Overview of neurological changes in Alzheimer’s disease

Eric Karran
Alzheimer’s disease

Alois Alzheimer
1864-1915

Auguste D.
1850-1906

Case presented November 26th 1906
Alzheimer's disease – major cause of dementia

- Alzheimer's disease 67%
- Parkinson's 8%
- Other 6%
- Vascular dementia 15%
- Injury 4%
AD – clinical features

AD is the most common cause of dementia:

Evidence of a decline in memory and thinking which is of a degree sufficient to impair functioning in daily living, present for six months or more.

According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), dementia is defined as memory impairment (amnesia) plus one or more of the following:

• aphasia - difficulty with language
• apraxia - problems with complex movements
• agnosia - difficulty with identifying objects
• impaired executive functioning - making everyday decisions

Additional symptoms:

• Psychosis and agitation
• Mood change and apathy

Diagnosis:

• Possible – atypical clinical features but no alternative diagnosis without histologic confirmation
• Probable – typical clinical diagnosis without histologic confirmation
• Definite – clinical diagnosis plus histologic confirmation
## Mini-Mental State Exam

<table>
<thead>
<tr>
<th>Orientation</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the (year) (season) (date) (day) (month)?</td>
<td>5</td>
</tr>
<tr>
<td>Where are we: (country) (city) (part of city) (number of flat/house) (name of street)?</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Registration</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name three objects: one second to say each. Then ask the patient to name all three after you have said them. Give 1 for each correct answer. Then repeat them until he learns all three. Count trials and record.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Attention and calculation</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serial 7s: 1 for each correct answer, stop after five answers. Alternatively spell 'world' backwards.</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recall</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask for the three objects repeated above. Give 1 for each correct answer.</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Language</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name a pencil and watch (2). Repeat the following: 'No ifs, ands or buts' (1). Follow a three-stage command: 'Take a paper in your right hand, fold it in half and put it on the floor' (3). Read and obey the following: Close your eyes (1). Write a sentence (1). Copy a design (1).</td>
<td>9</td>
</tr>
</tbody>
</table>

Total = 30
AD - pathology

Normal  AD
AD - pathology

‘Subtractive’ MRI

48 year old control over 11 months

46 year old AD patient over 14 months

Global loss of brain matter/year
Controls = 0.24%
At risk individuals = 1.0%
Mild to moderate AD = 2.20%

Nick Fox, Lancet 2001
Imaging pathology in the AD brain

71 years
MMSE 30

69 years
MMSE 21

Amyloid plaques

Brain tissue

Oxygen use
AD- Pathophysiology

Plaques

Largely Aβ peptide

Tangles

Hyperphosphorylated tau filaments
APP metabolism – 2 pathways

Plaques

Outside cell

APP

sAPPβ

β-secretase

γ-secretase

Aβ42

Inside cell

sAPPα

α-secretase

γ-secretase

AICD

p3
Amyloid plaque is fibrillar and extracellular.
Tau protein: intracellular role in stabilizing microtubules
Tau – can form aggregates in AD
Tau – multiple forms of the protein and multiple phosphorylations

Hyperphosphorylation reduces ability of tau to bind to microtubules

Spillantini & Goedert (1998)
Axon in plaque with PHF and dense bodies near the synapse.
The tangle is made up of paired helical filaments (PHF) composed of hyperphosphorylated Tau.
What causes dementia in AD?

- Loss of synapses
- Loss of neurons

Frontal cortex – Price 2003
The progression of AD

Development of Aβ-amyloid (n=2369)

Cases devoid of amyloid (n = 1369)

Amyloid deposits of stage A (n = 366)

Amyloid deposits of stage B (n = 366)

Amyloid deposits of stage C (n = 266)

Development of neurofibrillary changes (n=2369)

Cases devoid of changes (n = 582)

Stages I and II (n = 1248)

Stages III and IV (n = 409)

Stages V and VI (n = 130)

A

B

C

I-II

III-IV

V - VI
Disease progression

Symptomatic

Diagnosis

Remaining life span after diagnosis (~10 years)

Years

Ernst, Hay 1994
## AD Staging and cognitive decline

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pathology</th>
<th>Cognitive domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>I – II</td>
<td>Entorhinal Cortex Mild involvement of HPC (CA1)</td>
<td>Episodic memory</td>
</tr>
<tr>
<td>‘transentorhinal’</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III – IV</td>
<td>EC / HPC subiculum (mild), Basal forebrain, Some cortical (frontal / temporal)</td>
<td>Executive function</td>
</tr>
<tr>
<td>‘limbic’</td>
<td></td>
<td>Working memory</td>
</tr>
<tr>
<td>V – VI</td>
<td>Severe cortical association areas, amygdala, thalamic, striatal, SN</td>
<td>Extensive deficits not restricted to cognition</td>
</tr>
<tr>
<td>‘isocortical’</td>
<td></td>
<td></td>
</tr>
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</table>
## AD, PD, MS Comparison

<table>
<thead>
<tr>
<th></th>
<th>Alzheimer’s disease</th>
<th>Parkinson’s disease</th>
<th>Multiple sclerosis</th>
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<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>increases with age, most &gt;60</td>
<td>increases with age, mean 62</td>
<td>20 – 35</td>
</tr>
<tr>
<td><strong>Gender distribution</strong></td>
<td>slight increase F</td>
<td>slight increase M</td>
<td>F&gt;&gt;M</td>
</tr>
<tr>
<td><strong>Patients in U.S.</strong></td>
<td>4.3 million</td>
<td>~ 500,000</td>
<td>~ 300,000</td>
</tr>
<tr>
<td><strong>Initial clinical course</strong></td>
<td>insidious, gradually progressive</td>
<td>insidious, gradually progressive</td>
<td>relapsing/remitting</td>
</tr>
<tr>
<td><strong>Cognitive/behavioral change</strong></td>
<td>Early; most prominent</td>
<td>Normal early; change with advanced disease</td>
<td>May occur, especially with progression.</td>
</tr>
<tr>
<td><strong>Motor system change</strong></td>
<td>Mild parkinsonism in ~20%</td>
<td>Early change; bradykinesia, rigidity, resting tremor</td>
<td>Yes, many manifestations</td>
</tr>
</tbody>
</table>
Prevalence of AD - USA

Evans et al. Arch Neurol. 2003
Summary

- The pathology of AD has been rigorously documented: plaques and tangles are the hallmarks of the disease.
- The actual mechanism(s) by which neurons are killed in the disease remain(s) obscure.
- There are no therapies currently available that prevent or slow the progression of the disease.
- Current symptomatic therapies offer only modest improvements in cognitive performance for a limited period of time.