Alzheimer’s Disease Research Update

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Disclosures

• Financial Support
  Research
  – NIMH: Improving Antipsychotic Appropriateness in Dementia Patients
    ARRA: PI-Carnahan R18 HS019355-01
  – NIMH: Combined Illness Management: PI-Turvey 5R01MH086482
  – NIA: Alzheimer’s Disease Neuroimaging Initiative-2 National Institute of
    Health/NIA, 3U01 AG024904 PI: Weiner
  – NIA: The Alzheimer’s Disease Cooperative Study; Baxter Healthcare;
    Placebo Controlled Study of intravenous 10% IGIV for AD.
  – Nellie Ball Trust Fund- PIB imaging in Schizophrenia
  Other
  – Iowa Geriatric Education Center HRSA
  – CCOM UI Center on Aging
  – American Psychiatric Association
    • DSM-5
    • American Journal of Psychiatry

Alzheimer’s Disease: Unraveling the Mystery

What is Alzheimer’s disease (AD)?
  Dementia or Alzheimer’s?
  Alzheimer’s Disease and Alzheimer’s Dementia?
AD and the Brain: New Biomarkers
AD Research
  Alzheimer’s Disease Neuroimaging Initiative

Alzheimer’s Disease Cooperative Study (since 1991)

  A cooperative agreement between the National Institute on Aging (NIA) and UCSD
  To advance the development of drugs for Alzheimer’s disease (AD), particularly drugs that
  might not be developed by industry
    • Conducted over 30 clinical studies with the majority carried out at
      20 or more AD research centers and other academic sites
  Studies at Iowa
    • Valproate to Attenuate the Progression of Alzheimer’s Disease
    • Intravenous Immune Globulin (IVIg) for Alzheimer’s Disease
    • ALZHEIMER’S DISEASE NEUROIMAGING STUDY (ADNI-2)

Blood vessel health matters for memory!
Exercise!
Healthy diet
Take Home Message

• Research in last 5 years: AD need not be a postmortem diagnosis
• Amyloid and tau proteins
  – Can now be measured in life
  – In healthy adults!

Mild Cognitive Impairment?

**Normal Aging**
- Occasional loss of memory for words and names.
- Slowed processing speed.
- Difficulty sustaining attention when faced with competing environmental stimuli.
- No functional impairment.

**MCI**
- Memory impairment beyond that expected for age, increasing over last six to 12 months.
- Other cognitive functions generally unimpaired.
- Daily function not significantly impaired.
- No dementia diagnosis.

> Source: Dr. Pierre Tariot, University of Rochester Medical Center. “What is on the Horizon for Alzheimer’s Disease Research?”

North American ADNI

Site PIs, Core Directors, Study Coordinators
822 subjects enrolled since 2004

- Public-private research partnership coordinated by the ADCS tasked with identifying biomarkers to detect Alzheimer’s disease (AD).
- The study has gathered and analyzed thousands of brain scans, genetic profiles and biomarkers in blood and cerebrospinal fluid (CSF).
- Shared data access (like all ADCS studies)
**Mission:** To find more sensitive methods to detect AD pathology at earlier stages
- Mild Cognitive Impairment (MCI) samples presently too heterogeneous to be optimal intervention points.

**Measures**
- Cerebrospinal fluid amyloid and tau
- Amyloid Imaging (PIB in ADNI-1, AV-45 in ADNI-2)
- FDG PET Imaging
- Structural Imaging
- Genetic Biomarkers, Post-mortem data

**Neuroimaging in AD at Iowa**
- UI Magnetic Resonance and PET Centers
  - FDG PET, Amyloid (florbetapir) PET, CSF sampling (Neurology)
  - ADNI Collaborators: Laura Boles Ponto PhD, Yusuf Menda MD, Vince Magnotta PhD, Deema Fattal MD, John Sunderland PhD, Michael Graham MD, PhD, Hyungsub Shim MD
- C-11 PIB Amyloid Imaging
  - IND for C-11 PIB – Michael Graham, MD, PhD - sponsor
  - Laura Boles Ponto PhD and Yusuf Menda MD
  - Long-standing use of O-15 water for rCBF mapping of cognitive function

**Samples to Date**
- **ADNI-1** 2004-9
  - N= 200 Healthy Controls
  - N=200 Mild Cognitive Impairment
  - N=400 Alzheimer’s dementia
- **ADNI-GO** 2009-11
  - N=300 E-MCI (Early-Mild Cognitive Impairment)
- **ADNI-2** underway
  - N=150 Healthy Controls
  - N=150 Early-Mild Cognitive Impairment *
  - N=150 MCI (or Late MCI)*
  - N=150 Alzheimer’s dementia
  - *Based on edu-adjusted scores on Logical Memory II subscale from Wechsler Memory Scale-Revised
Papers to Date

- 225+ Publications

Amyloid Imaging

RED = maximum uptake
VIOLET = minimum uptake

University of Pittsburgh PET Amyloid Imaging Group

[11C]PIB (Pittsburgh Compound B)

- Amyloid Imaging
- General pattern is one of significant retention of tracer in areas with post-mortem documented amyloid deposits
  - Pike, et al, 2007, found that 97% of AD, 61% of MCI and 22% of healthy aging subjects had increased [11C]PIB retention.

florbetapir Amyloid Imaging

Amyloid Imaging

- 30% of entirely normal individuals may have elevated amyloid
- Longitudinal follow-up over YEARS is essential to understand why some amyloid+ people go on to have memory loss and others do not.
Imaging Brain Metabolism

FDG PET Scan of a Normal Brain

FDG PET Scan of a Brain with AD

Summary Thus Far

BIOMARKERS for AD
- PET: Positive Amyloid imaging
- Spinal Fluid
  - Low CSF amyloid
  - High CSF total tau and p-tau
- FDG PET Reduced cerebral metabolism
- MRI: Reduced medial temporal volumes

Table 1. ADNI Descriptive demographics

<table>
<thead>
<tr>
<th>DX</th>
<th>PIB Status</th>
<th>N</th>
<th>Age</th>
<th>Sex F/M</th>
<th>MMSE</th>
<th>ApoE (-/+)</th>
<th>Edu</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>-</td>
<td>73</td>
<td>75.6</td>
<td>38/35</td>
<td>29.0</td>
<td>69/4**</td>
<td>15.5</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>51</td>
<td>76.4</td>
<td>21/30</td>
<td>29.2</td>
<td>27/24</td>
<td>16.0</td>
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<tr>
<td>MCI</td>
<td>-</td>
<td>63</td>
<td>74.8</td>
<td>15/48</td>
<td>27.3</td>
<td>55/24</td>
<td>15.7</td>
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<tr>
<td></td>
<td>+</td>
<td>166</td>
<td>74.4</td>
<td>63/103</td>
<td>26.8</td>
<td>55/111</td>
<td>15.9</td>
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<tr>
<td>AD</td>
<td>+</td>
<td>122</td>
<td>74.9</td>
<td>47/85</td>
<td>23.6</td>
<td>36/76</td>
<td>15.1</td>
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</table>

Table 1, Continued

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<tr>
<td>HC</td>
<td>244.7 (27.6)**</td>
<td>62.0 (23.0)*</td>
<td>20.5 (8.0)*</td>
<td></td>
<td></td>
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<tr>
<td>HC PIB+</td>
<td>152.0 (27.6)</td>
<td>79.5 (37.6)</td>
<td>31.0 (19.1)</td>
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<tr>
<td>MCI</td>
<td>244.1 (26.9)**</td>
<td>62.6 (23)**</td>
<td>20.0 (7.8)**</td>
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<td></td>
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<tr>
<td>MCI PIB+</td>
<td>136.4 (26.0)</td>
<td>116.5 (62.8)</td>
<td>40.5 (17.5)</td>
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<tr>
<td>AD</td>
<td>142.5 (39.6)</td>
<td>121.5 (57.5)</td>
<td>102.4 (19.8)</td>
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<td></td>
</tr>
</tbody>
</table>

Table 1. Continued

<table>
<thead>
<tr>
<th>CSF Ab1-42, pg/ml</th>
<th>CSF total tau, pg/ml</th>
<th>CSF p-tau, pg/ml</th>
</tr>
</thead>
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ADNI thresholds: Ab42<192 t-tau>93 p-tau>23

Ratios: t-tau/Ab42 > 0.39 and p-tau/Ab42 >0.10


Survival plot for conversion from MCI to AD for PIB-PET(+) shown in red and PIB-PET(-) shown in black.
Revised Criteria

<table>
<thead>
<tr>
<th>Normal</th>
<th>Pre-clinical</th>
<th>MCI</th>
<th>Alz dementia</th>
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</thead>
<tbody>
<tr>
<td>Research setting</td>
<td>Early stages – no symptoms</td>
<td>Biological markers</td>
<td>Need validation</td>
</tr>
<tr>
<td>Research setting</td>
<td>Early stages – mild symptoms</td>
<td>Biological markers</td>
<td>Need validation</td>
</tr>
<tr>
<td>Clinical setting</td>
<td>Similar to criteria used today AD-C</td>
<td>Use of biological markers to improve diagnostic confidence: AD-P</td>
<td></td>
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</tbody>
</table>

The Iowa ADNI2 Study

- Tests include Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) florbetapir and FDG scans, CSF (spinal fluid) sampling conducted at regular intervals over 5 yrs.
- Participants will be between 55-90 (inclusive) years of age.
- Subjects will include:
  - Cognitively normal participants
  - Early Mild Cognitive Impairment (MCI)
  - Late Mild Cognitive Impairment (MCI)
  - Early Alzheimer’s Disease (AD)

Thank you!

This study is being conducted by the Alzheimer’s Disease Cooperative Study (ADCS) and supported by the National Institutes of Health (NIH) through the American Recovery and Reinvestment Act of 2009 funds.

- The Federal government’s lead agency for AD research is the National Institute on Aging (NIA), part of the National Institute of Health (NIH). NIH is part of the U.S. Department of Health and Human Sciences.
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- Research Nurse; 319 353-5158