Best Practices in the Diagnosis and Treatment of Alzheimer’s Disease

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Disclosures

Grants:
  National Institute of Health/National Institute of Aging
  Alzheimer’s Association
Course Objectives

• The diagnosis of MCI and Alzheimer’s disease (AD): A clinician’s perspective
  • Approach to clinical evaluation and diagnosis
  • Diagnostic changes and conceptualization
    • Definition of clinical stages of the AD continuum

• Modifiable Risk Factors for AD
  • Lifestyle variables and health history factors

• Treatment Options for AD
Alzheimer’s Disease

DIAGNOSIS
Case History, Ms. A.D.

- **51 year-old woman with progressive memory impairment**
  - Also suffers from delusions, periods of agitation and poor sleep, hoarding behavior

- **On neurologic examination**
  - Disoriented to time and place
  - Extremely poor memory for personal events
  - Responses are tangential and at times incoherent
  - Repeatedly mutters “I have lost myself”
Alzheimer’s Disease (AD)

- Described by Alois Alzheimer in 1906
- Presenile dementia with amnesia and psychosis
- Microscopic level
  - Amyloid plaque
  - Neurofibrillary tangle
Alzheimer’s Disease (AD)

Amyloid plaques
• Made of amyloid-β (Aβ)

Neurofibrillary tangles
• Made of tau
AD is an Impending Public Health Crisis

- **5.6 million** Americans have AD
- By 2025 this number will reach over **7 million**
- A treatment that would delay disease onset by 5 years would reduce costs by **57%**

Source: [www.alz.org](http://www.alz.org)
The Forgetful Veteran

• 70 year-old right-handed veteran with diabetes, high cholesterol
  • “My memory is terrible”
• Wife notes that in last 12 months…
  • Forgets conversations, TV programs
  • Repeats questions, stories
  • Memory for remote events spared
  • More quiet in social settings
  • Last month lost on the way home from endocrine appointment in SF
Approach to Patient with Cognitive Complaints

- HPI probes cognitive domains
  - **Memory**: misplacing items, repetitive, missing appointments, failing to pay bills
  - **Visuospatial**: getting lost, driving, recognizing faces
  - **Language**: production and comprehension, reading and writing
  - **Executive**: decision-making, judgment, multi-tasking
  - **Behavior**: personality changes, depression, apathy, disinhibition, psychosis
  - **Motor**: change in gait, falls, tremor, weakness

- **Cognitive testing better defines which domains are affected/spared**

- **Labs and structural imaging exclude treatable causes**
<table>
<thead>
<tr>
<th>Normal Aging</th>
<th>Mild Cognitive Impairment</th>
<th>Alzheimer’s Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decline with age:</strong></td>
<td>• Decline in memory or other cognitive functions</td>
<td>• Decline in memory or other cognitive function</td>
</tr>
<tr>
<td>• Processing speed</td>
<td>• Beyond what is expected for age</td>
<td>• Beyond what is expected for age</td>
</tr>
<tr>
<td>• Executive function</td>
<td>• Does not interfere with daily function</td>
<td>• Interferes with daily function</td>
</tr>
<tr>
<td>• Naming</td>
<td>• Multiple causes</td>
<td></td>
</tr>
<tr>
<td>• Memory</td>
<td>• May or may not progress to AD</td>
<td></td>
</tr>
<tr>
<td><strong>Improve with age:</strong></td>
<td>• Vocabulary</td>
<td></td>
</tr>
<tr>
<td>• General knowledge</td>
<td>• General knowledge</td>
<td></td>
</tr>
<tr>
<td>• Wisdom</td>
<td>• Multiple causes</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Evolution of AD
From Clinical Syndrome to Pathology

- Aβ
- Tau
- TDP-43
- α-synuclein
Cortical Atrophy in AD

Temporoparietal cortex
• Memory
• Language (left)
• Math, tool manipulation (left)
• Navigation, spatial reasoning (right)

Lateral frontal cortex
• Executive function

Medial frontal cortex spared
• Behavior, social function

Boxer et al., Arch Neurol 2003
Hippocampal Atrophy in AD

Blennoow et al., Lancet 2006
Biomarkers: Detecting AD Pathology in Cerebrospinal Fluid

- **CSF changes in AD**
  - Decrease in $A\beta_{1-42}$
  - Increase in total and phosphorylated tau
- **CSF Tau/$A\beta_{1-42}$ ratio**
  - 85% accurate in discriminating path-confirmed AD from controls (Shaw et al. *Ann Neurol* 2009)
  - Predicts conversion MCI-$\rightarrow$AD
Biomarkers:
Brain Hypometabolism in AD (FDG-PET)

Courtesy of William Jagust
Biomarkers: Imaging Amyloid Plaques (PIB-PET)

Amyloid plaques

Pittsburgh Compound B (PIB)

Rabinovici and Jagust
Biomarkers:
Imaging Amyloid Plaques (PIB-PET)

Clark, C. M. et al. JAMA 2011;305:275-283
Biomarkers:
PIB in Normal Elderly Correlates with Hippocampal and Cortical Atrophy

• Mormino et al., *Brain* 2009

• Oh et al., *Neuroimage* 2010
Model for Biomarker Cascade in AD

Jack et al., Lancet Neurology 2010
Introduction to the recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease

Clifford R. Jack Jr.\textsuperscript{a, *}, Marilyn S. Albert\textsuperscript{b}, David S. Knopman\textsuperscript{a}, Guy M. McKhann\textsuperscript{b}, Reisa A. Sperling\textsuperscript{c}, Maria C. Carrillo\textsuperscript{d}, Bill Thies\textsuperscript{d}, Creighton H. Phelps\textsuperscript{e}

Alzheimer’s & Dementia 7 (2011) 257–262

**Preclinical AD**

- $\text{A}\beta$ deposition
- CSF $\text{A}\beta_{42}$
- Amyloid PET

**MCI-AD**

- Neuronal Injury
- CSF Tau
- CSF $\text{p-Tau}$
- FDG PET

**AD Dementia**

- Cognition/Function
- Structural MRI
- Cognitive Test Performance
<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Biomarker Probability of AD Etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Markers of Neuronal Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI- Core Clinical Criteria</td>
<td>Uninformative</td>
<td>Conflicting/Untested</td>
<td>Conflicting/Untested</td>
</tr>
<tr>
<td>MCI due to AD- Intermediate Likelihood</td>
<td>Intermediate</td>
<td>Option 1: Positive</td>
<td>Option 1: Untested</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Option 2: Untested</td>
<td>Option 2: Positive</td>
</tr>
<tr>
<td>MCI due to AD- High Likelihood</td>
<td>Highest</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>MCI- Unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Case: At a Loss for Words

- 57 year-old practicing internist with 2 years of progressive word-finding difficulties
  - Struggles to come up with words that should be familiar. Results in reported embarrassment, both socially and professionally
  - Feels less efficient at accomplishing tasks
  - No other cognitive or physical symptoms
  - Has not impacted daily function
Case: At a Loss for Words

• General physical and neurological exams
  – Normal

• Global Cognition:
  – MMSE 30/30

• Language Testing:
  – Fluent speech with occasional pauses
  – Poor repetition
  – Mild difficulties with naming (Boston Naming Test: 12/15)
  – Comprehension/reading/writing intact

• Other Cognitive Domains:
  – Average to high average (including memory)
Case: At a Loss for Words
At a Loss for Words: Labs and Structural Imaging

- Basic laboratory work-up normal
- MRI: “age-appropriate global volume loss, mild periventricular white matter changes”
- Questions for the neurologist:
  - Is this normal aging?
  - If not, what is the diagnosis?
    - I’m worried about Alzheimer’s but my memory is fine
  - Can I keep working and if so for how long?
  - Should I take Aricept?
Case: At a Loss for Words: PET Results

- **Diagnosis:** MCI due to AD
- **Treatment**
  - Cholinesterase inhibitor
  - Referral to anti-Aβ clinical trial
### Diagnostic Category

<table>
<thead>
<tr>
<th>Probable AD Dementia</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Based on clinical criteria</strong></td>
<td>Uninformative</td>
<td>Unavailable/Conflicting</td>
<td>Unavailable/Conflicting</td>
</tr>
<tr>
<td>+pathophysiology</td>
<td>Intermediate Intermediate High</td>
<td>Unavailable/Ind. Positive</td>
<td>Positive Unavailable/Ind. Positive</td>
</tr>
</tbody>
</table>

### Possible AD Dementia (Atypical presentation)

<table>
<thead>
<tr>
<th>Based on clinical criteria</th>
<th>Uninformative</th>
<th>Unavailable/Conflicting</th>
<th>Unavailable/Conflicting</th>
</tr>
</thead>
<tbody>
<tr>
<td>+pathophysiology</td>
<td>High, doesn’t rule out 2nd etiology</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>
Redefining AD in 2011

- **NINCDS-ADRDA (1984)**
  - Must meet criteria for dementia
  - Memory loss required
  - No support from genetics, imaging, biomarkers

- **NIA-AA (2011)**
  - Prodromal AD
    - (+) biomarker with minimal or no symptoms
  - Can support diagnosis of AD even at MCI stage with biomarkers/genetics
  - Allow for non-memory presentations
#### Toward defining the preclinical stages of Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease

Reisa A. Sperling\(^{a,*}\), Paul S. Aisen\(^{b}\), Laurel A. Beckett\(^{c}\), David A. Bennett\(^{d}\), Suzanne Craft\(^{e}\), Anne M. Fagan\(^{f}\), Takeshi Iwatsubo\(^{g}\), Clifford R. Jack, Jr.\(^{h}\), Jeffrey Kaye\(^{i}\), Thomas J. Montine\(^{j}\), Denise C. Park\(^{k}\), Eric M. Reiman\(^{l}\), Christopher C. Rowe\(^{m}\), Eric Siemers\(^{n}\), Yaakov Stern\(^{o}\), Kristine Yaffe\(^{p}\), Maria C. Carrillo\(^{q}\), Bill Thies\(^{q}\), Marcelle Morrison-Bogorad\(^{f}\), Molly V. Wagster\(^{r}\), Creighton H. Phelps\(^{f}\)

*Alzheimer’s & Dementia 7 (2011) 280–292*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Aβ (PET or CSF)</th>
<th>Markers of Neuronal Injury</th>
<th>Evidence of Subtle Cognitive Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Asymptomatic cerebral amyloidosis</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Asymptomatic amyloidosis + “downstream” neurodegeneration</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Amyloidosis + neuronal injury + subtle cognitive/behavioral decline</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>
Longitudinal Conversion from Preclinical to MCI, NIA-AA Criteria

Alzheimer’s Disease

MODIFIABLE RISK FACTORS
Modifiable Risk Factors and AD Clinical Presentation

“Brain Pathology”
Under the Microscope

“Clinical Manifestation”
Face-Face Presentation

Alzheimer’s Disease
Dementia

Clinically Normal,
No Dementia

*Image courtesy of William Seeley & Stephen DeArmond*
AD Risk Factors

**Increase risk**
- **Age**
  - Prevalence:
    - 1% age 60-64
    - 35-40% over age 85
- **Female sex**
- **Head trauma**
- **Reduced mental/physical activity**
- **Vascular risk factors**
- **Genetics – ApoE4 & more**
  - Family history – 4x risk if first degree relative

**Decrease risk**
- **Higher Education**
- **A little alcohol**
- **Increased mental/physical activity**
- **Heart-healthy diet**
  - Mediterranean
- **Genetics – ApoE2**
Physical Exercise and BDNF

Cotman, C.W. et al. Alzheimer’s and Dementia. 2007. 3(2), S30-S37.

•Figure: Voluntary exercise induces BDNF.
Physical Exercise and the Hippocampus

• Erickson et al, 2011. PNAS, 108, 3017-322
Modifiable Risk Factors: Vascular Risk Factors Negatively Impact Aging

- **Metabolic Syndrome** -
  - Diabetes, visceral obesity, dyslipidemia, hypertension, prothrombotic and proinflammatory state

- **Cerebrovascular Disease and Vascular Brain Injury (VBI)** -
  - Most common forms of late life cerebrovascular disease (CVD): atherosclerosis, arteriolosclerosis, and cerebral amyloid angiopathy
  - Associated with lacunes, microinfarcts, AD pathology

- **Double hit hypotheses in Alzheimer’s disease**
Modifiable Risk Factors: High Levels of Inflammation Impact Memory

Learning vs Delayed Recall by CRP Group

- Undetectable CRP
- Detectable CRP

\( p = .01 \)

Bettcher et al, 2012; Brain, Behavior, & Immunity
Alzheimer’s Disease

TREATMENT OPTIONS
Millions of people with Alzheimer’s in the US

Cost to society in $ billions

Delay onset by 2 years

Delay onset by 5 years
Medications Typically Used for AD

• **Cholinesterase inhibitors**
  – Donepezil
  – Rivastigmine
  – Galantamine

• **NMDA-receptor antagonists**
  – Memantine

• **Psychiatric medications**
Current AD Therapy: Acetyl-Cholinesterase Inhibitors

- Ach-producing neurons lost early in AD
- Inhibition of Ach-E increases synaptic Ach
- Effective in mild to severe AD
  - Donepezil (Aricept)
  - Rivastigmine (Exelon)
  - Galantamine (Razadyne)
AD Treatments – Psychiatric Symptoms

- Cholinesterase inhibitors
- Memantine for agitation in moderate-severe
- SSRI/SNRI for depression
- Atypical neuroleptics
  - FDA black box warning due to increased mortality in multiple trials
  - Prefer quetiapine (Seroquel)
- Avoid typical neuroleptics, benzodiazepines
Failure of Amyloid Therapies: Wrong Target or Too Late?

- Amyloid-PET
- CSF Aβ
- CSF Tau
- FDG-PET
- MRI
- Atrophy
- Cognitive symptoms
- Functional decline

• Jack et al., Lancet Neurol 2010
Future Directions: Preventive Anti-Aβ Treatment

• Dominantly Inherited Alzheimer’s Network (DIAN), Alzheimer’s Prevention Initiative (API)
  • Registry of AD mutation carriers for longitudinal biomarker studies and preventive trials
  • Crenezumab trial

• Anti-Amyloid treatment in Asymptomatic AD (A4)
  • Asymptomatic individuals over age 70 with positive amyloid PET
  • First trial (solanezumab) in preparation
Future Directions

- **Anti-Tau Therapy**
  - Inhibit tau phosphorylation
    - GSK-3\(\beta\) (lithium), CDK5
  - Inhibit tau aggregation (methylene blue)
  - Immunotherapy
  - Microtubule stabilizing drugs (daveunitide)

- **ApoE modifying therapy**
  - Bexarotene (enhances ApoE production)

- **Network stabilization**
  - Levetiracetam (anti-epileptic)

- **Metabolic approaches**