Alzheimer’s Disease Diagnosis and Management
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Cleveland Clinic
March 20, 2013

Who’s Afraid of Alzheimer’s Disease

• Name the disease you are most afraid of getting:
  – One out of five picks Alzheimer’s
  – 14% - heart disease
  – 13% - stroke
• Only cancer tops Alzheimer’s among Americans in general
• Among adults aged 55 and older, the fear getting Alzheimer’s > fear of cancer

2006: MetLife Foundation Alzheimer’s Survey: What America Thinks

Six Degrees of Separation

• One in three Americans (35%) say they have a family member or friend with Alzheimer’s.
• More than three out of five people worry that they will have to eventually provide or care for someone with the disease.

2006: MetLife Foundation Alzheimer’s Survey: What America Thinks

Ronald Reagan Dies at 93

Learning Objectives

• Accurately diagnose dementia
• Differentiate Alzheimer’s Disease from other forms of dementia
• Discuss goals of pharmacotherapy with patients and caregivers
• Discuss non-pharmacological interventions

Just the Numbers

• Approx 5.4M Americans (all ages) have Alzheimer’s Disease
  – 5.2 million people age 65 and older
  – One in 8 eight people age ≥65 (13%)
  – Nearly half of people age ≥ 85 (45 %)
• 6th leading cause of death in USA
• ~$200B est cost for care in 2012
• 15M people provide unpaid care to person with AD or other dementia

2012: Alzheimer’s Association facts and figures
2012: Alzheimer’s Association facts and figures

**Incidence and Prevalence**

- **Incidence:**
  - ages 65 and 69: 0.6%
  - 70 and 74: 1.0%
  - 75 and 79: 2.0%
  - 80 and 84: 3.3%
  - 85+: 8.4%
- Prevalence also increases exponentially with age:
  - 3% - age 65-74
  - 50% - 85+

**Behaviors and the Caregiver**

- 60-100hr/week involvement
- 50% suffer depression
- 40% more illness
- 70% more prescriptions
- Need education, self care, and respite
DSM-IV Diagnostic Criteria
Dementia

- Development of multiple cognitive deficits manifested by both memory impairment and 1 or more of the following cognitive disturbances:
  - Aphasia
  - Apraxia
- Cognitive deficits cause significant impairment in social functioning and represent a significant decline from a previous level of functioning
- Course is gradual in onset with continuing cognitive decline
- Deficits are not due to any other CNS disorder, systemic illness, or substance-induced condition
- Deficits do not occur exclusively during the course of delirium


The Dementia Spectrum

When is Memory Loss Significant?

- Delayed recall of words, names
- Diminished multitasking ability

Amnestic subtype of mild cognitive impairment
- Memory complaint, preferably corroborated by an informant
- Memory impairment relative to age-matched and education-matched healthy people
- Typical general cognitive function
- Largely intact activities of daily living
- Not clinically demented

Neurofibrillary Tangle
Senile Plaque

APP
Cell membrane
Gamma-secretase
Alpha-secretase

Image courtesy of the National Institute on Aging/National Institutes of Health

Alzheimer’s Disease
NINCDS-ADRDA Criteria

- Definite Alzheimer’s disease:
  - Dx Probable AD (+) histopathologic proof
- Probable Alzheimer’s disease:
  - Dementia; progressive; ≥2 areas of cognition affected; onset between 40-90 years; absence of other diseases
- Possible Alzheimer’s disease:
  - Dementia syndrome; atypical onset, presentation or progression; no known etiology, co-morbidity producing dementia
- Unlikely Alzheimer’s disease:
  - Dementia syndrome, sudden onset, focal neurologic signs, or seizures or gait disturbance early in the course of the Illness
Braak Staging

<table>
<thead>
<tr>
<th>Anatomic Stage</th>
<th>Braak Stage</th>
<th>Medial Temporal Tau Pathology</th>
<th>Isocortical Tau Pathology</th>
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</thead>
<tbody>
<tr>
<td>Limbic</td>
<td>III-IV</td>
<td>Limited to transentorhinal</td>
<td>Minimal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and entorhinal involvement</td>
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<td></td>
<td></td>
<td>Transentorhinal, entorhinal</td>
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<td></td>
<td></td>
<td>Ammon's horn involvement</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Extensive medial temporal</td>
<td>Advanced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>involvement</td>
<td></td>
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</table>

CERAD staging

<table>
<thead>
<tr>
<th>Plaque Frequency</th>
<th>None</th>
<th>Sparse</th>
<th>Moderate</th>
<th>Frequent</th>
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<tbody>
<tr>
<td>50</td>
<td>0</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>50-75</td>
<td>0</td>
<td>B</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>0</td>
<td>A</td>
<td>B</td>
<td>C</td>
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</tbody>
</table>

Glossary: 0 no evidence of AD, A uncertain, B suggestive of AD, C indicative of AD.

“Definite AD” C plus clinical dementia.

“Probable AD” B plus clinical dementia.

“Possible AD” A plus clinical dementia or B or C and no dementia.

Plaque Progression

Stage A Stage B Stage C

CERAD staging

NFT Progression

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MMSE 20-29

Memory loss
<table>
<thead>
<tr>
<th>Language problems</th>
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</thead>
<tbody>
<tr>
<td>Mood and personality changes</td>
</tr>
<tr>
<td>Diminished judgment</td>
</tr>
<tr>
<td>Withdrawal from activities</td>
</tr>
</tbody>
</table>

MMSE 10-19

Mild
| Behavioral, personality changes |
| Unable to learn/recall new information |
| Long-term memory affected |
| Wandering, paranoia, aggression |
| Require assistance with IADLs |

MMSE 0-9

Severe
| Unstable gait |
| Incontinence |
| Motor disturbances |
| Bedridden |
| Dysphagia |
| Mute |
| Poor/No ADLs |
| LTC placement common |

Fast

• Stage 1
  - No functional decrement subjectively or objectively
• Stage 2
  - Complaints of forgetting location of objects
• Stage 3
  - Subjective work difficulties
  - Decreased functioning in demanding work settings evident to coworkers
• Stage 4
  - Difficulty traveling to new locations
  - Decreased ability to perform complex tasks (eg, planning dinner, shopping, or personal finances)
• Stage 5
  - Requires assistance selecting attire
  - May require assisting to bathe properly
  - Difficulty dressing properly
  - Requires assistance bathing (fear of bathing)
  - Difficulty with mechanics of toileting
  - Urinary incontinence
  - Fecal incontinence
  - Stage 6
    - Vocabulary limited to one to five words
    - Invariable vocabulary lost
    - Ambulatory ability lost

Lyketsos et al, JAMA 2002

Cardiovascular Health Study

3608 participants • 10 years
362 dx with dementia • NPI used

<table>
<thead>
<tr>
<th>Apathy</th>
<th>45.3%</th>
<th>Sleep</th>
<th>30.1%</th>
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</thead>
<tbody>
<tr>
<td>Depression</td>
<td>43.6%</td>
<td>Anxiety</td>
<td>25.4%</td>
</tr>
<tr>
<td>Agitation / Aggression</td>
<td>40.1%</td>
<td>Dysinhibition</td>
<td>18.2%</td>
</tr>
<tr>
<td>Irritability</td>
<td>34.0%</td>
<td>Aberrant Motor</td>
<td></td>
</tr>
<tr>
<td>Euphoria</td>
<td>3.0%</td>
<td>Hallucinations</td>
<td>16.3%</td>
</tr>
<tr>
<td>Eating</td>
<td>30.9%</td>
<td>Hallucinations</td>
<td>16.3%</td>
</tr>
<tr>
<td>Delusions</td>
<td>30.1%</td>
<td>Euphoria</td>
<td>3.0%</td>
</tr>
</tbody>
</table>


Risk Factors for LTC Placement

- ≥ 1 Dependency in ADL: HR 1.47
- Psychotic Symptoms: HR 1.32
- Dangerous: HR 1.25
- Wakes up Caregiver: HR 1.19
- Zarit Burden Score:
  - 0-9: HR 1.0
  - 10-14: HR 1.25
  - 15-19: HR 1.29
  - 20-32: HR 1.79

FDA Approved Therapies

Memantine and Donepezil Combination Therapy

Alzheimer Disease Cooperative Study - Activities of Daily Living Inventory

Memantine and Donepezil Combination Therapy

Alzheimer Disease Cooperative Study - Activities of Daily Living Inventory

Mild to Moderately Severe AD Study (MMSE 10-26) Rivastigmine Improved Cognition: ADAS-cog Total Score

Side Effects

<table>
<thead>
<tr>
<th></th>
<th>Donepezil</th>
<th>Galantamine</th>
<th>Rivastigmine</th>
<th>Memantine</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>5-19%</td>
<td>6-24%</td>
<td>6-12%</td>
<td>6-12%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8-15%</td>
<td>6-12%</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>Constipation</td>
<td>5%</td>
<td>9%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>10%</td>
<td>8%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Confusion</td>
<td>6-14%</td>
<td>5%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3-7%</td>
<td>7-9%</td>
<td>Flatulence 4%</td>
<td></td>
</tr>
<tr>
<td>FLATULENCE 4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3-8%</td>
<td>5%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>9%</td>
<td>9%</td>
<td>21%</td>
<td>7%</td>
</tr>
<tr>
<td>Syncope</td>
<td>2%/1-10%</td>
<td>2%/0.6-2.2%</td>
<td>3%/1-10%</td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2%/1-10%</td>
<td>3%/0.6-2.2%</td>
<td>3%/1-10%</td>
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</tr>
<tr>
<td>See Package Insert</td>
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</tbody>
</table>
Goals of Therapy

- Cognitive enhancement/stabilization
- Preservation of function
- Preservation of independence
- Reduction in care burden
- Delay in LTC placement
- NOT...
  - Improvement in cognition
  - Disease modifying

Validated Alzheimer’s Disease Biomarkers

<table>
<thead>
<tr>
<th>Pathophysiological Markers</th>
<th>Topographical Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrospinal Fluid</td>
<td></td>
</tr>
<tr>
<td>Amyloid β_{42}</td>
<td>YES</td>
</tr>
<tr>
<td>Total tau, Phosphorylated tau</td>
<td>YES</td>
</tr>
<tr>
<td>PET</td>
<td></td>
</tr>
<tr>
<td>Amyloid tracer uptake</td>
<td>YES</td>
</tr>
<tr>
<td>Fluorodeoxyglucose</td>
<td>NO</td>
</tr>
<tr>
<td>Structural MRI</td>
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</tr>
<tr>
<td>Medial Temporal Atrophy</td>
<td>NO</td>
</tr>
</tbody>
</table>

Dubois B et al, Lancet Neurol 2010

FDDNP-PET

- Healthy Control
- Mild Cognitive Impairment
- Alzheimer’s Disease

FDDNP-PET


Dubois B et al, Lancet Neurol 2010
Conclusions

• Dementia requires cognitive impairment with functional impairment
• Alzheimer’s Disease is the most common form of dementia in the elderly
• Be aware of other causes
• We are good at diagnosing, but current treatments limited

References

• http://www.ahrq.gov/clinic/tp/alzcogtp.htm
• http://www.alzheimers.org/clinicaltrials/search.asp