What can I do to prevent Alzheimer’s disease?

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Case 1

• A 64 year old judge was referred by her PCP for evaluation of memory loss. Her husband confirms her memory loss and “repeating questions” for about 18 months. Her colleagues and law clerks have expressed concerns due to several small mistakes. She reports that she has “fallen a little behind at work”, and is planning to retire in 1 month because she has lost the “trust and confidence” of her colleagues…
Case 1

- She has a history of well-controlled hypertension and takes only an anti-hypertensive medication. She has no other medical or psychiatric history. There is no history of stroke, TIA, alcohol abuse, gait disorder, falls, or head trauma. Her parents died in their 60s of “old age”. She works as a judge and lives with her husband. She states that at one time her IQ was “140”.
Risk factors for AD

- Age
- Family history/genetics
  - ApoE polymorphism
  - Minority (African-American, Hispanic)
  - Downs syndrome
- Diabetes, midlife obesity, metabolic syndrome
- Traumatic brain injury with loss of consciousness
- Smoking
- Stroke
- Low education, occupational level
10 Signs of Alzheimer’s

- Memory loss that disrupts daily life (amnesia)
- Challenges in planning or solving problems (executive dysfunction)
- Difficulty completing familiar tasks at home, at work, or at leisure (executive dysfunction)
- Confusion with time or place (disorientation)
- Trouble understanding visual images and spatial relationships (visual agnosias)
10 Signs of Alzheimer’s

- New problems with words in speaking or writing (dysnomia, anomia)
- Misplacing things and losing the ability to retrace steps (amnesia)
- Decreased or poor judgment (executive dysfunction)
- Withdrawal from work or social activities (apathy)
- Changes in mood and personality (depression, anxiety)
Case 1

- Pleasant, cooperative, and well-appearing elderly woman. Vital signs normal, as is the general medical examination. Mental status examination reveals good attention with deficits in memory, orientation, language, and visuospatial skills. The MMSE score is 25/30, with points off for orientation and memory, consistent with a mild dementia.
Case 1

• The remainder of the neurological examination reveals normal eye movements, strength, tone, sensation and coordination. There are no signs of parkinsonism. Reflexes are 2+ and symmetric – no signs of stroke. Gait is normal.
Case 1

- Blood tests, including thyroid function tests, and B\textsubscript{12} were all normal. A test for syphilis was negative. HIV test was negative.
- A head MRI revealed cortical atrophy and periventricular white matter changes. No tumor, hemorrhage, subdural hematoma, or large cerebral infarct.
- Neuropsychologic evaluation confirmed mild dementia, with deficits in memory, language, visuospatial skills, and frontal/executive function, and a lower than expected IQ.
Case 1

• …has multiple cognitive deficits which impair her functional abilities and represent a cognitive decline.
• There is no evidence for delirium or depression by history, examination, or laboratory evaluation.
• Diagnosed with mild dementia due to probable Alzheimer’s disease.
Case 1

• prescribed a cholinesterase inhibitor; effects and side-effects of the drug were discussed.
• advised to continue treatment for hypertension with her primary care physician.
• discussed prognosis, advance directives, and limitations concerning complex ADLs, including driving, handling finances, taking medications...
• recommended *ad libitum* physical activity, social activity, and mental activity.
• qualified and interested - enrolled in a 12 month clinical trial of drug x (add-on to current drug therapy).
How to preserve brain health with aging

- Exercise and physical activity
- Maintain ideal body weight
- Mediterranean diet (fruits, vegetables, nuts, beans, olive oil, fish…)
- Limit alcohol consumption (1-2 drinks/day)
- Mental and social activities
- Avoid traumatic brain injury (seat belts, helmets, fall prevention…)
- Adequate sleep
- No smoking
- Minimize stress
- Use visual and hearing aids – if needed
- Treat hypertension, diabetes, high cholesterol, sleep apnea, and depression with your doctor
- If memory problems develop, rule out thyroid disorder, vitamin B12 deficiency, and HIV with your doctor
A. Dementia
- Interferes with ability to function at work or at usual activities
- A decline from a previous level of functioning
- Not delirium or psychiatric disorder
- Diagnosed by history, examination
- Involves at least 2 cognitive domains:
  - Memory
  - Reasoning and judgment
  - Visuospatial
  - Language
  - Personality, behavior, comportment
Diagnostic criteria

A. Probable AD
   • Dementia
   • Insidious onset
   • Worsening of cognition over time
   • Amnestic vs. non-amnestic presentation
   • Not due to another dementia diagnosis

B. Probable AD with evidence of AD pathophysiology
   • Aβ (CSF or amyloid PET)
   • Neuronal injury (CSF tau, FDG-PET, structural MRI)

Alzheimer’s and Dementia, 2011
HIGHEST NATIONAL LIFE EXPECTANCY AT BIRTH: 1840-2000

Life expectancy in years

World population is graying rapidly

The centurions
Number of Japanese people aged over 100

Source: Ministry of Health, Labour and Welfare
Economist.com
AD Facts and Figures (Alz. Assoc.)

Percentage
- White
- African-American
- Hispanic

Age
- 65 to 74
- 75 to 84
- 85+

- 2.9
- 7.5
- 10.9
- 19.9
- 27.9
- 30.2
- 58.6
- 62.9

Legend:
- Black: White
- Purple: African-American
- Yellow: Hispanic
Genetics of sporadic AD

Apolipoprotein E (ApoE)

Strittmatter et al, Science 1993
## Genetics of Sporadic AD (top 10)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Ethnicity</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoE 2/3/4</td>
<td>All</td>
<td>3.7</td>
</tr>
<tr>
<td>BIN1</td>
<td>All</td>
<td>1.2</td>
</tr>
<tr>
<td>CLU</td>
<td>Caucasian</td>
<td>0.9</td>
</tr>
<tr>
<td>ABCA7</td>
<td>All</td>
<td>1.2</td>
</tr>
<tr>
<td>CR1</td>
<td>Caucasian</td>
<td>1.2</td>
</tr>
<tr>
<td>PICALM</td>
<td>Caucasian</td>
<td>0.9</td>
</tr>
<tr>
<td>MS4A6A</td>
<td>All</td>
<td>0.9</td>
</tr>
<tr>
<td>CD33</td>
<td>All</td>
<td>0.9</td>
</tr>
<tr>
<td>MS4A4E</td>
<td>All</td>
<td>1.1</td>
</tr>
<tr>
<td>CD2AP</td>
<td>All</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Genes are involved in:
- Protein trafficking/metabolism
- Cholesterol/lipid transport
- Immune system/inflammation
- Synaptic function/plasticity
- Protein turnover/degradation

[Alzforum.org](http://www.alzforum.org)
Neuropathology of AD

Cruz et al, PNAS 1997
## Reagan Pathologic Criteria for AD

<table>
<thead>
<tr>
<th>Likelihood</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuritic plaques and neurofibrillary tangles</td>
<td>A more limited distribution or severity</td>
<td>Limbic regions</td>
<td>Neocortex</td>
</tr>
<tr>
<td>CERAD plaque score</td>
<td>infrequent</td>
<td>moderate</td>
<td>frequent</td>
</tr>
<tr>
<td>Braak and Braak staging</td>
<td>I/II</td>
<td>III/IV</td>
<td>V/VI</td>
</tr>
</tbody>
</table>

*Neurobiology of Aging 18, S1-S2, 1997*
Amyloid Precursor Protein (APP) catabolism

$\text{NH}_2 \quad \text{A} \beta \quad \text{COOH}$

$\alpha$-secretase

$\beta$-secretase (BACE-1)

$\gamma$-secretase (presenilin)

$p3$

$\gamma$-secretase
Causes
Aging
ApoE4 > 3 > 2
Downs syndrome
Familial AD mutations

Drug treatments
donepezil
rivastigmine
galantamine
memantine

APP turnover
Aβ accumulation
Aβ oligomers, fibrils
amyloid plaques

neurotoxicity
neurofibrillary tangles

mild cognitive impairment (MCI)
microgliosis and astrocytosis
inflammation
focal encephalopathy
neuronal morbidity
synaptic and neurotransmitter loss

neuronal mortality
brain atrophy
white matter rarefaction
Dementia (AD)
dead

Biomarkers
low Aβ, high tau in cerebrospinal fluid
positive amyloid-PET
focal hypometabolism on FDG-PET
atrophy, white matter changes on MRI

Turner, in Alzheimer’s Disease, 2012
A mutation in APP (A673T) protects against AD and age-related cognitive decline

APP A673T reduces BACE-1 cleavage of APP

<table>
<thead>
<tr>
<th></th>
<th>1/OR</th>
<th>Odds Ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AD vs. population controls</td>
<td>4.24</td>
<td>0.23</td>
<td>4.2 x 10⁻⁵</td>
</tr>
<tr>
<td>AD vs. population controls &gt; 85</td>
<td>5.29</td>
<td>0.19</td>
<td>4.8 x 10⁻⁷</td>
</tr>
<tr>
<td>AD vs. cognitively intact controls &gt; 85</td>
<td>7.52</td>
<td>0.13</td>
<td>6.9 x 10⁻⁶</td>
</tr>
</tbody>
</table>

FDA-approved drugs for dementia due to AD

Mild-Moderate-Severe AD

• Donepezil (Aricept)
• Rivastagmine (Exelon)
• Galantamine (Razadyne, Razadyne ER)

Moderate-Severe AD

• Memantine (Namenda)
Donepezil (Aricept)

Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment.

Rogers et al, Neurology 1998
The continuum of Alzheimer’s disease

Cognitive function

Preclinical

Aging

MCI

Dementia

Years
Appearance of Plaques vs. Dementia

- **Amyloid Plaques at Autopsy**
- **Prevalence of AD Dementia**

**Percent positive (%)**

**Age (years)**

- 46-50
- 51-55
- 56-60
- 61-65
- 66-70
- 71-75
- 76-80
- 81-85
- 86-90

The graph shows the increasing prevalence of amyloid plaques at autopsy and AD dementia with age. The red arrow indicates a significant overlap in the age range where both conditions are present.
Diagnostic Criteria of MCI

Clinical and cognitive criteria
• Concern about a change in cognition reported by patient or informant or clinician (historical or observed evidence of decline)
• Objective evidence of impairment in one or more cognitive domains, typically including memory (formal or bedside testing)
• Preservation of independence in functional abilities
• Not demented

Assess etiology of MCI consistent with AD pathophysiology
• Rule out vascular, traumatic, medical causes of cognitive decline
• Provide evidence of longitudinal decline in cognition
• Report history consistent with AD genetic factors

Albert et al, Alzheimers Dement. 2011
Biomarkers

Biomarkers of Aβ amyloid deposition
• CSF Aβ42
• PET amyloid imaging

Biomarkers of neuronal injury
• CSF tau/phosphorylated tau
• Hippocampal volume or medial temporal atrophy
• Rate of brain atrophy
• FDG-PET imaging
• SPECT perfusion imaging
• Less well validated biomarkers: fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MRI spectroscopy, diffusion tensor imaging, voxel-based and multivariate measures

Associated biochemical change
• Inflammatory biomarkers (cytokines)
• Oxidative stress (isoprostanes)
• Other markers of synaptic damage and neurodegeneration

Albert et al. *Alzheimers Dement*. 2011
## Preclinical AD (A research construct)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>$\text{A}\beta$ (CSF or PET)</th>
<th>Markers of neuronal injury (tau, FDG, sMRI)</th>
<th>Evidence of subtle cognitive change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Asymptomatic cerebral amyloidosis</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Plus downstream neurodegeneration</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Plus subtle cognitive/behavioral decline</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

PET Amyloid and Tau Imaging

Amyloid-β (PiB)

Clinically Normal

Clinically Normal

Alzheimer’s Dementia

Tau (T807)
Age and ApoE4 Genotype Increase Amyloid PET

Mean cortical SUVRs

ALL healthy controls

Age 58

Age 71

ApoE4-

Age 76

ApoE4+

Age 61
CSF Biomarkers
Autopsy-confirmed data

Aβ42

Tau

AD

Normal

Shaw et al, Annals Neurology 2009
AD brains reveal atrophy -- particularly in regions mediating higher cognitive functions.
MRI atrophy in MCI & AD

McDonald et al, Neurology 2009
Solanezumab slows cognitive decline - in individuals with mild AD

Siemers et al., Alzheimer’s and Dementia 2015
<table>
<thead>
<tr>
<th>Treatment</th>
<th>MMSE Score Change at 54 Weeks</th>
<th>CDR-SB Score Change at 54 Weeks</th>
<th>Average Composite SUVR Change at 54 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 40)</td>
<td>-2.81</td>
<td>1.87</td>
<td>“Virtually unchanged”</td>
</tr>
<tr>
<td>1 mg/kg (n = 31)</td>
<td>-2.18</td>
<td>1.72</td>
<td>-0.055</td>
</tr>
<tr>
<td>3 mg/kg (n = 33)</td>
<td>-0.70 (P &lt; .05)</td>
<td>1.37</td>
<td>-0.135 (P &lt; .001)</td>
</tr>
<tr>
<td>6 mg/kg (n = 30)</td>
<td>-1.96 (P &lt; .001)</td>
<td>1.11</td>
<td>-0.210 (P &lt; .001)</td>
</tr>
<tr>
<td>10 mg/kg (n = 32)</td>
<td>-0.56 (P &lt; .05)</td>
<td>0.63</td>
<td>-0.268 (P &lt; .001)</td>
</tr>
</tbody>
</table>
Aducanumab reduces amyloid burden
MDP Studies in Progress, Planned

• Biomarker discovery and validation (normal, MCI, AD)
  – NIA: ADNI
  – DOD-ADNI
  – LEARN (Amyloid PET negative – part of A4 study)
  – Medicare/Alzheimer’s Association: IDEAS
  – Pilot fMRI studies with Dr. Jiong
  – Pilot EEG and NIRS study with Dr. Medvedev
MDP Studies in Progress, Planned

- **Therapeutic trials** for prodromal AD, MCI, AD

  - Biogen: Aducanumab
  - Merck: BACE-I
  - Lilly: Solanezumab
  - NIA/Toyama: TCAD
  - NIA: FYN
  - NIA/Lilly: Intranasal insulin
  - Lilly: BACE-I
  - Novartis: Nilotinib
  - NIA: Resveratrol?
MDP Studies in Progress, Planned

• **Prevention studies** for asymptomatic AD – healthy older normal individuals at risk
  
  – NIA/Lilly: A4, Solanezumab
  – Novartis: Alzheimer Prevention Initiative for ApoE4/4, amyloid vaccine or BACE-I
Summary

- We are witnessing a growing epidemic of dementia - most of which is AD
- The amyloid hypothesis is alive and well, and does not exclude other important and essential pathologic processes
- The genetics of familial AD provides the strongest evidence for the amyloid hypothesis
- Despite recent high-profile failures, many active trials target Aβ/amyloid generation or clearance
- Other AD trials target other essential pathologic processes, with the probable result of a therapeutic cocktail (as now...)
Summary

• Current (FDA-approved) therapies for AD provide consistent yet modest, temporary, and palliative benefits
• We are searching for disease-modifying treatments to halt dementia progression, or prevent dementia onset
• We are in need of validated biomarkers for: screening, diagnosis, prognosis, evidence of efficacy, reduction of clinical trial costs
• Treatments are increasingly target individuals with MCI and healthy high-risk individuals - prevention
• Future treatments will be tailored to ApoE genotype (pharmacogenomics, personalized medicine, precision medicine)
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