cortical Atrophy

<table>
<thead>
<tr>
<th>Core Features</th>
<th>Supportive Features</th>
<th>Neuroimaging Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCA</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| • Prominent visuoperceptual and visuospatial impairments but no significant impairment of vision itself | • Presenile onset  
• Alexia  
• Ideomotor or dressing apraxia  
• Prosopagnosia  
• Prolonged color-after images | • Greater atrophy of visual processing areas in parietotemporo-occipital cortex  
• Relative sparing of critical memory regions in the medial temporal lobe |
| • Relative preservation of memory and insight  
• Evidence of complex visual disorders (elements of Balint’s or Gerstmann’s syndrome; visual field defects; visual agnosia; environmental disorientation | | |
Posterior Cortical Atrophy: Early Stages

5-Year Anatomical Progression of PCA

Chan et al, 2015 Neurocase
Posterior Cortical Atrophy:
Typically Amyloid Positive Pathology

Ossenkoppele et al, 2015, Annals of Neurology
Early Onset Alzheimer’s Disease

• Early Onset Alzheimer’s Disease
  – ~22-64% show a non-amnestic, focal cortical presentation (Mendez et al, 2012)
  – Sometimes considered more frontal* or more behavioral
  – May include PCA, lvPPA
Faster Changes in Cortical Thickness in EOAD versus LOAD

Fig. 4. A statistical map of longitudinal declines in cortical thickness from baseline to Year 3 between the EOAD and LOAD groups (RFT corrected $p < 0.05$ and uncorrected $p < 0.005$). Abbreviations: EOAD, early-onset Alzheimer’s disease; LOAD, late-onset Alzheimer’s disease; RFT, random field theory.

Longitudinal changes of cortical thickness in early- versus late-onset Alzheimer’s disease

Hanna Cho a, Seun Jeon b, Sue J. Kang a, Jong-Min Lee b, Jae-Hong Lee c, Geon Ha Kim a, Ji Soo Shin a, Chi Hun Kim a, Young Noh a, Kiho Im d, Sung Tae Kim e, Juhee Chin a, Sang Won Seo a, Duk L. Na a,*

a Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
b Department of Biomedical Engineering, Hanyang University, Seoul, Korea
c Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
d Division of Newborn Medicine, Boston Children’s Hospital, Harvard Medical School, Boston, MA, USA
e Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
Genetics of Typical and Atypical AD

• Family history:
  — ~1% autosomal dominant in all AD: APP, PSEN1, PSEN2
  — Vast majority of EOAD and LOAD have no family history suggesting an autosomal dominant pattern

• APOE
  — Compared with people with the common ApoE E3/E3 genotype, people with the ApoE E4/E4 genotype are ~10-12 x more likely to develop Alzheimer's disease, respectively.
  — Nonetheless, ~40-50% of people with Alzheimer's disease do not carry the high-risk E4 allele.
  — Differences in grey matter structure seen even in infant E4 carriers
Alzheimer’s Disease

CLINICAL TRIALS
Failure of Amyloid Therapies: Wrong Target or Too Late?

Jack et al., *Lancet Neurol* 2010
Future Directions:
Preventive Anti-Aβ Treatment

- Dominantly Inherited Alzheimer’s Network (DIAN), Alzheimer’s Prevention Initiative (API)
  - Registry of AD mutation carriers for longitudinal biomarker studies and preventive trials
  - Crenezumab trial
- Anti-Amyloid treatment in Asymptomatic AD (A4)
  - Asymptomatic individuals with positive amyloid PET
  - Solanezumab trial
  - Ethics of amyloid scans in asymptomatic individuals
Other Approaches

• Anti-Tau Therapy
• ApoE modifying therapy
• Network stabilization
• Metabolic approaches
CU Anschutz Trial:
Why are people with rheumatoid arthritis protected against Alzheimer’s Disease?
CU Anschutz Trial:
GM-CSF Reduces Aβ Deposition In Vivo
Non-Pharmacologic Clinical Trials

• Physical Exercise!
  – Currently most promising non-pharmacologic intervention in terms of forestalling cognitive decline
  – Modifying effects on APOE
  – EXERT clinical trial
Physical Exercise and the Hippocampus

‘Standard of Care +’ Clinical Trials

- Medicare Amyloid Imaging Trial

Alzheimer’s research — another step forward

referring physicians’ information

From www.ideas-study.org
Take Home Points!

• Much to be excited about with upcoming clinical trials!

• CU Anschutz: Rocky Mountain Alzheimer’s Disease Center
  – Memory Disorders Clinic Available
  – Registry for Interested Research Participants
  – Large, Longitudinal Study to Help Us Understand Alzheimer’s Disease in both Typical Aging Older Adults and Adults with Down Syndrome.
Thank you!

• Thank you to our wonderful team at the Rocky Mountain Alzheimer’s Disease Center!
  – Hunt Potter, PhD
  – Jonathan Woodcock, MD
  – Victoria Pelak, MD
  – Chris Filley, MD
  – Tim Boyd, PhD
  – Heidi Chial, PhD
  – Luis Medina, PhD
  – Joseph Daniels, MPH
  – Helen Gray, MBA
  – Kate Heffernan, BS