Neurobiology of Learning and Memory
Prof. Anagnostaras

Lecture 10: Alzheimer's Disease and Cognitive Decline in Aging

Dementia
A syndrome characterized by a decline in cognitive functions sufficient to cause impairment in social and occupational performance

Risk of Dementia is Unrelenting with Age

Causes of Dementia
- Alzheimer's Disease (AD): 65%
- AD & Vascular: 10%
- Lewy body: 7%
- AD and Lewy body: 5%
- Vascular: 5%
- Other: 8%

Projected Number of American's with AD

Prevalence of AD


Source: GAO, January 1998
Alzheimer’s Disease Outline

**Incidence:** approx. 4 million Americans

Late onset: 65+ yrs (can occur earlier, but less than 10% of cases do - and in those cases caused by a specific gene mutation)

Women more likely to have it (b/c longer life span)

Can’t be diagnosed for certain until death

Terminal disease: live an avg. 8 yrs post-diagnosis

Currently linked to several genes (transgenic mouse models)

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The Implications of an Aging Society for AD Prevalence

- 40% of persons turning 65 in 2000 will survive to age 85
- 30-50% of persons reaching age 85 will have AD

Source: NEJM, 2000

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Overview

- Progressive, degenerative brain disease characterized by
  - Increasing memory loss
  - Other cognitive decline
  - Changes in behavior, personality, judgment and ADL’s (Activities of Daily Living)
  - Most common cause of dementia among people aged 65 or over

AD Characteristics

- Beta amyloid (protein) plaques & neurofibrillary tangles form most prevalently in brain areas assoc. w/memory & cognitive function (entorhinal ctx, hippocampus, frontal ctx, parietal ctx)
- Involves death of many cells, but esp. Ach-producing cells in the basal forebrain
- Symptoms: dementia, memory loss, confusion, language loss
- No cure; treat with Ach agonists (help w/early cognitive deficits)

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Ten Early Warning Symptoms

- Memory Loss That Affects Job Skills
- Difficulty Performing Familiar Tasks
- Problems with Language
- Disorientation of Time and Place
- Poor or Impaired Judgment

- Problems with Abstract Thinking
- Misplacing Things
- Changes in Mood or Behavior
- Changes in Personality
- Loss of Initiative

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Severe Alzheimer’s Disease

**The person cannot:**

- Communicate verbally
- Understand words or instructions
- Recognize self in the mirror or pictures
- Recognize family members
- Provide care for themselves

Usually die within 15 years (4th leading killer of adults)
Alzheimer's Disease

Alzheimer's Disease (MRI)

Alzheimer's Disease (cellular)

Alzheimer's Disease (PET)

Alzheimer's Disease (degeneration)
Alzheimer's disease: plaques & tangles in memory areas

- affects entorhinal ctx (1), then hpc (2), frontal (3), parietal (3) lobes

Alzheimer's Disease (plaques & tangles)

- Neurons with external plaques
- Normal neuron
- Neuron with internal neurofibrillary tangles (disrupted microtubules)

Microtubules are “Railroad” for nutrients, NT transport w/ neuron

- The Major Internal Features of a Typical Neuron

Alz Recent Research: Tangles

- Tau = protein that keeps microtubules (“RR tracks”) aligned down length of neuron (tau = “RR ties”)
- Pts with Alz have problematic tau → curls & tangles microtubules (“RR tracks in jumble”)
- Since neurons can’t get nutrients down length of axon…dies

- Pin-1 (an enzyme), causes the bending of tau in Alz
- Block Pin-1 → block problematic tau?
- Still researching…

Alz Recent Research: Plaques

- Amyloid plaques in human Alz (70 yrs old)
- Amyloid plaques in transgenic mouse

Study of Dementia in Swedish Twins – Concordance Rates

<table>
<thead>
<tr>
<th></th>
<th>Monozygotic(%)</th>
<th>Dizygotic(%)</th>
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</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>75</td>
<td>26</td>
</tr>
<tr>
<td>All dementias</td>
<td>50</td>
<td>33</td>
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</tbody>
</table>

781 twins
aged 50 and over
surveyed every three years since 1970’s

Source: J Gerant, 1997
Genetics of Alzheimer's Disease

Several genetic Loci in Alzheimer's Disease:
- Chromosome 21 (APP): Early Onset FAD-6/50 amyloid precursor protein—amyloid beta
- Chromosome 1 (PS2): Volga German FAD presenilin2 (γ-secretase activity)—risk factor
- Chromosome 14 (PS1): Early Onset FAD presenilin1 (γ-secretase activity)—40/44
- Chromosome 19: Apo-E4 late onset risk factor apolipoprotein E4+, E3—, E2 lethal
  E4- het = 3x, homo = 15x

Expression profile of AD tangle and normal CA1 neurons (Ginsberg et al., 2000)

Expression of many genes affected in AD (Loring et al., 2001)

Plaque vaccine for Alz
Inject Alz (PDAPP) transgenic mice with beta-amyloid vaccine, can prevent plaques in young-aging mice AND can decrease plaques in mice that already have them

Schenk (2002)
Pharmacotherapy

- There is no cure yet.
- There are three drugs that AD patient could take to slow the progression.
- They are: tacrine (Cognex), donepezil (Aricept), and rivastigmine (Exxelon).

Normal Aging of the Brain

- Increase in time required to retrieve information
- Less able to register and retain new information
- Decrease in attention and concentration

Normal Aging Versus Dementia

- Minimal memory impairment
- Little or no progression of impairment
- No functional consequences

Mild Cognitive Impairment (MCI)

- Subjective memory complaints
- Objective memory impairments
- MMSE ≥ 24
- No/minor functional impairment
- No diagnosis of AD

Annual Rates of Conversion from MCI to Dementia Over 48 Months

<table>
<thead>
<tr>
<th>Months</th>
<th>Alzheimer's Disease</th>
<th>MCI</th>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>22</td>
</tr>
<tr>
<td>12</td>
<td>68</td>
<td>64</td>
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<tr>
<td>24</td>
<td>76</td>
<td>52</td>
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<td>36</td>
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<td>48</td>
</tr>
<tr>
<td>48</td>
<td>52</td>
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Prevalence of Undetected, Mild Cognitive Impairment – Study Population

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Undetected dementia (n = 200)</td>
<td>22 (11)</td>
</tr>
<tr>
<td>Undetected MCI (n = 179)</td>
<td>17 (10)</td>
</tr>
</tbody>
</table>

Source: Hermann, Sager 2002
Summary

Most cognitive impairments in aging due to dementia or pre-dementia

Most dementia is AD

Large heritable component

Large environmental component - e.g., diet

Gene expression among mice of same strain, age, sex, housing [6584 possible genes] (Lockhart & Barlow, 2001)