Alzheimer’s Disease

William Petrie, MD
Psychiatric Consultants, PC
Differential Diagnosis

Source: Alzheimer’s Association 1995

ALZHEIMER’S DISEASE
- Gradual onset
- Relentless progression
- Underlying vascular disorder not always present
- Degeneration in a broad range of intellectual abilities

VASCULAR DEMENTIA
- Abrupt onset
- Underlying vascular disorder present (eg. HTN or Heart Disease)
- Early impairment in motor skills
- Brain scans show evidence of strokes or stroke-related changes
Alzheimer’s Disease Prevalence

- According to projections by the US Census Bureau, the number of AD patients is now estimated at 4.5 million.
- By 2030, it is estimated that the number will double to approximately 9 million Americans.
- By 2050 it is estimated that 14 million Americans will suffer from Alzheimer’s disease.
Elderly Population in the United States
Projected Growth and Distribution

Alzheimer’s Disease Prevalence

% Prevalance of AD

65-74

75-84

84+

0
5
10
15
20
25
30
35
40
45
50

65-74

75-84

84+
Causes of Dementia

DEMENTIA

- Alzheimer's Dementia (>60%)
- Vascular Dementia
- Others Dementias (Rare)
  - eg. AIDS related; Parkinsonian; Alcohol Induced
Relative Frequency of Dementia D/O in Old Age

- Dementia- Alzheimer type (DAT) 52%
- Multi-Infarct Dementia (MID) 17%
- Combination of DAT & MID 14%
- Brain Tumors (& rare neurological disease ie Huntington’s, Pick’s, etc) 7%
- Parkinson’s Disease 2%
- Psychiatric Conditions 1%
- Unknown Causes 7%
Dementia Pugilistica
Repeated Blows
Summary of Prevalence & Economic Impact of AD

- Approximately 4.5 million Americans currently have AD
- > 100,000 people die from AD annually
- Estimated that 14 million Americans will have AD by 2050
- Cost of healthcare $90 billion annually
- AD is the 3rd most expensive disease to treat in US following cancer and heart disease
## Estimated Annual Pt Costs

Total Yearly Costs to American Society

$90 billion

<table>
<thead>
<tr>
<th>TYPE OF CARE</th>
<th>ESTIMATED ANNUAL COSTS PER CASE</th>
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<tbody>
<tr>
<td>Nursing Home Care</td>
<td>$36,000</td>
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<tr>
<td>Home Care</td>
<td>$18,000</td>
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</table>
Reversible Causes of Dementia

- Adverse drug reaction
- Depression
- Metabolic changes
- Nutritional deficiencies
- Head injuries
Head Injuries
Common Syndromes of Subcortical Dementia

- **Degenerative**
  - Parkinson’s Disease
  - Huntington’s Disease
  - Progressive Supranuclear palsy

- **Vascular**
  - Lacunar state
  - Thalamic infarction

- **Other**
  - Multiple sclerosis
  - HIV associated dementias
  - Normal pressure hydrocephalus
  - Lewy Body Dementia
Folstein MMSE
(Mini Mental Status Exam)

- **Orientation**
  - Year, Season, Date, Day & Month (1 pt for each)
  - Country, state, county, city, present location (1 pt for each)

- **Attention and Calculation** (subtract serially 7’s from 100 (93, 86, 79, 72, 65) - 1 pt each OR
  - Spell” WORLD” backwards (DLROW) 1 pt each

- **Recall** (3 objects (apple, book, coat) - 1 pt each)
Folstein MMSE
Possible Score 30/30

Language

- Identify 2 objects (pencil, watch) 1 pt each
- Repeat-”No ifs, ands, or buts” - 1 pt
- 3 step command - 1 point each
  1) Take this piece of paper in your right hand
  2) Fold it in half
  3) put it on the floor
- Read and obey: Close your eyes - 1 pt
- Write a complete sentence 1 pt
- Copy this design- (2 intersecting pentagons)
Risk Factors for AD

ESTABLISHED

- Age
- Family History
- Down’s Syndrome

POSSIBLE

- Previous head trauma
- Environmental factors
- Infectious agents

Source: Costa PT et al 11/96
You’ve Got a Hard Head
Charlie Brown
Risk Factor: Head Size
Warning Signs of AD

- Difficulty learning and retaining new information
- Difficulty performing complex tasks
- Diminished reasoning ability
- Problems with spatial orientation
- Language problems
- Changes in personality, mood, or behavior

Source: Agency for Health Care Policy and Research Guideline 19 Overview; 1996
GIFT OF LOVE

A group of nuns are donating their brains to science to help fight Alzheimer's Disease

The Nun Study
Sisters of Notre Dame
NIMH study - Dr. David Snowdon

- 678 Catholic sisters studied
- Ages 75-103
- Longitudinal study beginning in 1991
- Annual assessments of cognitive and physical functioning
- Autopsy of brain upon death
- Similar lifestyles
Neuronal Degeneration

The pathobiology of Alzheimer’s disease is characterized by:

- Amyloid plaques
- Neurofibrillary tangles
Amyloid Plaques

- Plaques are extracellular structures that are more prevalent in the Alzheimer’s patient’s brain, particularly in the hippocampus and neocortex.

- Amyloid (neuritic) plaques in Alzheimer’s disease are dense and insoluble structures.

- Plaques consist of a central core of beta-amyloid protein surrounded by abnormal axons and dendrites.
Amyloid Plaques
The Amyloid Hypothesis

Amyloid Deposits

- Correlate with AD pathology and reduced cognitive function
- Accumulate with advancing age

Accumulate in neuritic plaques over span of 30 years

Composed of β-A4 protein

Selkoe, DJ *N Eng J Med* 1989
Formation of B–A 4

B–APP
B = amyloid protein precursor

B–APP770
B–APP751
B–APP714
B–APP695

B–A4
B - amyloid

- B-amyloid is normally cleared by α-secretase into fragments largely cleared from the brain. Gene mutations cause cleavage by B-secretase and δ-secretase, producing B-amyloid (1-42). This aggregates into B-pleated sheets which make up characteristic amyloid plaques.
Amyloid Plaques & Neurofibrillary Tangles
Neurofibrillary Tangles

- Intra cellular inclusion bodies consisting of paired helical filaments that appear in a characteristic double-helix shape
- Filaments appear to be composed of a hyperphosphorylated microtubule-associated protein called tau.
- Remains of damaged neuronal microtubules.
The Protective Value of Multiple Pathways
Cognitive Dysfunction Syndrome

- Disorientation
- Altered or decreased interaction with family
- Loss of Housetraining
- Decreased greeting behavior
- Change in sleep-wake cycle
- Change in activity
Pathogenesis: The Cholinergic Synapse
Current Aspects of Alzheimer’s Disease Research

- Cholinergic dysfunction
- Noncholinergic deficits
- Genetics
- Treatment-Cholinesterase Inhibitors
  - Cognex- Tacrine Hydrochloride
  - Aricept- Donepezil HCL
  - Exelon- Rivastigmine tartrate
Genetic Research

- Research has produced evidence of a link between Alzheimer's Disease and chromosomes 1, 14, 19 and 21.
- Chromosomes 1, 14 and 21 have been linked with early-onset Alzheimer’s disease, an extremely rare form of the disease.
- ApoE4 gene located on chromosome 19 has been associated with late-onset Alzheimer's disease, the most common form of the disease.
Importance of Social Relations

- Individuals living alone, with poor social relations and with limited family contacts, have an increased risk of dementia (both vascular and Alzheimer’s Disease) by 60%

> Fratiglioni et al. 2000
Impact of Estrogen upon the Disease Progression

Estrogen replacement for one year did not slow disease progression in mild to moderate Alzheimer’s patients.

(MMSI 12-28)

Mulhard et al. 2000
3 Key Domains of Global Functioning

- Cognition
- Behavioral
- Activities of Daily Living (ADLs)

The acetylcholinesterase inhibitors target these areas of functioning.
<table>
<thead>
<tr>
<th>DRUG</th>
<th>ACTIVITY</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognex</td>
<td>Acetylcholinesterase inhibitor</td>
<td>Compensate loss of cholenergic neurons</td>
</tr>
<tr>
<td>Aricept</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exelon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampakines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen, Other NSAIDS</td>
<td>Enhance activity of AMPA receptor</td>
<td>Improve memory by enhancing long-term potentiation</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Anti-inflamatory</td>
<td>Prevent inflammatory damage to neurons</td>
</tr>
<tr>
<td>Premarin</td>
<td>Antioxidant</td>
<td>Protects against the Radical damage</td>
</tr>
<tr>
<td></td>
<td>Female hormone</td>
<td>Promotes neuronal survival</td>
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## Possible Drugs for Preventing or Treating AD

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<tr>
<th>DRUG</th>
<th>ACTIVITY</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve growth factor</td>
<td>Maintain cholinergic neurons in brain</td>
<td>Promotes neuronal survival</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Inhibit calcium ion entry into neurons</td>
<td>Reduce calcium toxicity</td>
</tr>
<tr>
<td>Cholesterol lowering drugs</td>
<td>Lower apoE4 concentration</td>
<td>Prevent apoE4 toxicity to neurons</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Block B-amyloid production</td>
<td>Prevent neuronal loss to B-amyloid toxicity</td>
</tr>
</tbody>
</table>
Donepezil HCL (Aricept)

- Reversible acetylcholinesterase inhibitor
- Chemically unrelated to tacrine
- Enhances cognitive function
- Once daily dosing
- 5 mg to 10 mg doses are clinically effective
- No Liver function testing required
Donepezil HCL (Aricept) Dosing

- One tablet daily at bedtime
- May be taken with or without food
- Both the 5 mg and 10 mg daily doses are clinically effective
- Some patients might derive additional benefit by dosage escalation to 10 mg daily after 4-6 weeks of 5 mg therapy
Rivastigmine Tartrate (Exelon)

- Reversible acetylcholinesterase inhibitor
- Enhances cognitive function
- Twice a day dosing
- Recommended with food (breakfast and supper)
Rivastigmine Tartrate (Exelon)

- 1.5; 3.0; 4.5 and 6.0 mg capsules
- 6-12 mg target dosing range
- Not metabolized via C-450 pathway
- No liver function testing required
Galantamine
(Reminyl)

- Prevents the breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in the brain.

- 4mg –BID (8mg/day) Increase by 8mg/day after 4 weeks to 8mg, BID (16mg/day). After another 4 weeks, increase to 12mg, BID (24mg/day), if well tolerated.

- Possible Side effects: Nausea, vomiting, diarrhea, weight loss
AD Drugs under Development

- Acetylcholinestrase inhibitors
  - Eptastigmine (Mediolanum)
  - Metrifonate (Bayer)
  - Physostigmine (Forest)

- Acetylcholine precursors
  - Acetyl-1-carnitine (sigma-Tau Pharmaceuticals)

- Muscarinic agonists
  - Af-102B (Forest/TEVA/Snow Brand)
  - Milameline (Warner Lambert/Hoechst Marion Rossel)
  - SB 202026 (SmithKline Beecham)
  - SR 46559 (Sanofi)
Most Common Adverse Events
Acetylcholinesterase Inhibitors

- The most common adverse events associated with ARICEPT, EXELON and REMINYL treatment includes nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia.

- These adverse events were often of mild intensity and transient, resolving during continued treatment without the need for dose modification.
AD Drugs under Development

- **Metabolic Enhancers**
  - Nicergoline (Pharmacia)
  - Xanomeline (Eli Lilly)
  - Propentofyline (Hoechst Marion Roussel)

- **Others**
  - Corticotrophin releasing factor (Neuocrine Biosciences)
  - Sabeluzole (Johnson and Johnson)

Sources: The Genesis Report/Rx 1995
Pharmaceutical Research and Manufacturers of America Survey 1995
Alzheimer’s Disease

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Differential Diagnosis

Source: Costa PT et al 1996

ALZHEIMER’S DISEASE

- Irreversible decline in short-term memory
- Irreversible decline in other cognitive abilities
- Functional impairment
- Psychiatric symptoms

NORMAL AGING

- Benign decline in short-term memory
Alzheimer’s Disease Prevalence
Alzheimer’s Disease (AD)

- AD is one of the top 10 leading causes of death in Americans over 65 years of age.
- AD is the 3rd most costly disease, after heart disease and cancer.
- Federal funding for AD is 4-7 times lower than for heart disease, cancer or AIDS.
### Estimated Annual US Incidence (1983) of AD by Age and Gender

<table>
<thead>
<tr>
<th>Age group (yr)</th>
<th>Males (%)</th>
<th>Females (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-69</td>
<td>0.37</td>
<td>0.20</td>
</tr>
<tr>
<td>70-74</td>
<td>0.70</td>
<td>1.16</td>
</tr>
<tr>
<td>75-79</td>
<td>1.37</td>
<td>1.16</td>
</tr>
<tr>
<td>≥80</td>
<td>3.00</td>
<td>2.25</td>
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# Signs and Symptoms at Different Stages of AD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td><strong>Mild</strong></td>
<td>Confusion &amp; memory loss</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Difficulty w/ADLs</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>Loss of speech</td>
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Neurofibrillary Tangles
Hormones and Paragraph Recall

Women who received any of the active hormonal preparations maintained their scores on Paragraph-Recall pre- to postoperatively (hysterectomy and bilateral salpingo-oophorectomy) while scores decreased significantly in women receiving placebo.
Treatment with Estrogen Replacement Therapy

- Open label clinical trials and 1 randomized trial have shown cognitive impairment in female patients with dementia who were treated with estrogen replacement therapy.

  - Haroutunian et al. 1998; 1999
  - Heyman et al. 1987
Donepezil HCL (Aricept) ADAS-cog Placebo Washout Effect

Mean change from baseline score

Weeks of Drug Treatment

Aricept 5 mg
Aricept 10 mg
Placebo