Alzheimer’s Disease and Mild Cognitive Impairment

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Differential diagnosis over time

• Early AD: normal aging and MCI --- continuum
• Later: the other dementias

• Limited tools: no specific diagnostic test except pathology
• Probabilistic diagnosis
Dementia

- Alzheimer’s disease
- Frontotemporal dementia
- Vascular dementia
- Dementia with Lewy bodies
- Parkinson-related dementia
  - Corticobasal degeneration
  - Progressive supranuclear palsy
  - Multiple system atrophy
  - FTD with parkinsonism linked to chr 17
- Normal pressure hydrocephalus
- Creutzfeldt-Jakob disease (prion)
- Rapidly progressive dementia
Alzheimer Disease

Amyloid plaque
Neurofibrillary tangle
Amyloid angiopathy
Probable AD

Deficits in *two or more domains* of cognition
- Memory
- Language
- Perceptual skills
- Attention
- Constructive abilities
- Orientation
- Problem solving
- Functional abilities

Progressive *decline* of *memory and other* cognitive functions

Preserved consciousness

Onset between ages 40 and 90

Absence of systemic or other brain disease that could account for symptoms
Epidemiology

- Common
- Incidence doubling every 5 years over 65
  - 65-69: 2.8/1000 person year
  - 70-74: 5.6/1000 person year
  - 75-79: 12/1000 person year
  - 80-84: 14/1000 person year
  - 85-89: 28/1000 person year
  - 90+: 56/1000 person year
- Women (likely longevity)

Projected prevalence of AD

- No intervention
- 2 year delay
- 5 year delay
In the context of normal aging

• Meta analysis of cognitive impairment prior to AD diagnosis
  – Global functioning
  – Episodic memory (largest effect delayed recall)
  – Perceptual speed
  – Executive functioning

• Still under research – available normative data likely contaminated with MCI
Mild cognitive impairment (MCI)
Petersen criteria

- Cognitive complaint (usually memory) (informant)
- Cognitive impairment (usually memory) for age and education (neuropsych testing Z-score -1.5)
- Normal general cognitive testing
- Largely preserved activities of daily living
- Not demented
# MCI subtypes

<table>
<thead>
<tr>
<th>Degen-erative</th>
<th>Vascular</th>
<th>Psych</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD</strong></td>
<td></td>
<td><strong>Depression</strong></td>
<td></td>
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<tr>
<td><strong>AD</strong></td>
<td><strong>VaD</strong></td>
<td><strong>Depression</strong></td>
<td></td>
</tr>
<tr>
<td><strong>FTD</strong></td>
<td></td>
<td><strong>Psychiatric</strong></td>
<td></td>
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<tr>
<td><strong>DLB</strong></td>
<td><strong>VaD</strong></td>
<td><strong>Psychiatric</strong></td>
<td></td>
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</table>
Conversion to AD

• 1-25 % per year in various studies
• Likely methodological differences
• All MCI versus amnestic MCI only
• Amnestic MCI: 25 % per year
Alzheimer disease: definitions, lexicon

Dual clinico-pathological entity

Biomarkers

Dual clinico-biological entity

The clinico-pathological diagnosis implies a probabilistic approach ante mortem
Clinico-biological definition

• Phenotype
• Biomarkers: pathophysiology or topography

<table>
<thead>
<tr>
<th></th>
<th>Pathophysiological markers</th>
<th>Topographical markers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebrospinal fluid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amyloid $\beta_{42}$</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Total tau, phospho-tau</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>PET</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amyloid tracer uptake</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fluorodeoxyglucose</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Structural MRI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial temporal atrophy</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Uncouples from severity: no need to cross the dementia threshold if biomarkers are present
Sensitivity 96.4%

**Aβ_{1-42} concentration (pg/mL)**

- AD
- MCI
- NC

**Aβ_{1-42} cutoff = 192 pg/mL**

- 257±26 MCI converters to NC
- 146±38 MCI converters to AD
Red-yellow = diff small-diff big

Single domain amnestic

Red-yellow = diff small-diff big

Multidomain Z score <= -2

Mild AD MMSE 20-26
PET metabolism and amyloid imaging
New diagnostic criteria (Dubois)

Core criteria
A. Presence of an early and significant *episodic memory* impairment

Supportive features
B. Presence of medial temporal lobe atrophy
C. Abnormal cerebrospinal fluid biomarker
D. Specific pattern on functional neuroimaging with PET
E. Proven AD autosomal dominant mutation within the immediate family

Exclusion criteria

Probable AD: A plus one or more supportive features B, C, D, or E

Definite AD
Both clinical and histopathological (brain biopsy or autopsy) evidence of the disease
Both clinical and genetic evidence (mutation on chromosome 1, 14, or 21) of AD
Atypical AD:
episodic memory deficit absent

• Primary progressive non-fluent aphasia (DDG: FTD)
• Logopenic aphasia (DDG: FTD)
• Posterior cortical atrophy
• Frontal variant of AD (DDG: FTD)
AD Treatment

- Cholinesterase inhibitors
- NMDA receptor antagonist
- Vitamin E and C
- Modifiable risk factors
- Correctable causes
Kaplan-Meier estimates of the rate of progression from amnestic mild cognitive impairment (aMCI) to Alzheimer disease in depressed subjects with aMCI stratified by the three treatment groups
Donepezil in aMCI
AD: Cholinesterase inhibitors

Figure 2. Summary estimates for the change in Alzheimer’s Disease Assessment Scale–cognitive subscale (ADAS-cog) scores.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Mean Difference in ADAS-Cog Score (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil vs. placebo (all severity levels in AD)</td>
<td></td>
</tr>
<tr>
<td>Burns et al., 1999 (9)</td>
<td>-2.80 (-3.40 to -2.20)</td>
</tr>
<tr>
<td>Rogers et al., 1998 (17)</td>
<td>-3.10 (-4.29 to -1.91)</td>
</tr>
<tr>
<td>Rogers et al., 1998 (18)</td>
<td>-2.88 (-4.27 to -1.49)</td>
</tr>
<tr>
<td>Seltzer et al., 2004 (10)</td>
<td>-2.30 (-4.11 to -0.49)</td>
</tr>
<tr>
<td>Tune et al., 2003 (29)</td>
<td>-2.09 (-4.96 to 0.78)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>-2.80 (-3.28 to -2.33)</td>
</tr>
<tr>
<td>Donepezil vs. placebo (mild cognitive impairment)</td>
<td></td>
</tr>
<tr>
<td>Petersen et al., 2005 (32)</td>
<td>-0.06 (-1.18 to 1.06)</td>
</tr>
<tr>
<td>Salloway et al., 2004 (21)</td>
<td>-1.90 (-3.29 to -0.51)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>-0.93 (-2.73 to 0.87)</td>
</tr>
<tr>
<td>Donepezil vs. placebo (mild to moderate vascular dementia)</td>
<td></td>
</tr>
<tr>
<td>Black et al., 2003 (22)</td>
<td>-2.24 (-3.35 to -1.13)</td>
</tr>
<tr>
<td>Wilkinson et al., 2003 (23)</td>
<td>-2.07 (-3.32 to -0.82)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>-2.17 (-2.99 to -1.34)</td>
</tr>
<tr>
<td>Galantamine vs. placebo (mild to moderate AD)</td>
<td></td>
</tr>
<tr>
<td>Brodaty et al., 2005 (46)</td>
<td>-2.80 (-3.76 to -1.84)</td>
</tr>
<tr>
<td>Bullock et al., 2004 (45)</td>
<td>-3.10 (-4.74 to -1.46)</td>
</tr>
<tr>
<td>Raskind et al., 2000 (41)</td>
<td>-0.10 (-1.23 to 1.03)</td>
</tr>
<tr>
<td>Tarot et al., 2000 (39)</td>
<td>-3.10 (-4.18 to -2.02)</td>
</tr>
<tr>
<td>Wilcock et al., 2000 (42)</td>
<td>-2.90 (-4.00 to -1.80)</td>
</tr>
<tr>
<td>Wilkinson and Murray, 2001 (44)</td>
<td>-3.00 (-5.23 to -0.77)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>-2.45 (-3.48 to -1.42)</td>
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<tr>
<td>Galantamine vs. placebo (AD and vascular dementia)</td>
<td></td>
</tr>
<tr>
<td>Erkinjuntti et al., 2002 (43)</td>
<td>-2.70 (-3.95 to -1.45)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>-2.70 (-3.95 to -1.45)</td>
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<tr>
<td>Rivastigmine vs. placebo (all severity levels in AD)</td>
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</tr>
<tr>
<td>Corey-Bloom et al., 1998 (51)</td>
<td>-3.78 (-4.87 to -2.69)</td>
</tr>
<tr>
<td>Forette et al., 1999 (11)</td>
<td>-4.80 (-6.04 to -3.56)</td>
</tr>
<tr>
<td>Karaman et al., 2005 (53)</td>
<td>-5.27 (-5.73 to -4.81)</td>
</tr>
<tr>
<td>Rosler et al., 1999 (56)</td>
<td>-1.60 (-2.84 to -0.36)</td>
</tr>
</tbody>
</table>
Which cholinesterase inhibitor?
FDA approved for mild to moderate AD

- Side effects: nausea, vomiting, diarrhea
- Donepezil (Aricept)
  - Once a day
  - High dose studied
  - Vivid dreams: morning dosing
- Rivastigmin (Exelon)
  - Pseudo-irreversible inhibitor
  - More side effects
  - Patch option
- Galantamine
  - Nicotinic receptor too
  - Theory: additional benefit
  - Reality: no additional benefit, but cardiac death more
Memantine

• FDA approved for moderate to severe AD
• Side effects not a lot
• Does seem to help behavioral symptoms
• One observational cohort study suggested that starting both early is better
• No double blind data on combination therapy straight away versus staggered start: first cholinesterase inhibitor then memantine
Vitamin E in AD

**Endpoints**

**A**

Event-free Survival (%)

- Selegiline
- Placebo

0 100 200 300 400 500 600 700

**B**

Event-free Survival (%)

- Alphatocopherol
- Placebo

0 100 200 300 400 500 600 700

**Table 3. Percentage of Patients Reaching Each End Point, According to Study Group.**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo</th>
<th>Selegiline</th>
<th>Alpha-tocopherol</th>
<th>Selegiline and Alpha-tocopherol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of ability to perform activities of daily living</td>
<td>31</td>
<td>28</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>Clinical Dementia Rating of 3</td>
<td>51</td>
<td>43</td>
<td>48</td>
<td>47</td>
</tr>
<tr>
<td>Institutionalization</td>
<td>39</td>
<td>33</td>
<td>26</td>
<td>35</td>
</tr>
<tr>
<td>Death</td>
<td>12</td>
<td>10</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>
Vitamin E increased all cause mortality
Dose response for all cause mortality
Discontinuation of drugs

- 295 community-dwelling patients
- Treated with donepezil for at least 3 months
- Moderate or severe Alzheimer's disease
- 4 arms:
  - continue donepezil
  - discontinue donepezil
  - discontinue donepezil and start memantine
  - continue donepezil and start memantine
- 52 weeks
- Coprimary outcomes
- SMMSE
- Bristol Activities of Daily Living Scale
BPSD
Behavioral-psychiatric symptoms of dementia

- Apathy
- Agitation
- Anxiety
- Depression
- Sleep disturbance
- Psychosis
- Disinhibition
- Hallucinations
- Delusion: paranoid, unfaithful, misidentification

Often the most significant problem for caregivers
First careful assessment

• Often related to changes in caregiver, surroundings
• Measure: e.g. NPI
• Try non-pharmacological intervention first
  – Distraction
  – Redirection
  – Exercise
Pharmacological intervention

• Atypical atipsychotics
  – For psychosis

• Black box warning: increased death in demented patients

• Discussion with family

• If no effect DC after 10-12 weeks

• Periodically try to taper
Catie-AD trial

Adverse effects offset efficacy

FDA black box warning:

Increased risk of death and stroke
And now what?

• Establish the dangerousness of the situation
  – physical safety of the patient or others is at significant risk, and the patient does not respond quickly to behavioral strategies. Acute treatment with pharmacotherapy could be considered.

• Establish a clear diagnosis/etiology (to the extent possible) for the symptoms.
  – Rule out delirium (e.g., urinary tract infection, subdural hematoma, pneumonia).
  – Rule out iatrogenic causes (medications).
  – Rule out physical discomfort (e.g., arthritis pain, unrecognized fracture, constipation).
  – Explore for common antecedents to symptom flares that are potentially modifiable (e.g., seeing a certain person, increased noise level, social isolation).
  – Explore other common causes of behavioral disturbances in dementia (e.g., depression, anxiety, insomnia).

• Establish the severity and frequency of the symptoms.

• Explore past treatments/caregiver strategies used to address the symptoms and their level of success and/or problematic outcomes of such treatments.

• Discuss risks and benefits of treatments.
Management of symptoms associated with dementia

- Delusion: olanzapine, quetiapine
- Aggression, agitation: olanzapine, quetiapine, trazodone
- Depression/apathy: Fluoxetine
- Depression/anxiety: Escitalopram, buspirone
- Insomnia: Trazodone
- Sun-downing: Trazodone
- Apathy: Donepezil, rivastigmine
Descent into Alzheimer disease