The earliest signs of Alzheimer’s Disease

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Institute on Aging
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“Earliest Signs of Alzheimer’s Disease”

• FINANCIAL DISCLOSURE: NONE
• UNLABELED/UNAPPROVED USES DISCLOSURE: NONE
Why is it Important to Diagnose Early & Cure Alzheimer’s Disease?

- 5.3 million Americans currently have dementia due to Alzheimer’s disease (AD)
- A new case is diagnosed every 70 seconds
- 13 million Americans will have AD by 2050
- 78 million Baby Boomers started turning 65 in 2011
- 6th leading cause of death in the US
- $200 billion spent annually to care for patients with AD; + $200 billion in uncompensated caregiving
Deaths due to AD are increasing; other causes are decreasing

Change in death rate from 2000 to 2010

Source: Alzheimer’s Association Facts and Figures 2013
Drs. Alzheimer, Kraepelin, Gaupp & Nissl
Frau Auguste D. (1906)
Amyloid Plaques
Mature Amyloid Plaque
Amyloid Plaques
Neurofibrillary Tangles
Alzheimer’s Disease - Tangles

- **Earliest Alzheimer’s** – changes may begin 20 years or more before diagnosis.
- **Mild to moderate Alzheimer stages** – generally last from 2 - 10 years.
- **Severe Alzheimer’s** – may last from 1 - 5 years.
Brain Areas Affected by AD

- Frontal Lobe: Behavior
- Parietal Lobe: Spatial Function
- Temporal Lobe: Speech
- Hippocampus: Memory
- Cingulate: Memory Recall
Temporal Lobes are affected in AD.
Cell loss of the hippocampus in normal aging, MCI, and AD

Normal Elderly Brain

MCI

Moderate AD

Korf et al., 2004
Symptoms of AD map onto amyloid lesions

Posterior Cingulate

Functions include: Memory and self reflection

Our research is uncovering brain behavior relationships in AD and mapping their evolution
68 year old healthy older adult

68 year old with Alzheimer’s

MRI
Glucose PET
Amyloid PET
71 year old with Mild Cognitive Impairment
How Early in Life do AD changes begin?

64 year old healthy older adult with family history of Alzheimer’s

MRI                     Glucose PET              Amyloid PET

Normal                      Normal                      Abnormal

MRI                           Glucose PET                  Amyloid PET
Lag between plaque appearance and dementia is about 10 yrs

R. Sperling et al 2011 Alz and Dementia
Trajectories in AD

Clinical Syndrome:
1) 2 or more thinking abilities affected
2) Change from baseline
3) Affecting day to day life
Dementia is...

- **Syndrome (cluster of symptoms):**
  - Deficits in 2 or more thinking abilities
  - Change from previous abilities
  - Affecting day to day life
  - Not explained by something else

- What does the term AD mean? The dementia syndrome, or the disease causing the dementia?
Causes of Dementia

- Alzheimer's Disease (AD): 65%
- AD & Vascular: 10%
- Lewy body: 7%
- AD and Lewy body: 5%
- Vascular: 5%
- Other: 8%

Data from www.alz.org
# Types of Memory

<table>
<thead>
<tr>
<th></th>
<th>Aging</th>
<th>Early AD (mci)</th>
<th>Mild AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working Memory</td>
<td>![Symbol]</td>
<td>![Symbol]</td>
<td>![Symbol]</td>
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<tr>
<td>Episodic Memory (events)</td>
<td>![Symbol]</td>
<td>![Symbol]</td>
<td>![Symbol]</td>
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<tr>
<td>Semantic Memory</td>
<td>![Symbol]</td>
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<td>![Symbol]</td>
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<tr>
<td>Classical Conditioning</td>
<td>![Symbol]</td>
<td>![Symbol]</td>
<td>![Symbol]</td>
</tr>
<tr>
<td>Procedural or Skill Memory</td>
<td>![Symbol]</td>
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</tbody>
</table>
Changes with age:

- Learn at a slower rate (less efficient; need more repetition)
- Processing speed and reaction time slows
- Free recall more difficult (need cues)
- Word and name finding problems
Summary so far

• Dementia is a syndrome
• Many different causes of dementia
• Alzheimer’s most common
• Amyloid can now be tested (PET imaging)
• However, not all people with AD brain changes get dementia
Questions Wisconsin ADRC is addressing

- How early in life does Alzheimer’s begin?
- What is the time window between earliest Alzheimer’s brain changes and clinical symptom onset?
- If we can intervene in this time window, can we prevent or slow Alzheimer’s Disease?
Identifying people at risk for AD

- Risk Factors
  - Age
  - Parental history of AD \( x3 \)
  - APOE gene \( x2.5 \) or \( 5x \)
  - Gender (2:1 Female : Male)
  - Lifestyle, fitness, education and diet
  - Other genes
Wisconsin Registry for AD Prevention (WRAP)

N=1500 baseline evals;
- 1065 adult children of AD; 435 with no parental hx AD
- Age 40-65 at baseline; mean age was 52
- Natural history longitudinal study
- Multi-domain neuropsych evaluation
- Blood labs; medical history, symptom questionnaires, lifestyle and diet questionnaires
- Consent to serial testing; consent to be approached for add-on imaging studies
• Current mean age 63
• Among adult children, 46% are APOE4+
• 2nd wave is 4 years after baseline
• Subsequent waves are every two years
WRAP: Parental hx of AD

1. Different patterns of brain activation (Johnson 06, 07, Xu 08)

2. Lower brain energy metabolism (blood flow) in certain areas (Okonkwo 2013)

3. Altered white matter (Bendlin, 2010, Racine in prep)

4. Hippocampal atrophy over 4 years (Okonkwo 2012)
Cerebral Blood Flow with pcASL
Lower neural function in maternal FH

mFH vs -FH
N=111 vs 75
APOE+ 51%, 21%
Covariates: APOE age, sex, Gray matter vol
Mean age =59

Apply AD result as an ROI mask

ASL CBF maps show areas affected in 24 AD vs 28 controls

Okonkwo et al 2013, Cerebral Cortex
4 year decline in hippocampal volume
age 54 to 58: Parental FH

N=108; No baseline differences observed; No baseline or followup differences in cognition

Okonkwo et al. *Neurology* 2012
75% of MCI cases are amyloid positive
Stable normal
Characteristics of amyloid positive subjects

Table 1. Baseline characteristics of participants (n=201)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Amyloid negative, n=83</th>
<th>Amyloid Intermediate, n=82</th>
<th>Amyloid Positive, n=36</th>
<th>p value$^$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
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<tr>
<td>FH positive, %</td>
<td>69.9</td>
<td>67.1</td>
<td>83.3</td>
<td>.189</td>
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<td>Maternal FH positive, %</td>
<td>41.0</td>
<td>42.7</td>
<td>63.9</td>
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<tr>
<td>APOE4 positive, %</td>
<td>38.6</td>
<td>35.4</td>
<td>55.6</td>
<td>.110</td>
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<tr>
<td>Female, %</td>
<td>54.2</td>
<td>75.6</td>
<td>77.8</td>
<td>.005</td>
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<tr>
<td>Age at PiB scan</td>
<td>59.33 (5.67)</td>
<td>60.05 (6.16)</td>
<td>62.78 (4.33)</td>
<td>.010</td>
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<tr>
<td>Education</td>
<td>16.04 (2.38)</td>
<td>16.01 (2.34)</td>
<td>16.50 (2.35)</td>
<td>.548</td>
</tr>
</tbody>
</table>
Amyloid positive subjects

- No cognitive deficits
- No brain atrophy
- No brain metabolism deficits
- Mean age of 60
- May or may not get symptoms—this is the focus of our research
Impact of Treatment

Cognitive Function

Age

Death

Normal aging

MCI

AD syndrome

Interventions
Finding a solution in people at risk for AD

• New drugs are tested at the dementia stage—not good

• When cognition is the primary outcome in a clinical trial, you would need >1000 subjects.
  • Too expensive; too long!

• Problem 1: How to identify non-symptomatic candidates for a prevention clinical trial?

• Problem 2: How to tell if a drug is working?

• Brain Imaging: 1) Enrich trial with people who are most likely to convert to dementia 2) More sensitive outcomes

Collaboration with Professor Vikas Singh, PhD Biostats/Computer Science
How many subjects are needed in a prevention trial?

About 100 at the MCI stage
About 200 presymptomatic stage

- We would need ~200 subjects to detect a treatment effect of a 25% reduction in rate of change in hippocampal volume over 4 years.
  - Based on Okonkwo et al *Neurology* 2012
Summary

• AD is the disease of our time

• The brain changes before symptoms—this will be the optimal time to intervene

• Amyloid imaging is a major new research and clinical tool for charting the beginnings of AD

• Research at Wisconsin ADRC focused on imaging outcomes in clinical trials for presymptomatic adults

• Harness the intellectual power of the UW in a team approach
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