Diagnosis and Treatment of Alzheimer’s Disease

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Outline
- Introduction
- Alzheimer’s disease (AD) Guidelines - revised in 2011
  - National Institute on Aging and Alzheimer’s Association
- Clinical Evaluation
  - Clinical assessment
  - Laboratory tests
- Treatment of AD

Revised Diagnostic Criteria for Alzheimer’s disease
- No revision since 1984
- Changes include
  - Pre-dementia prodrome*
  - Diagnostic guidelines for MCI
  - Potential significance of biomarkers
    - Physiological, biochemical, or anatomic measures
    - Reflect disease-related pathophysiology
  - Changes are flexible - allow for future advances

*not for clinical use at this time
AD Biomarkers

- Abnormal years before clinical symptoms
- Useful in research setting
- Clinical use requires further validation

Categories of AD Biomarkers

- Markers of brain amyloid
  - Cerebrospinal fluid amyloid
  - PET: amyloid imaging
- Markers of neuronal injury
  - Cerebrospinal fluid tau & phosphorylated-tau
  - FDG-PET: metabolic activity
  - Hippocampal volume or medial temporal atrophy by volumetric measures or visual rating

The continuum of Alzheimer’s disease
Hypothetical Course of Aging Brain and biomarker changes

Amyloid Imaging

MRI: Volumetric Measures
Preclinical Stage of AD

- Clinical symptoms not yet evident
- Biological markers present
- Risk of progression to dementia unknown
- Only for research purposes

Drug intervention at this stage may be more likely to achieve disease modification
MCI

- MCI core criteria
  - Cognitive concern by patient, informant, or clinician
  - Independence not compromised
  - Cognitive testing impaired
- Guidelines do not specify test or cut-off scores
- Allows for clinician flexibility
- Rule out other conditions

MCI Categories

- MCI Core Criteria
  - Defines presence of MCI
- Biomarkers assess likelihood of AD
- MCI due to AD
- MCI unlikely due to AD

MCI Categories

- Biomarkers assess likelihood of AD
- Not all MCI progresses to AD
- Intended for research use
- May be applied in clinic

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD pathology</th>
<th>CSF Ab42 or CSF Ab1-42</th>
<th>Normal range</th>
<th>Normal range</th>
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</thead>
<tbody>
<tr>
<td>MCI core clinical criteria</td>
<td>Uninformative</td>
<td>Conflicting/intermediate</td>
<td>Uninformative/intermediate</td>
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<tr>
<td>MCI due to AD - moderate likelihood</td>
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<td>Conflicting/intermediate</td>
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<tr>
<td>MCI due to AD - high likelihood</td>
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<td>MCI unlikely due to AD</td>
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Abnormalities: AD, Alzheimer's disease; Ab, amyloid-beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging.
Dementia Criteria: Cognitive Changes
- Interferes with daily function
- Cause a decline from previous level of performance
- Not due to other condition (including depression)
- Evident in clinical history
- Evident on cognitive tests
  - Memory
  - Executive functioning
  - Visuospatial
  - Language
  - Behavior/personality

AD Dementia Criteria
- Meets dementia criteria
- Insidious onset symptoms over months to years
- Gradual worsening of symptoms
- Amnestic presentation:
  - Most prominent deficits in short term memory
  - Deficit in at least one other cognitive domain
  - Language, visuospatial, and executive function variants exist

Psychiatric Symptoms
- Depressive symptoms
- Apathy
- Psychosis generally occurs later
  - Paranoid delusions
  - Visual hallucinations
- Agitation
- Wandering
- Sleep disturbances
Differential Diagnosis
- Frontotemporal dementia
- Lewy Body dementia
- Vascular dementia
- Creutzfeldt-Jakob disease
- Corticobasal degeneration
- Progressive supranuclear palsy
- Normal pressure hydrocephalus
- Multiple system atrophy
- Others

The Clinical Evaluation

History of Present Illness
- Consider separating patient and informant
- History of onset and progression
  - Memory: appointments, current events, meds, etc.
  - Language loss
  - Behavioral/personality changes
  - Delusions/hallucinations
- Compare current and previous abilities
  - Activities of daily life
  - Withdrawal from previous activities
Change from Prior Performance Level in Activities of Daily Life (ADLs)

- Instrumental ADLs (Early)
  - Finances
  - Shopping
  - Taking meds
  - Preparing meals
  - Housekeeping
  - Telephone use
  - Independent travel

- Personal ADLs (Middle to Late)
  - Bathing
  - Grooming
  - Toileting
  - Walking
  - Dressing
  - Eating meals

Past Medical History

- Past medical history
- Social history
  - Level of education
  - Social support network
  - Family history of dementia
  - Medications

In-Clinic Cognitive Testing

- No standard
- Physician preference
- Should include:
  - Attention
  - Orientation
  - Short and long term memory
  - Language
  - Visuospatial abilities
  - Executive functioning
The Mini-Mental State Examination

- The MMSE is useful for detecting dementia
- Cut-off score=24
- Specificity is 82%
- Sensitivity is 87%
  - Not sensitive in mild dementia
  - Scores are spuriously low in people with a low education level and poor vision
- Can track AD progression: 3-4 points/yr

Crum et al, 1993
Routine Laboratory Studies
- MUST rule out reversible causes
  - B12 (cobalamin)
  - Thyroid stimulating hormone
  - Complete blood count
  - Chemistry Panel
  - Brain CT or MRI

Non-Routine Labs
- Erythrocyte sedimentation rate
- Urinalysis
- Toxicology
- Heavy metal screen
- Syphilis (RPR)
- Human immunodeficiency virus
- Cerebrospinal fluid examination
- Genotyping
Imaging Studies

- Generally unremarkable
- Diffuse cortical atrophy is expected
- Head CT or MRI is a MUST
  - rule out other CNS disease
- Functional imaging reserved for atypical presentations
  - Positron emission tomography

MRI Brain: Normal vs. AD
### Medical Treatment

#### Acetylcholinesterase Inhibitors
- Donepezil (Aricept™)
- Rivastigmine (Exelon™)
- Galantamine (Razadyne™)

#### NMDA Antagonist
- Memantine (Namenda™)

<table>
<thead>
<tr>
<th>MOA</th>
<th>Cholinesterase Inhibitors</th>
<th>NMDA-Receptor Antagonist</th>
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<tbody>
<tr>
<td>Drug</td>
<td>Donepezil</td>
<td>Galantamine</td>
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<tr>
<td>Indication</td>
<td>Mild-moderate AD; severe AD</td>
<td>Mild-moderate AD</td>
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<tr>
<td>Initial dose</td>
<td>Tablet: 5 mg qd</td>
<td>Tablet/oral solution: 4 mg bid ER capsule: 8 mg qd</td>
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<tr>
<td>Maximal dose</td>
<td>Tablet: 10 mg qd 23mg (mod-sec)</td>
<td>Tablet/oral solution: 12 mg bid ER capsule: 16 or 24 mg qd</td>
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ER = extended-release; MOA = mechanism of action; NMDA = N-methyl-D-aspartate.

Participation in Clinical Trials
- Potential access to novel therapies
- Randomization to study drug vs placebo
- Close (and free) medical care during study

Categories of Investigational Therapies
- Symptomatic therapies
- Disease-modifying therapies
  - Amyloid-based interventions
    - Immunotherapy
    - Secretase inhibitors/modulators
    - Anti-aggregants
  - Tau-based interventions
- Neuroprotectants

Agitation and Psychosis
- No FDA approved drugs
- Anti-psychotic drugs
  - Widely used
  - Use lower doses
  - Modest efficacy
    - 1 in 5 shows symptomatic benefit
- Atypical antipsychotics preferred
  - Less likely to produce extrapyramidal syndromes
  - 17x increased death rate (meta-analysis)
- Avoid/limit benzos
Atypical Antipsychotics

Quetiapine
Olanzapine
Risperidone

Depression

- Clinical trial data conflicting
- Consensus statements emphasize SSRIs
- Use low doses
- Titrate based on response and side effects
- Avoid TCAs - anticholinergic properties

Anti-Depressants

SSRIs:
- Citalopram
- Fluoxetine
- Escitalopram
- Sertaline

Others:
- Mirtazapine
- Venlafaxine
- Bupropion
Insomnia

- Sleep hygiene
- No data
- Suggested meds:
  - Trazodone 25-100mg QHS
  - Mirtazapine 15mg QHS
  - Zolpidem 5-10mg QHS
- Benzos not recommended
- Diphenhydramine not recommended

Questions?