Alzheimer's Disease 2011: What have we learned? Where are we going? How will we get there?"

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Disclosures

• **Consultant/Advisory Boards:**
  – Bristol Myers Squibb, Eisai, Lilly, Merck, Novartis, Pfizer, PsychoGenics

• **Off-Label Discussion:**
  – None
Overview

• A behavioral case study
• From rare disease to population crisis
• Risk factors: genes, lifestyle, the overlap with vascular risks, and 'resistance' to cognitive changes
• The continuum of pathological changes
• Imaging and biomarkers of the continuum of change: leveraging biomarkers against the limits of clinical detection
• Amyloid imaging: in vivo detection and its role in the continuum
• Therapies for amyloid and beyond...and the real meaning of 'the Amyloid Hypothesis”
• In the 25th anniversary year of the McKhann Criteria for AD, new criteria emerge--for AD, MCI, and preclinical detection
• With apologies to the Rolling Stones...Time is (not) on our side...
Case Study

46 year old married female

- General good health; on no medications
- No major medical problems
- Sub-acute onset of pathological jealousy
- Onset of dysnomia (calls a pitcher a ‘milk pourer’)
- Difficulties with short term memory
- General medical examination normal
- Neurological examination normal except for mental status
- Progressive cognitive decline, death 4 years later
Alzheimer’s original patient: Auguste D.

“I have lost myself.”
Alzheimer’s Disease

Memory loss
Language disturbances
Visuospatial deficits
“Frontal-Dysexecutive”:
  Impaired judgment,
  motivation, insight,
decreased social cognition
Neuropsychiatric symptoms:
  depression, anxiety,
sleep disturbance
psychosis

The anatomical/circuitry correlates of these behaviors are now largely identified

Alzheimer’s original patient: Auguste D.
From Clinic to Community: characterizing the clinical picture of AD

Alois Alzheimer
Germany, 1907:
- single case report
- rare, unusual disease of middle-aged
- “pre-senile dementia”

Martin Roth and colleagues
Newcastle, 1964:
- community survey
- fairly common disease of elderly
- “senile dementia”

 Majority of cases of dementia in late life are AD, with many cases showing additional co-morbidities
1976 Katzman editorial: an alarm is sounded


- Predicted a massive increase in the number of cases of Alzheimer’s Disease in the 21st century

- No clear difference between presenile and senile onset with respect to symptoms or pathology

- Stimulated research in aging and AD brain
Prevalence of Mild, Moderate/Severe and Total Cases of AD: 2000-2050

Assume no new therapy

Increasing Global Burden of AD
Risk Factors and Interventions

- Age
- Family history
- Apoe4
- Down’s syndrome
- Education
- Midlife ↑BP
- Midlife ↑cholesterol
- Homocysteine
- α-macroglobulin
- CYP46
- Family Hx of Down’s
- Statins
- HRT
- NSAIDS
- Alcohol
- Seafood
- Caffeine
- Vitamin E
- Vitamin C
- B12, folate
- Ginkgo
- Fats

- Leisure activity
- Cognitive activity
- Physical activity
- Depression
- Diabetes
- Head injury
- EM fields
- Vaccines/passive immunization

From Brodaty, 2003
Modifiable Risk Factors & Interventions

- Age
- Family history
- Apoe4
- Down’s syndrome
- Education
- Midlife ↑BP
- Midlife ↑cholesterol
- Homocysteine
- $\alpha$-macroglobulin
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From Brodaty, 2003
Diet and AD Risk/Healthy Brain/Increase “Brain Reserve”
All are associations, not proven

• **Dark-skinned fruits and vegetables**
  – have the highest levels of naturally occurring **antioxidants**, which protect the brain from **free radical** formation.
  – eggplant, red bell peppers, beets, broccoli, spinach, Brussels sprouts, red grapes, cherries, oranges, and all kinds of berries (blueberries, blackberries, cranberries, strawberries, and raspberries are great choices).

• **Coldwater fish**
  – contain **omega-3 fatty acids**, which are beneficial to cell membranes.
  – tuna, mackerel, anchovies, trout, herring, salmon, sardines, and whitefish.

• **Other foods that contain omega-3 fatty acids**
  – Nuts also contain vitamin E, which is a potent **antioxidant**.
  – green leafy vegetables, avocados, Brazil nuts, cashews, pistachios, walnuts, canola oil, flaxseed oil, olive oil, and peanut oil.

• **Supplements like vitamins B-12, C, E, and folate may also help maintain a healthy brain.**
  – better to obtain these nutrients directly from food, if possible.
Vascular factors that increase AD risk

- Hypertension
- Hypercholesterolemia
- Homocysteine elevation
- Inflammatory states, increased CRP
- Diabetes mellitus
- Carotid & Circle of Willis stenosis
## Genes and Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Location</th>
<th>Gene Product</th>
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</thead>
<tbody>
<tr>
<td>Chromosome 21 (APP)</td>
<td>amyloid precursor protein</td>
</tr>
<tr>
<td>Chromosome 14</td>
<td>Presenilin 1 (PS1) transmembrane protein</td>
</tr>
<tr>
<td>Chromosome 1 Presenilin 2 (PS2) (Volga German Kindreds)</td>
<td>transmembrane protein</td>
</tr>
</tbody>
</table>

**“Risk Alleles:**

<table>
<thead>
<tr>
<th>Location</th>
<th>Gene Product</th>
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</thead>
<tbody>
<tr>
<td>Chromosome 19</td>
<td>apolipoprotein E (apoE)</td>
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APOE and Alzheimer’s Disease

**ALLEL FREQUENCY:**

<table>
<thead>
<tr>
<th>Allele</th>
<th>Normal Population</th>
<th>In AD</th>
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</thead>
<tbody>
<tr>
<td>E2</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>E3</td>
<td>79%</td>
<td>40-50%</td>
</tr>
<tr>
<td>E4</td>
<td>14%</td>
<td>40-50%</td>
</tr>
</tbody>
</table>

Potential mechanisms:
- Impaired removal of beta amyloid
- Diminished neural regeneration
- Allele frequency twice as high in Africans & African Americans as in Caucasians
Alzheimer’s Disease: Course, Prevention, Treatment Strategies

Clinical State

- Normal
- Pre-symptomatic AD
- Mild Cognitive Impairment
- AD

Disease Progression
Linking Clinical Symptoms With Degree of Pathology

Intervention

Clinical State

Normal
Pre-symptomatic AD
Mild Cognitive Impairment
AD

Brain Pathologic State

No Disease
No Symptoms
Early Brain Changes
No Symptoms
AD Brain Changes
Mild Symptoms
Mild, Moderate, or Severe Impairment

Disease Progression

Primary Prevention
Secondary Prevention/Early Tx
Treatment
Major Pathological Changes in AD

- Brain shrinkage (atrophy)
- Neuritic Plaques
  - altered metabolism of APP
  - Deposition of beta amyloid
- Neurofibrillary Tangles
  - Cytoskeletal pathology [girders and trusses]
  - Altered metabolism of tau protein
- Neuronal death in specific brain regions (why some regions and not others?)
- Specific Neurotransmitter deficits (especially ACh, serotonin, norepinephrine, glutamate)
The ‘inflammatory surround’ consists of distorted and degenerating synaptic processes, activated microglia, and astrocytic processes.
Amyloid Precursor Protein (APP)

- **Soluble APPα**
- **Soluble APPβ**

**Amyloid plaques, Inflammation, Neuron loss**

**Amyloid Metabolism**

- **Monomers → Dimers → Oligomers**

**Nicastrin**

**Presenilin 1/2**

**APH-1**

**PEN-2**

**BACE-1**

**γ-cleavage site**

**β & γ cleavage**

**Aβ domain**
Tau (Microtubule Associated Protein MAP2): Axonal Dissolution and Dysfunction in AD
Neurofibrillary Tangles

- Major lesion of Alzheimer’s disease and other neurodegenerative diseases
- Found inside neurons
- The paired helical filaments are the microtubule associated protein tau in an abnormally phosphorylated state
- Highly insoluble
- Associated with neuronal death
- Good correlation with cognitive impairment
- Focus on prevention: inhibit GSK3 or other kinases?

Tangles from the brain of Auguste D.
Tangle (NFT) & Plaque (NP) Distribution In AD at Autopsy: The Static View of the 1980s-90s

S. Arnold, Cortex, 1991
Biochemical pathway of neurofibrillary degeneration

Stages

S0

S1

S2

S3

S4

S5

S6

S7

S8

S9a

S9b,c

S10

A35

A28

A34

A38

A20

A21

A22, 10, 39

A44

A4

A18

A17

Brodman areas

n=30

n=3

trans-entorhinal

n=4
+ entorhinal

n=16
+ hippocampus

n=10
+ anterior temporal ctx

n=12
+ inferior temporal

n=11
+ mid temporal

n=15
+ anterior frontal, superior temporal, inferior parietal

n=5
+ Broca area

n=6
+ motor cortex

n=13

n=27
All cortical areas affected.

n=3
trans-entorhinal

n=4
+ entorhinal

n=16
+ hippocampus

n=10
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All cortical areas affected.

Distribution of PHF-Tau

Evolution of Neuroimaging in AD

- Computed Tomography
- MRI
- Volumetric MRI
- Co-registration of MRI
- Functional MRI
- FDG Glucose PET
- Amyloid Imaging


Brain Maps: Alzheimer’s Disease Spreading

Initially 6 months later 12 months later 18 months later

www.loni.ucla.edu/~thompson/AD_4D/dynamic.html.
Biomarkers for Earlier Diagnosis

Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS–ADRDA criteria


The NINCDS–ADRDA and the DSM-IV-TR criteria for Alzheimer’s disease (AD) are the prevailing diagnostic standards in research; however, they have now fallen behind the unprecedented growth of scientific knowledge. Distinctive and reliable biomarkers of AD are now available through structural MRI, molecular neuroimaging with PET, and cerebrospinal fluid analyses. This progress provides the impetus for our proposal of revised diagnostic criteria. Our criteria stipulate that there must also be at least one or more abnormal biomarkers among structural neuroimaging with MRI, molecular neuroimaging with PET, and cerebrospinal fluid analysis of amyloid β or tau proteins. “

Lancet Neurol 2007; 6: 734–46
Framework for Biomarkers

- Molecular Pathology of AD
  - CSF Abeta 42
  - CSF tau/ phospho tau
  - Amyloid Imaging

- Downstream Measures of Structural Change
  - Hippocampal Volume
  - Medial Temporal Lobe Atrophy

- Downstream Measures of Functional Change
  - FDG PET
  - SPECT Perfusion
Role of Biomarkers

• Clarify nature of underlying pathology:
  – Evidence of amyloid burden considered of primary importance in confirming that pathology of AD is present

• Prediction of progression from MCI to Alzheimer’s dementia:
  – Acknowledge that measures of structural and functional change may be more useful in prediction of progression
Use of Biomarkers in Diagnosis

• Accumulation of amyloid is seen first and is followed by other changes
  – more work needs to be done to confirm this trajectory
• Different biomarkers provide different levels of certainty in diagnosis of MCI due to AD
• Criteria using biomarkers outline testable hypotheses regarding the levels of certainty conferred by categories of biomarkers
• Can apply in academic research settings and clinical trials and determine utility of this framework
CSF in Alzheimer’s Disease: Low Aβ and High Tau

CSF in MCI has elevated tau, decreased β-amyloid

A combination of CSF T-tau and A42 at baseline yielded a sensitivity of 95% and a specificity of 83% for detection of incipient AD inpatients with MCI. The relative risk of progression to AD substantially increased in patients with MCI who had pathological concentrations of T-tau and A42 at baseline (hazard ratio 17·7, p<0.0001). The association between pathological CSF and progression to Alzheimer’s disease was much stronger than, and independent of, established risk factors including age, sex, education, APOE genotype, and plasma homocysteine.

Hansson et al., 2006
Best markers across a broad range are MRI and FDG-PET.
**Immunization, Prevention, and Treatment of Aβ**

**Prevention**
Q 6 week immunization from age 6 weeks to 1 yr

**Treatment**
Q 6 week immunization from age 12 mo to 18 mo

Histology at 12 Months

**No Treatment**

**Q 6 week immunization**

12 Months

18 Months no Tx

18 Months Tx

Schenk et al, 1999
Immunization reduces Aβ Deposition in Hippocampus of AD Transgenic Mice and Prevents Memory Deficit

Immunized Mice Perform Better than Controls in Memory Tests

Schenk et al., Nature, 400:173-177, 1999
Aβ Immunization Reduced Monkey Cerebral Aβ

Lemere et al, Am J Pathol 2004

Plaque Burden in Frontal Cor

![Graph showing plaque burden in frontal cortex. The x-axis represents monkey age in years, and the y-axis represents plaque burden. The graph compares controls and immunized monkeys.](image)

- **Controls**
- **Immunized**

*23 yr, 22 yr, 21 yr, 17 yr, 16 yr*
AN1792-201 Phase II Study Design

• Randomized, parallel group, double-blind, placebo-controlled trial
• 375 mild-moderate AD patients (372 enrolled) in 30 centers (USA and Europe)
• Study halted due to CNS inflammation; 5-6% developed meningoencephalitis

Orgogozo et al., Neurology, 2003
Pathology, but Amyloid Removal...

Neuropathology of human Alzheimer disease after immunization with amyloid-β peptide: a case report

Plaques in untreated AD Subjects

Nicoll et al., 2003

Plaques in Immunized Subject
Alternative Strategies:

**Passive Transfer of Aβ Antibodies**

- Direct application of Aβ antibodies to brain surface of APP tg mice clears local plaques

- I.P. injections decreased brain Aβ, increased Aβ in blood, improved behavior

Weekly i.p. anti-Aβ42 for 6 weeks in PDAPP tg mice.

Clinical Trials
Imaging Amyloid *in vivo* in Humans

- Amyloid Cascade **Hypothesis:**
  - Amyloid deposition begins years before clinical sx

- Ability to image brain amyloid will impact:
  - Diagnosis (sensitivity and specificity TBD)
  - Prognosis (different patterns of progression?)
  - Monitoring anti-amyloid therapeutic interventions
  - Efficiency of drug development

- Current ligands, more in development:
  - PiB (GE), AV-45 (Avid/Lilly), Florbetaben (Bayer)

- PiB: Now in use in over 60 centers around the world

- F18-PiB in development at both GE and Pittsburgh
  - Just as accurate as C11-PiB
PIB PET in AD and Control

University of Pittsburgh
PET Amyloid Imaging Group
PIB Regional Distribution in a Mild AD Patient (57 y/o; MMSE=25)
Correlating PiB Retention *In Vivo* with Aβ Levels Determined Post-Mortem

- 61 year old female with severe AD
- Followed for 1 year at Univ. of Pittsburgh ADRC
- MMS = 1 at last visit
- Died 10 months after PiB scan

Ikonomovic et al., Brain 2008
In Vivo – In Vitro Correlations: Autopsy Validation of the Tracer

Autopsy tissue

MRI scan

PiB PET scan

6-CN-PiB density map

In Vivo – In Vitro Correlations:
Autopsy Validation of the Tracer
PiB Imaging in MCI

Average MCI group deposition of PiB is significantly greater than controls.

In INDIVIDUAL CASES, PiB deposition is either elevated or in the range of normal controls.
PIB Retention  Distribution Volume Ratio (DVR)

<table>
<thead>
<tr>
<th>C-8</th>
<th>C-2</th>
<th>MCI-2</th>
<th>MCI-10</th>
<th>MCI-4</th>
<th>AD-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.06</td>
<td>1.64</td>
<td>1.04</td>
<td>1.62</td>
<td>2.59</td>
<td>2.48</td>
</tr>
</tbody>
</table>

Frontal DVR
Prediction of Outcome Utilizing PiB Imaging in MCI: PiB+ Cases Develop AD; PiB- Cases Do Not

23/26 patients have had follow-up ADRC evaluations
Mean f/u: 24.0 months
(6-57 months)

13 PiB positive
(Mean f/u: 23.6 months)
10 PiB negative
(Mean f/u: 24.5 months)

Wolk, et al., 2009
Prevalence of Plaques Precede DAT

Appearance of plaques and DAT

- Amyloid Plaques (Braak & Braak)
- DAT - Average of Three Studies

Proportion (%) vs. Age (years)
Mean Cortical PIB Binding in Nondemented Controls and AD (N=41)

Mintun et al, 2006, Neurology
Longitudinal Change in PiB Retention in a Questionably Positive Control over Two Years
Heterogeneity of Amyloid Binding in Asymptomatic Normal Elderly

Courtesy of Reisa Sperling, Harvard Univ.
Summary

• In diagnosis, morphologic imaging will serve as a powerful adjunct to clinical measures for diagnostic purposes
• Identification/prognostic evaluation of MCI
  – Aid case selection for AD interdiction and prevention therapies
• Functional imaging with disease-specific markers
  – Promising for staging disease in vivo
  – Monitoring therapeutic interventions more quickly and with fewer cases than just cognitive/behavioral outcomes
• Screening for clinical trials: AD, MCI, Prevention
  – Assure the disease is AD
  – Speed up studies
• Similar uses for structural imaging
• Biomarkers will likely be important in all future studies
Strategies for Future Therapy

- **Symptomatic improvement** (cognitive and behavioral)
- **Non-specific** therapies
  - Antioxidants, Anti-inflammatory agents, others
  - None so far successful
- **Specific** therapies:
  - Anti-amyloid therapy
  - Anti-neurofibrillary tangle strategies
  - Neurotrophins
  - Genetics-guided interventions
Overview of Phase III AD Trials

- **Negative Phase III:**
  - Xaliproden (5HT1A agonist with neurotrophic effects in vitro)
  - Tramiprosate (GAG anti-aggregant)
  - Tarenflurbil (R flurbiprofen, gamma secretase modulator)
  - Rosiglitazone (Peroxisome proliferators activated receptor PPAR-γ)
  - Leuprolide (LHRH endocrine)
  - Dimebon (5HT6 antagonist, H1 antagonist + mitochondrial transition pore)
  - Semagacestat (gamma secretase inhibitor)

- **Phase III in progress**
  - Bapineuzumab (passive immunotherapy; monoclonal Ab N-terminal)
  - Solanezumab (passive immunotherapy; monoclonal mid domain Ab)
  - IVIG (passive immunotherapy; polyclonal pooled Abs)
  - Dimebon (5HT6 antagonist, H1 antagonist + mitochondrial transition pore)
  - Tau Rx (methylene blue, anti tau aggregant)
Phase II Bapineuzemab Study

“Due to varying doses and a lack of statistical precision, this Class II ascending dose trial provides insufficient evidence to support or refute a benefit of bapineuzumab.”
Loss of amyloid on PET Scan—how much is enough?

Rinne et al., Lancet Neurology 2010
Revised Diagnostic Criteria

Preliminary recommendations from the NIA/Alzheimer’s Association Workgroup

- We can see evidence of Alzheimer pathology in the brain prior to any symptoms: how should that affect our diagnosis and recommendations for therapy?
  - Pre-Clinical AD
  - Mild Cognitive Impairment
  - Alzheimer’s Disease

DeKosky et al Revision of the criteria for Alzheimer’s disease: A symposium
Dementia Prevention Objectives

- Identify presymptomatic persons and persons at elevated risk
- Actions (public health measures) to prevent dementia or significantly delay its onset
- Treat asymptomatic persons with disease-modifying medications to delay onset of symptoms of dementia
- Identify earliest symptoms in the general population
- All prevention trials either negative (Ginkgo GEM trial; DeKosky et al, 2009) or stopped for toxicity (ADAPT, NSAIDs; WHIMS (estrogen, estradiol))
- Barring breakthrough in design, such studies will take years to complete
Why Prevention is important: 5 years of delay of onset equals a 50% decrease in prevalence

Coronary Heart Disease
Age-Adjusted Death Rates: Actual and Expected
United States 1950-2000

- 1,329,000 Projected Deaths in 2000
- 815,000 Deaths Prevented in 2000
- 514,000 Actual Deaths in 2000