Overview

- Alzheimer’s Disease Basics
- Developments in Diagnosis
- Treatment – where are we?
- The role of prevention
- Current research

Alzheimer’s Disease
Progress and Challenges

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Alzheimer’s: A Disease of Aging

The Aging U.S. Population

Population: 1960 to 2050

Elderly

Every 8 seconds a Baby Boomer turns 60
By 2030, 20% of the U.S. population will be ≥ 65

Source: US Bureau of the Census
Projected Growth in Prevalence of Alzheimer’s Disease

Alzheimer’s Disease: A leading cause of death in the U.S.
6th overall
5th in adults ≥ 65

Costs of care are approximately 3 times higher for persons with Alzheimer’s or other dementia than without

Projected cost of care in 2050: $1.1 trillion
7-fold increase in Medicare payments
5-fold increase in Medicaid, Out-of-Pocket and Other payments
80% of home care provided by family
Estimated value of unpaid care in 2010: $202 billion

*Data are in 2011 dollars.
Source: Model developed by The Lewin Group for the Alzheimer’s Association.**6 e-billions. "Other" payment sources include private insurance, health maintenance organizations, other managed care organizations and uncompensated care.

Alzheimer’s Disease: History

Dr. Alois Alzheimer

Fr. Auguste D.

Autopsy Findings: Auguste D. 1906

"Scattered through the entire cortex, especially in the upper layers, one found ... foci that were caused by the deposition of a peculiar substance in the cerebral cortex ..."

"In sections prepared with the Bielschowsky silver method, remarkable changes in the neurofibrils appeared. In the interior of a cell that otherwise appeared normal, one or several fibrils stood out due to their extraordinary thickness and impregnability. At a later stage, many fibrils appeared, situated side by side and altered in the same way. Then they merged into dense bundles and gradually reached the surface of the cell. Finally, the nucleus and the cell disintegrated, and only a dense bundle of fibrils indicated the site where a ganglion cell had been."


Pathologic Features of Alzheimer’s Disease

Beta Amyloid (Aβ) Plaques

Neurofibrillary Tangles

American Health Assistance Foundation

Beta Amyloid (Aβ) formation

Neurofibrillary Tangle (NFT) formation


Diagnosis

- Definite AD (autopsy-proven)
- Probable AD
- Possible AD
- Not AD

Clinical Diagnostic Criteria:
National Institute on Neurological Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA)

- Major impairments in ≥ 2 cognitive domains
- Impairments interfere with work, usual social activities or relationships
- Impairments represent a decline from a previous level of functioning
- Impairments are insidious at onset and progressive
- Impairments are not better explained by some other process

New Draft Diagnostic Criteria

- NIA/Alzheimer’s Association Workgroup 2010
  - Use of biomarkers/imaging/genetics
  - Better identify earlier stages of disease

Preclinical AD  Mild Cognitive Impairment  Alzheimer’s Disease
**Draft Diagnostic Criteria: AD**

- Pathologically proved AD
  - Clinical diagnosis with pathological correlation
- Probable AD
  - Meet clinical and cognitive criteria
  - Positive evidence from biomarkers or AD gene mutation carrier
- Possible AD
  - Meet clinical and cognitive criteria, but
  - Atypical or uncertain course or progression
  - Negative biomarkers
  - Mixed presentation

**Draft Diagnostic Criteria: MCI due to AD**

- Concern regarding a change in cognition
- Impairment in ≥ 1 cognitive domain
- Preservation of independence in function
- Not demented
- Level of certainty/evidence from biomarkers
  - MCI of a neurodegenerative etiology
  - MCI of the Alzheimer type
  - Prodromal Alzheimer’s Disease

**Biomarkers for Alzheimer’s Disease:**

- 3 groups: Mild AD, MCI, Normal
- Develop standardized neuroimaging and biomarker methods for clinical trials
- Validate biomarker and imaging findings by correlating with behavioral test data
- Make all findings available to the public

**Identification of an Alzheimer’s Disease “Signature”**

- Low Aβ_{42}/High p-tau in CSF
- Present in 90% with mild AD (n=114)
- Present in 76% with MCI (n=200)
- Present in 36% with normal cognition (n = 114)

Alzheimer’s Disease “Signature”

Red = AD signature; Green = “healthy” signature

MCI converters  AD with autopsy

Progressor  Non-Progressor

Amyloid (+) MCI subjects more likely to progress to clinical AD at 2 years (50% vs 19%)

In Amyloid (+) MCI subjects, hippocampal atrophy predicted time to conversion to clinical AD


Biomarkers for AD

- CSF studies: Low $A\beta_{42}$/High $p$-tau
- Amyloid imaging
- MRI atrophy
- Plasma biomarkers
- Research utility
- Clinical utility

Treatment

CHALLENGES
I expected times like this - but I never thought they’d be so bad, so long, and so frequent.
Currently Available Treatments

- Cholinesterase inhibitors
- NMDA-Receptor Antagonists

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Tacrine</td>
<td>Donepezil</td>
<td>Rivastigmine</td>
<td>Memantine</td>
<td>Galantamine</td>
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</tbody>
</table>

The Cholinergic Hypothesis:
Acetylcholine (Ach) a key neurotransmitter in learning and memory
Loss of cholinergic neurons seen in Alzheimer’s Disease
Restoring cholinergic function may improve dementia symptoms
Cholinesterase inhibitors prevent breakdown of ACh, raising levels of neurotransmitter

Cholinesterase Inhibitors
- Donepezil, Rivastigmine, Galantamine
- All similarly effective
- Average 2.7 point improvement on 70-point ADAS-Cog scale
- Unpredictable response
- Side effects: GI, bradycardia


NMDA Receptor Antagonism:
Overactivation of NMDA receptor by excitatory neurotransmitter glutamate leads to neuronal injury and death
Excitotoxic cell death seen in neurodegenerative disorders, including Alzheimer’s
Blocking excessive activation of NMDA receptors may prevent neuronal injury and death

Lipton SA. Curr Drug Targets 2007 May;8(5):621-32
NMDA Receptor Antagonists

- Memantine
  - Small beneficial effects
  - Moderate to severe AD
    - 2.97 points on 100-point Severe Impairment Battery (SIB)
    - 1.27 points on 54-point ADCS-ADL scale
- Mild to moderate AD
  - 0.99 points on 70-point ADAS-Cog scale


New Approaches: Disease Modifying Therapies

The Amyloid Hypothesis

- ↑ Aβ production and accumulation
- Formation of Aβ oligomers and plaques
- Synaptic dysfunction and neuronal injury
- Neuronal cell dysfunction and death
- Neurotransmitter deficits
- Dementia

The Amyloid Hypothesis

**Amyloid Based Approaches to Treatment**

- Inhibit β-secretase
- Inhibit γ-secretase
- Activate α-secretase
- ↓ aggregation
- ↑ clearance

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**α-secretase activation**


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**α-secretase activators**

- Phase II Clinical Trials
  - EHT-0202
  - Bryostatin 1

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**β-secretase inhibition**

**β-secretase**

- Beta-amyloid cleaving enzyme (BACE-1);
- Difficult target: inhibitor must be large enough to bind to catalytic domain but small enough to cross BBB


**β-secretase inhibitors: CTS-21166**

- Potent, selective, brain-penetrating BACE-1 inhibitor
- 2008: Phase I trial in healthy males
- Single IV dose reduced plasma Aβ
- Phase II trials planned


**γ-secretase inhibition**

- Large enzyme complex
- Controls ratio of Aβ₄₂ to Aβ₄₀
- Presenilin mutations in aggressive, early onset AD
- >50 known substrates

Semagacestat – Phase III IDENTITY Trial

- Randomized, placebo-controlled trial of 2,600 subjects with mild-moderate AD
- Planned interim analysis at 21 months:
  - Worsening cognition and function with drug
  - Increased skin cancer with drug
- Trial stopped August, 2010

Insufficient selectivity for APP?
- Accumulation of neurotoxic Aβ precursor?
- Subjects already too impaired?

γ-secretase inhibitors in clinical development

<table>
<thead>
<tr>
<th>Compound</th>
<th>Pros</th>
<th>Cons</th>
<th>Status</th>
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<tbody>
<tr>
<td>Semagacestat</td>
<td>↓production of new Aβ in CSF of healthy humans.</td>
<td>↑cognition/function, ↑ skin cancer in AD patients. Neurotoxic in mice. No data on cognitive effects in animals.</td>
<td>Discontinued</td>
</tr>
<tr>
<td>(LY-450139)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF-3084014</td>
<td>Notch-sparing. Good brain penetration. Long-lasting effects on Aβ levels in animals. No rebound effect on plasma Aβ in animals.</td>
<td>Lack of data on brain Aβ deposition, cognitive effects in animals. Poor PK/PD profile in humans.</td>
<td>Discontinued</td>
</tr>
<tr>
<td>MK-0752</td>
<td>↓Aβ levels in CSF of healthy humans.</td>
<td>Inhibits Notch cleavage. GI toxicity in humans.</td>
<td>Discontinued</td>
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<tr>
<td>BMS-708163</td>
<td>Notch-sparing. ↓Aβ levels in CSF of healthy humans.</td>
<td>Lack of data on brain Aβ deposition, behavioral effects in animals. Poorly tolerated in AD patients.</td>
<td>Phase II</td>
</tr>
<tr>
<td>Begascestat</td>
<td>Notch-sparing. Good brain penetration. Improves memory in mouse model.</td>
<td>Lack of data on brain Aβ in mice. No decrease in CSF Aβ in AD patients. Plasma Aβ rebound in animals.</td>
<td>Phase II</td>
</tr>
<tr>
<td>(GSI-953)</td>
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<td></td>
</tr>
<tr>
<td>ELND-006</td>
<td>Notch-sparing. Good brain penetration. ↓ brain Aβ in mouse model.</td>
<td>Plasma Aβ rebound in animals. Lack of data on behavioral effects in animals.</td>
<td>Phase I</td>
</tr>
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</table>


Inhibiting amyloid aggregation

- Scyllo-inositol
  - Decreased CSF Aβ
  - No improvement in cognition or function in mild-moderate AD
  - Subgroup with positive effect?
  - Phase III trial planned
- Tramiprosate (Alzhemed)
  - Phase III trial “inconclusive”
  - Vivimind™
**Increasing Aβ Clearance: Immunization**

AN-1792 (Betabloc) Aβ$_{42}$ vaccination

- Survival time
- Time to severe dementia


**Increasing Aβ Clearance: Antibodies**

- Human monoclonal antibodies to Aβ
  - Bapineuzumab
  - Solanezumab
- Natural human antibodies to Aβ
  - IVIg

**Beyond the amyloid hypothesis**

- Tau-based therapies
  - Inhibiting phosphorylation
  - Anti-aggregants
- Anti-inflammatories
- Antioxidants
NIH State-of-the-Science Conference
April, 2010

“Currently, firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or Alzheimer’s disease. “

Factors Consistently Associated with Risk of Cognitive Decline in Older Adults

- Increased Risk
  - Hypertension
  - Diabetes
  - Metabolic Syndrome
  - Depression
  - Current smoking

- Decreased Risk
  - Physical activity
  - Other leisure activities

Overall quality of evidence is low

**Insulin Resistance**

- Insufficient response to insulin in target tissues
- Cornerstone of Metabolic Syndrome
- Accompanies/precedes diabetes
- Best proxy: central obesity

**Insulin in the Brain**

- Multiple roles of insulin
  - Regional glucose metabolism
  - Vascular function
  - Signaling pathways - learning and memory
  - Facilitates reduction of Aβ to less toxic forms
  - Inhibits tau phosphorylation
- Support of normal cognitive functioning
- Abnormal insulin action may promote the development and progression of AD

**Obesity, Diabetes, Abnormal Glucose or Insulin and AD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
<th>% Weight</th>
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<tbody>
<tr>
<td>Achenbach 2006</td>
<td>Diabetes</td>
<td>1.14 (0.80, 2.00)</td>
<td>4.03</td>
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<tr>
<td>Arvonen 2004</td>
<td>Diabetes</td>
<td>1.00 (1.00, 2.00)</td>
<td>5.04</td>
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<tr>
<td>Lastone 2007</td>
<td>Diabetes</td>
<td>2.97 (1.96, 2.71)</td>
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<tr>
<td>Lastone 2007</td>
<td>Diabetes</td>
<td>1.07 (0.84, 0.01)</td>
<td>7.50</td>
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<tr>
<td>Luchinger 2007</td>
<td>Diabetes</td>
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<td>0.00</td>
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<tr>
<td>Luchinger 2004</td>
<td>Hyperinsulinemia</td>
<td>2.96 (1.96, 2.96)</td>
<td>8.62</td>
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<tr>
<td>MacKinnon 2003</td>
<td>Diabetes</td>
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<td>4.48</td>
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<tr>
<td>Ok 1999</td>
<td>Diabetes</td>
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<td>Pfeils 2002</td>
<td>Diabetes</td>
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<tr>
<td>Xu 2004</td>
<td>Diabetes</td>
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<tr>
<td>Xu 2007</td>
<td>Elevated fasting glucose</td>
<td>1.00 (1.00, 2.97)</td>
<td>4.80</td>
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<tr>
<td>Mondy 2006</td>
<td>Obesity</td>
<td>0.00 (0.00, 2.17)</td>
<td>1.22</td>
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<tr>
<td>Mondy 2006</td>
<td>Obesity</td>
<td>2.43 (0.04, 5.79)</td>
<td>1.00</td>
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<td>Herdman 2006</td>
<td>Obesity</td>
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<tr>
<td>Krainer 2006</td>
<td>Obesity</td>
<td>1.00 (1.00, 2.17)</td>
<td>4.85</td>
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<tr>
<td>Luchinger 2007</td>
<td>Obesity</td>
<td>0.00 (0.00, 1.00)</td>
<td>4.85</td>
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<tr>
<td>Wheller 2007</td>
<td>Obesity</td>
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<td>0.05</td>
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<tr>
<td>Xu 2007</td>
<td>Obesity</td>
<td>1.15 (0.04, 2.98)</td>
<td>4.70</td>
</tr>
<tr>
<td>Xu 2007</td>
<td>Obesity</td>
<td>1.00 (1.00, 1.00)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Insulin Resistance is associated with brain dysfunction**

- Cognitively normal older adults with newly diagnosed diabetes/prediabetes vs healthy controls
- FDG-PET: rest and delayed memory test
- Negative relation between IR and cerebral glucose metabolism – MCI/AD pattern
- More diffuse/extensive activation pattern
- Worse performance on memory test

IR: An early marker of AD risk?

Insulin Resistance and AD

- Does IR cause AD?
  - Peripheral and central IR
- What mechanisms are involved?
  - Cerebrovascular – lower threshold
  - Neurodegenerative
- Does improving IR improve cognition?

POEM Study
Pioglitazone Or Exercise to treat MCI

Rationale for Endurance Exercise

- Improves insulin resistance
- Cognitive benefits of exercise training demonstrated in:
  - Longitudinal epidemiologic studies
  - RCTs in cognitively normal older adults
  - Older adults with subjective memory complaints
  - Older adults with MCI

Rationale for Pioglitazone

- Decreases insulin resistance
- Decreases inflammation
- Repression of BACE1 gene expression
- Improves vascular function
- TZDs associated with improvements in cognition in small clinical trials
Primary Outcome

- Change in cognitive function from baseline in each of 4 domains:
  - Memory
  - Language
  - Executive Function
  - Visuospatial

Secondary Outcomes

- Insulin resistance
  - 40 mU/m²/min hyperinsulinemic-euglycemic clamp
- Inflammatory markers
  - IL-1β, IL-6, IGF-1, Leptin, hs-CRP and TNF-α
- Vascular function
  - Arterial stiffness, endothelial dysfunction, echo
- Metabolic markers
  - Body composition, fasting lipids, HbA1c, fasting glucose, insulin, leptin

Conclusions

- The projected growth of AD poses a major challenge to our health care system and society
- There are no effective treatments or preventive measures
- Efforts to find disease modifying treatments and modifiable risk factors are ongoing

Conclusions

- Insulin is important for normal cognitive functioning; abnormal insulin action may promote the development and progression of AD
- Improving insulin resistance may help delay or prevent cognitive decline
Acknowledgements

- Robert Schwartz, MD
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- Kerrie Moreau, PhD
- Toby Wellington
- Diane Bouhall

"These drugs will effect your short term memory, so you better pay me now."

03/30/2011