Biomarkers for Alzheimer's Disease in Down Syndrome

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Outline

• Rationale for Studying AD in Down Syndrome
• Background of Alzheimer’s Disease
• Biomarkers for Alzheimer’s Disease
• Details and Findings of the Natural History of Amyloid Deposition in Adults with Down Syndrome
• Recent Findings of the Role of Amyloid in Alzheimer’s Disease
• What’s New in Waisman Center Down Syndrome Research?
Research Rationale and Goals

- Adults with Down syndrome (DS) are at an extremely high risk for developing Alzheimer’s disease (AD), with most individuals over age 40 evidencing amyloid deposits.

- The goal of our research is to track biomarkers of AD in adults with DS and to follow these individuals to understand the course of cognitive, imaging and biochemical changes and their effects on functioning over time.

- This offers an opportunity to deepen our understanding of the pathophysiology of AD in DS but may also offer information that will prove useful in the prevention and treatment of AD in the general population.
Alzheimer’s Disease (AD) and Down Syndrome

• The prevalence of dementia in the general population
  – less than 5% among those 65 years and younger
  – 15 - 30% for those beyond the age of 80 years

• The prevalence of dementia in the DS population
  – 9% of adults with DS will be diagnosed between 40 and 49 years
  – 18% for individuals in the 50-54 year age span
  – 32% for those greater than 50-59 years of age.
  – 70-80% for individuals in their 60’s
What is Alzheimer’s Disease?
Characteristics of Alzheimer’s Disease

• Dementia – progressive deterioration of cognitive function that ultimately prevents a person from independently performing their daily activities

• Alzheimer’s Disease – accounts for 70% of cases of dementia
  – Symptoms include difficulty in:
    Language, memory, perception, emotional behavior, cognitive skills (e.g. judgment)
Why is AD a public policy issue?

• 5.3 million Americans have AD
  – 110,000 in Wisconsin

• 7th leading cause of death

• The elderly are already the fastest growing segment of US. This will increase.
  ~ 10,000 Baby Boomers turned 65 per day
Down Syndrome and APP

http://en.wikipedia.org/wiki/

Pathology of Alzheimer’s Disease
AD Pathology
- tangles and plaques

Healthy and Diseased Neurons

Healthy Neuron
- Normal Tau Protein
- Normal Microtubule

Diseased Neuron
- Disintegrating Microtubules
- Hyperphosphorylated Tau
- Formation of Tau Tangles

Neurofibrillary Tangles

Preclinical AD
Mild to Moderate AD
Severe AD

www.nia.nih.gov

WAISMAN CENTER
β – Amyloid Plaques

Non-amyloidogenic

Amyloidogenic

www.nia.nih.gov
Aβ plaques

Fibrils

Oligomers

Beta-amyloid Peptide

sAPPβ

Cell Membrane

Inside Cell

Cell Surface

Beta-secretase

Gamma-secretase

APP
Tau Tangles in AD

Changes in tau protein

www.nia.nih.gov
Biomarkers for Alzheimer’s Disease

Biomarker for AD – a biological measure that is an indicator of Alzheimer’s disease or AD related pathology

Potential Biomarkers for AD

- Cerebrospinal Fluid Biomarkers: Aβ(1-42), Total tau, ptau
- Blood-based: Aβ, inflammatory, proteins, lipids, metabolites
- Genetics
- Brain Imaging: PET and MRI
- Behavioral and Cognitive Testing
The use of medical imaging in the study of Alzheimer’s Disease
Magnetic Resonance Imaging (MRI)  
 Positron Emission Tomography (PET)
Alzheimer’s Disease: FDG

Healthy Control

AD Subject
Brain Scanning in Aging and Dementia
- early identification of β-amyloid

PET image of [C-11]PIB

MRI scan

[C-11]PIB binding in AD

[C-11]PIB binding HC

Amyloid Binding

Rowe CC, et al., Neurology 2007; 68:1718-1725
Measuring Tau and Amyloid in the AD Progression

Cognitively Normal

PiB

THK-5117

AD Dementia

PiB

THK-5117

Betthauser, HAI 2016
The presence of amyloid in the brain precedes cognitive change.
What is the progression of β-amyloid in people with Down Syndrome?
Experimental Details

<table>
<thead>
<tr>
<th>Measure</th>
<th>Informant/ Participant</th>
<th>Time (minutes)</th>
<th>Screen/ Baseline</th>
<th>Follow-Up Visit</th>
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<td><strong>Day 1 (Informant and Neuropsychological Measures)</strong></td>
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<tr>
<td>Informed Consent</td>
<td>Caretaker &amp; Subject</td>
<td>45-60</td>
<td>X</td>
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<td>DSDS Interview</td>
<td>Caregiver</td>
<td>30</td>
<td>X</td>
<td>X</td>
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<tr>
<td>SIB/IQ/Neuropsych</td>
<td>Subject</td>
<td>120-150</td>
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<td>Psychiatric Assessment</td>
<td>Subject</td>
<td>15</td>
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<td>Vineland/Reiss Screen</td>
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<td>X</td>
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<tr>
<td>Medical/Psychiatric Hx</td>
<td>Caregiver</td>
<td>15</td>
<td>X</td>
<td>X</td>
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<td><strong>Day 2 (Neuroimaging Measures)</strong></td>
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<td>MRI</td>
<td>Subject</td>
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<td>PiB PET Scan</td>
<td>Subject</td>
<td>90</td>
<td>X</td>
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</table>
Down Syndrome PiB Results

PiB Status

- Tissue ratios calculated for cortical regions-of-interest (ROI) and normalized to cerebellum (SUVR)

- PiB+ = above the cutoff (>1.5) in 5 cortical areas defined using the iterative outlier approach
Results: Association with age

- = PiB+ threshold, o = PiB-, Δ = PiB+, Filled shapes = APOE4 carrier


SNMMI 2015
Results: PiB Positivity in Down syndrome

- Sparse k-means clustering used to determine a ROI-specific threshold
- PiB positive classification: At least one ROI having a mean SUVR exceeding its threshold

<table>
<thead>
<tr>
<th>ROI</th>
<th>PiB+ SUVR threshold</th>
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<tr>
<td>Anterior Cingulate (AC)</td>
<td>1.59</td>
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<tr>
<td>Frontal Cortex (FC)</td>
<td>1.48</td>
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<tr>
<td>Parietal Cortex (PC)</td>
<td>1.51</td>
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<tr>
<td>Precuneus (P)</td>
<td>1.64</td>
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<tr>
<td>Striatum (S)</td>
<td>1.45</td>
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<tr>
<td>Temporal Cortex (TC)</td>
<td>1.37</td>
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<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>AC</th>
<th>FC</th>
<th>PC</th>
<th>P</th>
<th>S</th>
<th>TC</th>
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Summary:
- 52 PiB+ in no ROI (PiB-); 35.0±6.0 yrs
- 4 PiB+ in one ROI; 41.8±5.3 yrs
- 5 PiB+ in several ROIs; 45.6±6.9 yrs
- 11 PiB+ in all ROIs; 44.9±3.5 yrs
Independent Living Skills

- communication, daily living, socialization

Vineland Adaptive Behavior Scales
(Sparrow, Cicchetti & Balla, 2005)
Behavior Problems

- aggression, paranoia, depression

Reiss Screen for Maladaptive Behavior
(Reiss, 1990, 1997)
Executive Control and Working Memory

Cat and Dog Stroop Test

# Errors

Switch Trial - Naming Trial Time

* P < 0.05 using one-tailed

Sigan L. Hartley et al. Gatlinburg 2012
Visuospatial Working Memory

Corsi Block Tapping Test
(Corsi, 1974)

* P < 0.05 using one-tailed
Sequence of Changes in AD Progression

Rate of β-amyloid Deposition
- in general population

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls with low **C-PiB retention (n=74)</th>
<th>Healthy controls with high **C-PiB retention (n=38)</th>
<th>p value*</th>
<th>MCI with low **C-PiB retention (n=8)</th>
<th>MCI with high **C-PiB retention (n=24)</th>
<th>p value*</th>
<th>p value</th>
<th>AD with high **C-PiB retention (n=18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ deposition (SUVr per year)</td>
<td>0.022 (0.02)</td>
<td>0.046 (0.03)</td>
<td>&lt;0.0001</td>
<td>0.025 (0.02)</td>
<td>0.049 (0.02)</td>
<td>0.017</td>
<td>0.64</td>
<td>0.026 (0.03)</td>
<td>0.064</td>
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<tr>
<td>Episodic memory decline (SD per year)</td>
<td>-0.03 (0.28)</td>
<td>-0.19 (0.28)</td>
<td>0.0037</td>
<td>-0.09 (0.15)</td>
<td>-0.22 (0.21)</td>
<td>0.10</td>
<td>0.59</td>
<td>-0.15 (0.18)</td>
<td>0.059</td>
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<tr>
<td>Non-memory decline (SD per year)</td>
<td>-0.06 (0.12)</td>
<td>-0.16 (0.22)</td>
<td>0.0044</td>
<td>-0.11 (0.15)</td>
<td>-0.26 (0.24)</td>
<td>0.13</td>
<td>0.09</td>
<td>-0.52 (0.37)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Grey matter atrophy (cm² per year)</td>
<td>-1.6 (2.2)</td>
<td>-2.0 (2.2)</td>
<td>0.0093</td>
<td>-0.6 (1.9)</td>
<td>-2.6 (2.9)</td>
<td>0.13</td>
<td>0.71</td>
<td>-4.7 (3.3)</td>
<td>0.028</td>
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<tr>
<td>Hippocampal atrophy (cm² per year)</td>
<td>-0.031 (0.04)</td>
<td>-0.052 (0.06)</td>
<td>0.0019</td>
<td>-0.043 (0.03)</td>
<td>-0.093 (0.05)</td>
<td>0.039</td>
<td>0.0098</td>
<td>-0.028 (0.09)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

**C-PiB=Carbon-11-labelled Pittsburgh compound B. MCI=mild cognitive impairment. AD=Alzheimer’s disease. Aβ=amyloid β. SUVr=standard uptake value ratio. *Compared with participants in the same clinical group with low Aβ burden (low **C-PiB). †Compared with healthy controls with high Aβ burden (healthy controls with high **C-PiB retention).

Table 3: Rates of amyloid β deposition, grey matter and hippocampal atrophy, and cognitive decline in participants who had amyloid β accumulation during the study.

New Research in Down Syndrome

Natural History of Amyloid Deposition in Adults with Down Syndrome
- funded since 2010 to study the presence of amyloid deposition and its effect on functioning over time

NiAD: Neurodegeneration in Aging Down Syndrome
- newly funded grant by the National Institutes of Health to study clinical, cognitive, imaging, genetic and biochemical biomarkers
Conclusions

• Advances in healthcare have dramatically increased the life expectancy for adults with Down syndrome, now approaching 60 years, making them at greater risk for developing AD.

• Approximately 30% of the DS subjects have been found PiB+.

• Despite having elevated amyloid binding, few show signs of dementia.

• Subjects with elevated amyloid have reduced cognitive function, but this has not yet affected their living skills.

Future Directions

• We will be examining a wide range of clinical, cognitive, imaging and biochemical data to identify biomarkers for AD in Down syndrome
Thanks to our Participants!

Stray Cats  Dan from Wisconsin Harvey A. Stevens International Collection of Art by People with Developmental Disabilities, by the Friends of the Waisman Center

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