Early Diagnosis, Prevention, and Treatment of Alzheimer’s disease

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Alzheimer’s Disease Dementia

• Most common cause of dementia
• Progressive neurodegenerative disease
  – Insidious clinical progression over years
  – Typically begins with impaired short term memory
  – Eventually affects general cognition, behavior, and daily functioning
• Epidemic: >5 million people in U.S. carry a diagnosis of AD dementia (Alzheimer’s Association 2012)
  – 20 million more at risk for developing dementia over next 30 years
  – Prevalence doubles every 5 years
  – Cost estimates: > $150 billion/year
Early Diagnosis of AD

- The underlying pathological changes begin 10-15 years prior to clinical diagnosis
- Critical need for early diagnosis, when disease-modifying agents would be most effective
- Mild Cognitive Impairment (prodromal AD)
  - Memory impairment
  - Essentially intact general cognition and daily functioning
  - Precursor to dementia (mostly AD): 10-15% progress to dementia annually (Petersen 1999)
Temporal lag of about 10 years between amyloid accumulation and development of dementia

Concept of preclinical stage of disease

- Multiple examples in other diseases
  - Carcinoma in situ
  - Heart disease detected on cardiac cath or stress test
- Symptoms not required to diagnose disease
  - Renal insufficiency or liver dysfunction often detected by blood test; osteoporosis by bone density scan
  - Treatment can prevent emergence of symptoms
- Not all individuals with risk factors or early pathology will manifest symptoms
  - Hyperlipidemia or hypertension
Preclinical AD

- New research criteria proposed to diagnose AD in preclinical stage based on “positive” biomarkers
- Preclinical: Continuum from asymptomatic to very early symptomatic individuals who do not meet criteria for MCI yet
- 3 stages:
  - Asymptomatic cerebral amyloidosis
  - Asymptomatic amyloidosis and “downstream” neurodegeneration
  - Amyloidosis, neurodegeneration, and subtle cognitive/behavioral decline

Modified from Sperling et al. *Alzheimers Dement* 2011

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Alzheimer’s Disease Trajectory

Modified from Sperling et al. *Alzheimers Dement* 2011
Advances in Early Diagnosis

• Neuropsychological tests
• “Bedside” assessment: MMSE, Blessed, MoCA, CDR, CERAD, ACE
• Fluid biomarkers
  – Cerebrospinal fluid (Aβ_{1-42}, tau), blood, urine
• Brain imaging
  – Brain Structure: volumetric MRI (CT)
  – Brain Function: FDG-PET (SPECT), functional MRI
  – Molecular imaging of pathology: Amyloid PET imaging (PiB, F-18 agents), Tau PET
• Genetic testing: when family history suggestive of autosomal dominant inheritance (PS1, PS2, APP)

CSF Biomarker Signature of AD

• Aβ_{1-42} < 192 pg/ml  
  (sensitivity 96%, specificity 77%)
• Total tau > 93 pg/ml  
  (sensitivity 70%, specificity 92%)
• Phospho-tau > 23 pg/ml  
  (sensitivity 68%, specificity 73%)
• Total tau / Aβ_{1-42} > 0.39  
  (sensitivity 86%, specificity 85%)
• Phospho-tau / Aβ_{1-42} > 0.10  
  (sensitivity 91%, specificity 71%)

Shaw et al. Ann Neurol 2009
Structural Magnetic Resonance Imaging (MRI) in Alzheimer’s disease

Normal older individual (age = 77)

Patient with mild AD dementia (age = 77)

Structural MRI in AD

Patient with severe AD dementia (age = 86)
18F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) in AD

Normal older individual

AD dementia

Amyloid Imaging
$^{11}$C PiB-PET (Pittsburgh compound B)

Normal older individual

AD dementia
About 1/3 of clinically normal older individuals harbor amyloid in their brain (consistent with preclinical AD)

Harvard Aging Brain Study
Sperling, Johnson NeuroMolecular Med 2010

Amyloid burden increases with age in clinically normal older individuals

Rodrigue et al. Neurology 2012
PiB retention is associated with APOE4 carrier status in clinically normal older individuals

Kantarci et al. Neurology 2012

Amyloid burden is associated with a greater annual rate of atrophy in clinically normal older individuals

Chetalat et al. Neurology 2012
Older individuals with amyloid and normal cognition demonstrate brain dysfunction similar to AD dementia patients

Amyloid, APOE4, and neurodegeneration predict cognitive decline over time in clinically normal elderly

Sperling et al. Neuron 2009

Mormino et al. Neurology 2014,
Mormino et al. JAMA Neurol 2014
Amyloid imaging: F-18 agents

- Longer half-life than PiB (~2 hrs vs. 20 min)
  - More practical for clinical use
- Florbetapir (Amyvid™, 18F-AV-45)
  - Widely used in clinical trials
  - Approved by FDA for detecting amyloid in vivo in symptomatic patients in April, 2012
  - Visual rating training for radiologists available
- Flutemetamol (Vizamyl™, 18F-GE067)
  - Approved by FDA October, 2013
- Florbetaben (Neuroceu™, 18F-BAY94-9172)
  - Approved by FDA March, 2014
- IDEAS (Imaging Dementia—Evidence for Amyloid Scanning)

Florbetapir PET amyloid imaging correlates well with post-mortem findings

- Low amyloid on PET and autopsy
- Intermediate amyloid on PET and autopsy
- High amyloid on PET and autopsy

Visual rating:
- Sensitivity 92%
- Specificity 100%

Clark et al. JAMA 2011; Clark et al. Lancet Neurol 2012
T807 PET Tau imaging

<table>
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<th>Age</th>
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<td>AD</td>
<td>V-VI</td>
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Hypothetical model of dynamic biomarkers of the AD pathological cascade

Jack et al. Lancet Neurol 2013
Hypothetical model of AD pathophysiological cascade

- Age
  - Genetics
  - Cerebrovascular risk factors
    - Other age-related brain diseases

- Amyloid-β Accumulation

- Synaptic Dysfunction
  - Glial Activation
  - Tangle Formation
  - Neuronal Death

- Brain and cognitive reserve
  - Environmental factors

- Cognitive Decline

Sperling et al. Alzheimers Dement 2011
FDA Approved Medications for AD dementia

1993 tacrine (Cognex®)
1997 donepezil (Aricept®)
2000 rivastigmine (Exelon®)
2001 galantamine (Razadyne®)
2003 memantine (Namenda®)

• Cholinesterase-inhibitors (ChE-I): donepezil, rivastigmine, galantamine, tacrine* (no longer clinically used)
  • All FDA approved for treatment of mild to moderate AD dementia
  • Donepezil also FDA approved for treatment of severe AD dementia (2006)
  • Galantamine available as a generic since 2/09; donepezil since 12/10

• NMDA (glutamate) receptor antagonist: memantine
  • FDA approved for treatment of moderate to severe AD dementia (generic 2015)

AD Dementia Medications: Symptomatic Benefit

• ChE-I and Memantine: shown in multiple randomized, double-blind, placebo-controlled trials of AD dementia to provide modest but clinically significant improvements for groups of participants
  – Daily functioning, cognition, neuropsychiatric symptoms, caregiver burden (and potentially saving money)

• Individual results vary
  – Highly variable effects across time between and within individuals
Lifestyle Modifications

- **Mediterranean diet** (Scarmeas 2006, Féart 2009)
  - High in vegetables, legumes, fruits, nuts, cereals, fish, olive oil
  - Low in saturated fats
  - Reduces risk of developing AD dementia and slows cognitive decline
- **Physical exercise** (Larson 2006, Scarmeas 2009)
  - Exercise 3 or more times per week or vigorous exercise 1 hour per week reduces risk of developing AD dementia
- **Cognitive training** (ACTIVE, Ball 2002, Willis 2006, Rebok 2014)
  - Reduced decline in reasoning, processing speed, IADL

Lifestyle Modifications: Cardiovascular risk factors

- **Hypertension** (Syst-Eur trial, Forette 2002)
  - Treated with nitrendipine (± enalapril, HCTZ)
  - Reduced risk of developing dementia
- **Hyperlipidemia** (HPS, Lancet 2002; PROSPER trial, Shepherd 2002)
  - Treatment with statins did not prevent dementia
- **Diabetes** (ACCORD-MIND trial, Launer 2011)
  - No difference between intensive diabetes therapy vs. standard therapy in preventing dementia
- **PreDIVA trial** (Netherlands)
  - 6-year nurse-led intensive management of cardiovascular risk factors for dementia prevention
  - Trial ongoing
Lifestyle Modifications: Multidomain interventions

• FINGER trial (Findland, Kivipelto 2013)
  – 2-year multidomain intervention: nutrition, exercise, cognitive training, social activity, management of cardiovascular risk factors for cognitive decline prevention
  – Preliminary results: mild improvement in cognition

• MAPT trial (France, Gillette-Guyonnet 2009)
  – 3-year multidomain intervention: nutritional, physical, and cognitive training, as well as omega-3 fatty acids supplementation for cognitive decline prevention
  – Trial ongoing

Nutraceuticals / Supplements

• Antioxidants (Sano 1997, Petersen 2005, Galasko 2012, Dysken 2014)
  – Vitamin E (high doses) modest benefit in treating mild to severe AD dementia (not in MCI); prevention trial ongoing
  – Vitamin C, Alpha lipoic acid, Coenzyme-Q10 ineffective in biomarker trial in AD dementia

• Ginkgo biloba (Le Bars 1997, DeKosky 2008, Vellas 2012)
  – Ineffective in preventing dementia (in normal elderly and MCI)
  – Possible modest benefit in treating AD dementia

• Omega 3 fatty acids / fish oil (DHA) (Quinn 2010, Sydenham 2012)
  – Multiple studies: ineffective in preventing cognitive decline or dementia or treating AD dementia

• Folic acid/vitamin B6/vitamin B12 (Aisen 2008)
  – Ineffective in treating AD dementia

• Huperzine, a naturally occurring ChE-I (Rafii 2011)
  – Ineffective in treating AD dementia
Medications approved for different indications tested in AD

- **NSAIDs** (naproxen, rofecoxib, celecoxib; Aisen 2003, Thal 2005, Martin 2008, Breitner 2011)
  - Multiple studies: ineffective in treating AD dementia or MCI; unclear benefit in prevention of AD dementia
- **Statins** (atorvastatin, simvastatin; Feldman 2010, Sano 2011)
  - Ineffective in treating or preventing AD dementia
  - Estrogen ± progesterone increased risk for dementia
- **Diabetes medications**
  - Rosiglitazone (Gold 2010): ineffective in AD dementia
  - Intranasal insulin (Craft 2011): benefit in pilot study of MCI and mild AD dementia

## Treatment of Alzheimer’s Disease

![Diagram showing the natural history of Alzheimer's Disease with symptomatic therapy and disease-modifying therapy](image)
**The Next Generation of Medications for AD**

- Most medications aimed at underlying pathology
- May or may not have much symptomatic improvement
- Primarily amyloid based approaches
- Also starting to target tau pathology
- Latrepirdine (Dimebon): mitochondrial mechanism (neuroprotection) (Doody 2008)
  - Phase III trial failed to replicate positive results of phase II trial in AD dementia
- RAGE inhibitor (Galasko 2014)
  - Reduced amyloid entry into brain
  - Phase II trial failed to show efficacy in AD dementia

**Amyloid Modifying Drugs**

- Disease modifying drugs
  - Less likely to yield symptomatic improvements
  - Likely better early in disease course (MCI/prodromal or even preclinical stage)
  - Initial trials in mild-moderate AD dementia
- Decrease production of toxic form of amyloid (Green 2009, Doody 2013)
  - Gamma and beta secretase inhibitors/modulators
  - Phase III trials failed with tarenflurbil (Flurizan), semagacestat
  - Phase III trial failed with verubecestat (MK-8931)
- Decrease amyloid aggregation (Salloway 2011)
  - Tramiprosate (Alzhemed, failed phase III trial), scyllo-inositol (failed phase II trial)
  - Chelation agents: clidoquinol, PBT2 (failed phase II trial)
- Increase amyloid clearance – Immunotherapy
  - Failures: active vaccine, IVIG, bapineuzumab, gantenerumab, solanezumab
Amyloid Immunotherapy

- Active amyloid vaccine
  - AN-1792 phase II trial in mild-moderate AD dementia
    - Stopped early due to 6% rate of meningoencephalitis
    - Autopsy studies showed amyloid removal but no clinical benefit noted with long-term follow-up
  - Newer safer vaccines currently in phase II trials
- Passive amyloid immunization (humanized monoclonal antibodies)
  - IVIG (completed phase III trial, failed)
  - Bapineuzumab (completed phase III trials, failed)
  - Gantenerumab (completed phase III trial, failed)
  - Solanezumab (completed phase III trials, failed)

Amyloid Immunotherapy

- Bapineuzumab phase III trials (Salloway & Sperling 2014)
  - Mild-moderate AD dementia, 18 month follow-up
  - Divided into APOE4 carriers and non-carriers
  - Primary outcome: No clinical efficacy (cognition, ADL)
  - Mild-moderate AD dementia, 18 month follow-up
  - Primary outcome: No clinical efficacy (cognition, ADL) in mild-moderate AD dementia
  - Secondary outcome: Reduced cognitive decline in mild AD dementia group only (not in moderate)
  - Open label extension (2 years): in mild AD dementia group, those who started on drug in the placebo-controlled period, retained an advantage (suggesting disease-modification)
  - Phase III trial failed in only mild AD dementia (results presented 10/16; small effect sizes)
**Biomarker Results: Bapineuzumab Phase II & III PiB-PET**

Bapineuzumab phase III biomarker results in APOE4 carriers (Liu 2015):
- Reduced PiB burden
- Reduced CSF phospho-tau

Similar amyloid PET imaging results seen with Gantenerumab but no clinical efficacy (Ostrowitzki et al. Arch Neurol 2012)

**Bapi phase III: Baseline distribution of PiB-PET**

Recent clinical trials and future ones being designed are including biomarker criteria (mostly amyloid status) for inclusion of MCI and even AD dementia participants

Liu et al. Neurology 2015
Aducanumab phase Ib

- 12-month phase Ib trial of monoclonal antibody in prodromal and mild AD dementia (elevated amyloid on PET)
- N=166, 4 dose groups (1, 3, 6, and 10 mg/kg) vs. placebo
- Biomarker outcomes: decreased amyloid on PET in 3 highest doses (dose-dependent)
- Clinical outcomes: improved global functioning (CDR-SB) in 10 mg/kg, stabilized global cognition (MMSE) in 3 and 10 mg/kg
- Safety: amyloid-related imaging abnormality edema (ARIA-E)
  - Dose-dependent, 41% for 10 mg/kg (55% if APOE4 carrier)
  - 35% of ARIA-E symptomatic, of which 22% rated severe
- Phase III underway
  - Prodromal and very mild AD dementia
  - Doses being adjusted based on APOE4 carrier status

Aducanumab: Decreases on Amyloid PET

### Tau Modifying Drugs

- **Glycogen synthase kinase-3β (GSK-3β) inhibitors**
  - Reduce tau hyperphosphorylation
  - Valproate: phase III trial in AD dementia failed (Tariot 2011)
  - Lithium: maybe too toxic for population; small phase II trial in mild AD dementia failed (Hampel 2009); lower doses being explored

- **Tau aggregation inhibitors** (Wischik 2015, Gauthier 2016)
  - Methylene blue (methylthionine chloride, Rember) phase II trial in AD dementia suggested benefit but failed phase III trial with the methylthioninium moiety (LMTM)

- **Davunetide** phase II/III trial in PSP failed (Boxer 2014)
  - Reduce tau hyperphosphorylation (other mechanisms)

- **Passive tau immunization** (antibody)
  - Phase I trial in PSP and phase II trial in prodromal and mild AD dementia are ongoing
Challenges Ahead

• Large and lengthy trials – need patients and families willing to volunteer
• “Surrogate markers” of disease modifying effects may shorten duration of trial (Neuroimaging, CSF)
• Trials in mild-moderate AD dementia are failing
  – >10 phase III trial failures over the past decade
  – Are we targeting the wrong mechanism of action or is it too late in the disease course?
• Disease modifying therapies may work best prior to dementia (and stage of irreversible brain cell loss)
  – MCI/prodromal or even preclinical stage
  – Delaying dementia by 5 years would reduce projected Medicare costs by nearly 50%

Current AD clinical trials

• Moving earlier in the disease process
• Trials in prodromal AD: MCI with positive AD biomarker (ex: amyloid imaging, CSF)
  – Phase II trial of gamma secretase inhibitor in MCI with low CSF Aβ (prodromal AD) recently completed, failed
  – Phase II trial of active amyloid vaccine in MCI with positive amyloid PET (florbetapir) recently stopped due to futility
  – Phase II/III trial of gantenerumab (anti-amyloid monoclonal antibody) in MCI with positive amyloid PET recently stopped due to futility
  – Other trials ongoing
Trials in preclinical AD Underway

• Secondary prevention trials in preclinical at risk populations

• Dominantly Inherited Alzheimer Network (DIAN) (Bateman 2012)
  – Asymptomatic, MCI, or mild dementia participants with autosomal dominant AD (PS1, PS2, APP); 2-year trial; drugs: solanezumab, gantenerumab

• Alzheimer Prevention Initiative (API) (Reiman 2011)
  – Asymptomatic autosomal dominant AD (PS1 family in Columbia); 5-year trial drug: crenezumab
  – Asymptomatic ApoE ε4/4; 5-year trial; drug: anti-amyloid vaccine (CAD106), BACE inhibitor

Trials in preclinical AD

• TOMMORROW Trial
  – Asymptomatic elderly enriched for APOE4 and TOMM40; 5-year trial; drug: pioglitazone

• Anti-Amyloid Treatment in Asymptomatic AD (A4 Trial) (Sperling 2013)
  – Asymptomatic elderly with elevated amyloid on PET; ages 65-85; 3-year trial; drug: solanezumab

• EARLY (‘A5’’) Trial
  – Similar design to A4; ages 60-85; 4.5-year trial; drug: BACE inhibitor

• “A3” Trial: Getting closer to primary prevention
A4 Trial

• Secondary prevention trial in clinically normal older individuals (age 65-85) with elevated amyloid on flrabetapir PET imaging
• Solanezumab (amyloid passive immunization)
• 3 years and 3 months
• 1150 participants (1:1 drug vs. placebo)
• Ethics component: Disclosure of amyloid status
• LEARN (Longitudinal Evaluation of Amyloid Risk and Neurodegeneration)
  – Natural history arm (no intervention)
  – 500 participants who do not have elevated amyloid

EARLY (A5) Trial

• A more global study - launched in Europe, Australia, started in US in fall 2016
• BACE inhibitor
• Same “amyloid positive” clinically normal criteria as A4 (by PET or CSF)
• Broader age range: 60-85 years old
  – Participants age 60-65 must have additional risk factor
• Broader cognitive range than A4
• Longer trial: up to 4.5 years
A3 Trial

- Will leverage A4 /A5 screening to identify people with “subthreshold” amyloid levels who are at high risk for continued amyloid accumulation
- 4-year Phase IIb/IIIa 4 trial - BACE inhibitor
- Primary outcomes are biomarkers – rate of amyloid accumulation, tau spreading, MR atrophy
- Exploratory sensitive cognitive outcomes
- Public-private-philanthropic partnership (P4)
  - NIH grant funded
  - Will choose industry partner

Prevention trials: A4, EARLY (“A5”), and A3

CART Clinical Trials

- Actively enrolling trials:
  - A4 trial
  - Janssen/ATRI EARLY (“A5”) trial
  - Biogen aducanumab: Phase III trial of an anti-amyloid monoclonal antibody in MCI and very mild AD dementia
  - AbbVie: Phase II trial of a tau antibody in MCI and very mild AD dementia
- Upcoming trials:
  - Novartis/Banner API asymptomatic ApoE ε4/4 trial
  - Eisai BACE inhibitor in MCI and very mild AD dementia
  - Roche/Genentech gantenerumab: Phase III trial of an anti-amyloid monoclonal antibody in MCI and mild AD dementia
Contact Information

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  – bwhmemory@partners.org
• Alzheimer’s Association Massachusetts/New Hampshire Chapter
  – 617-868-6718 or 800-272-3900
  – www.alzmass.org