Approach to Memory Loss: Screening

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Definition of Dementia and Mild Cognitive Impairment (MCI)

**Disclosures**

**Research Support**
1. National Institutes of Health – NIA
2. Alzheimer's Disease Cooperative Study

**Objective:**

1) Review definitions of Mild Cognitive Impairment and dementia
2) Review cognitive assessment and screening instruments for Mild Cognitive Impairment and early dementia

**Speakers Bureau**

Forest

**Clinical Trials**

Pfizer, Janssen
Alzheimer Immunotherapy, Bristol Meyers Squibb, Phylogeny

**Consultant**

Lilly

I own no stocks or equity in any pharmaceutical company

Normal

Mild Cognitive Impairment

Dementia
Dementia Definition

- Syndrome of acquired persistent intellectual impairment
- Persistent deficits in at least two of the following:
  - memory
  - language
  - visuospatial
  - personality or emotional state
  - cognition
- Resulting in impairment in Activities of Daily Living (ADL)

Mild Cognitive Impairment (MCI) Definition

- Memory complaint usually corroborated by an informant
- Objective memory impairment for age - that represents a change in function for the person
- Essentially preserved general cognitive function
- Largely intact functional activities
- Not demented

Cognitive Assessment and Screening

We can use cognitive assessment and screening to help identify MCI and early dementia cases

- CSF Biomarkers and neuroimaging are too expensive or invasive for screening but could be used for high risk patients or those demonstrating cognitive impairments
- Cognitive biomarkers with good specificity and sensitivity need to be validated

Petersen J Int Med 2004;256:183-194
### Importance of Early Diagnosis of MCI and Dementia

- Amyloid plaques possibly start 15 to 20 years before clinical symptoms of AD
- Over 100 million worldwide projected to have AD by 2050
- Current AD patients progress slower if medications are started earlier
- Disease modifying agents are coming
- Preventing or delaying AD could save billions of dollars and lead to improved quality of life for patients and families

### Barriers to Early Diagnosis of MCI and Dementia

- Patients with MCI and early dementia have impaired insight
- First present to the doctor an average of 3.5 years after cognitive symptoms start
- Physicians may not notice subtle cognitive deficits in routine office visits
- Little reimbursement for cognitive screens
- Often too much time or personnel resources required to administer testing

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Examples of Brief Cognitive Assessment/Screening Tests

- MMSE
- Mini-Cog
- AD8
- Montreal Cognitive Assessment (MOCA)
- St. Louis University Mental Status Examination (SLUMS)
- Self-Administered Gerocognitive Examination (SAGE)

MMSE

- Score: 0 (worst) - 30 (best)
- Tests orientation, attention, mental control, calculations, delayed memory (no clueing), language, and constructional praxis
- Easy to use, well known
- Not great for frontal or executive functions
- Sensitivity 78% and specificity 84% for dementia with a cutoff of 26/30
- Takes 7 to 10 minutes; needs examiner
- PAR bought rights – costs $1.23 per use
Mini-Cog

- 3-item recall and clock drawing
- Easy to use
- Limited in evaluating other cognitive domains
- Sensitivity 76% and specificity of 89% for dementia
- Score not influenced by language or education
- Takes 3 minutes; needs examiner

Borson S et al. JAGS 2003;51:1451-1454

AD8

Borson S et al. JAGS 2003;51:1451-1454

Galvin et al. Neurology 2006;67:1042-1048

Figure 1. The Mini-Cog scoring algorithm. The Mini-Cog uses a three-item recall test for memory and the intuitive clock-drawing test. The latter serves as an “informative distractor,” helping to clarify scores when the memory recall score is intermediate.
AD8

- Score: 0 (best) - 8 (worst)
- Informant rates changes in the patient's judgment, interests, memory, functioning, and orientation
- Easy to use
- Does not measure patient cognition directly
- Sensitivity 84% and specificity 80% for dementia with a cutoff of 2 or greater
- Takes 3 minutes; needs examiner and informant


Montreal Cognitive Assessment (MOCA)

- Score: 0 (worst) - 30 (best)
- Tests orientation, memory, clock drawing, constructions, verbal fluency, naming, repetition, attention, abstraction, calculations, executive (trails B)
- Not easy to give in primary care office
- Sensitivity 100% and specificity 87% for dementia vs normal controls with a cutoff of 25/30
- Cannot distinguish between MCI and dementia
- Takes 10-13 minutes; needs examiner


MOCA

St. Louis University Mental Status (SLUMS)

- Score: 0 (worst) - 30 (best)
- Tests orientation, memory, clock drawing, constructions, verbal fluency, naming, repetition, attention, abstraction, calculations, executive (trails B)
- Not easy to give in primary care office
- Sensitivity 100% and specificity 87% for dementia vs normal controls with a cutoff of 25/30
- Cannot distinguish between MCI and dementia
- Takes 10-13 minutes; needs examiner

St. Louis University Mental Status (SLUMS)

- Score: 0 (worst) - 30 (best)
- Tests orientation, memory, calculations, verbal fluency, mental control, clock drawing, visuospatial, and comprehension skills
- Not easy to give in primary care office
- SLUMS and MMSE had comparable sensitivities and specificities for dementia but improved receiver operator curves (ROC) for mild cognitive impairment.
- Takes 10-13 minutes; needs examiner

Self-Administered Gerocognitive Exam (SAGE)
sagetest.osu.edu

- Cognitive assessment instrument
- Brief: ≈ 10-15 minutes with pen and paper
- Unique: Self-administered
- Not requiring office personnel time or special equipment
- Designed to detect cognitive impairment including MCI and early dementia
SAGE

- SAGE download: sagetest.osu.edu
- Score range: 0-22
- Orientation: month, date, year (4 points)
- Language: picture naming (2 points) and verbal fluency (2 points)
- Calculations: (2 points)
- Memory: (2 points)
- Abstraction: (2 points)
- Executive: modified Trails B (2 points) and problem solving task (2 points)
- Visuospatial: copying 3-dimensional constructions (2 points) and clock draw (2 points)

SAGE and MMSE

Spearman rank correlations to Specific Neuropsychological Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>N = 61</th>
<th>HVLT Learning</th>
<th>Retention</th>
<th>WCSTPE</th>
<th>FAS</th>
<th>Boston</th>
<th>Let-Num</th>
<th>Blk-Des</th>
<th>Sum 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAGE</td>
<td>0.66</td>
<td>0.55</td>
<td>0.51</td>
<td>0.52</td>
<td>0.63</td>
<td>0.57</td>
<td>0.37</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>0.67</td>
<td>0.61</td>
<td>0.35</td>
<td>0.39</td>
<td>0.52</td>
<td>0.68</td>
<td>0.33</td>
<td>0.76</td>
<td></td>
</tr>
</tbody>
</table>

HVLT: Hopkins Verbal Learning Test; WCSTPE: Wisconsin Card Sort Test Perseverative Errors; Let-Num: Letter-Number subtest of WAIS III; Blk-Des: Block Design subtest of the WAIS III; Sum 7: Total summed score of the 7 neuropsychological tests
**SAGE: Validity Against Neuropsychologic Tests**

- **Regression Equation:** 
  \[ y = 13.4b + 107.26 \] 
  \[ R^2 = 0.666 \]

- **ROC for SAGE: Differentiating Normal vs Cognitive Impaired**
  - Area under curve for SAGE = 0.92 (0.80 for MMSE)

  - **SAGE Specificity** is 95% (90% for MMSE) and **sensitivity** is 79% (71% for MMSE)

**Sum 7, SAGE and MMSE scores: Normal, MCI, and Dementia**

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=21)</th>
<th>MCI (n=21)</th>
<th>Dementia (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sum 7</strong></td>
<td>381 ± 45 (478–292)</td>
<td>318 ± 31 (371–272)</td>
<td>238 ± 52 (333–152)</td>
</tr>
<tr>
<td><strong>SAGE</strong></td>
<td>Mean ± SD (Range)</td>
<td>Median ± SD (Range)</td>
<td>Median ± SD (Range)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>19.8 ± 2.0 (22–15)</td>
<td>16.0 ± 2.2 (21–9)</td>
<td>11.4 ± 3.9 (17–4)</td>
</tr>
<tr>
<td>MMSE max = 30</td>
<td>28.7 ± 1.1 (30–26)</td>
<td>27.7 ± 2.2 (30–23)</td>
<td>22.1 ± 3.5 (28–16)</td>
</tr>
</tbody>
</table>

**Age Effect on SAGE Score**

- **One point should be added to those age ≥ 80.**
**Education Effect on SAGE Score**

- SAGE test may be hard to interpret in those with under 12th grade education.
- One point should be added for those with 12 years or less of education.

**SAGE /MMSE Score Changes over time in Worried Well /MCI /Converter /AD**

- N = 186

**Annual Percentage Change of SAGE (max=22) /MMSE (max=30) in Worried Well /MCI /Converter /AD**

**SAGE Scores**

- 17-22: Very likely to be normal; no further evaluation
- 15-16: Likely to have MCI; staged screening evaluation recommended
- 0-14: Likely to have a dementia condition; staged screening evaluation recommended
Staged Screening

Staged Screening Approach

- Age over 65?
  - Yes: Screen if concerns
  - No: SAGE Test

- <17
  - SAGE Test
  - Schedule appointment with patient and informant

- AD8 > 1
  - MOCA < 26
    - Consider dementia evaluation

- AD8 < 2
  - MOCA > 25
    - Re-screen in 1 year or consider neuropsychological testing

- Age over 80?
  - Yes: Re-screen yearly
  - No: Re-screen in 2 years


Summary

- Mild Cognitive Impairment can be detected and differentiated from dementia
- Mental status examinations help to identify potential etiologies
- Cognitive assessment and screening instruments can be used to identify early cognitive problems
- Cognitive screening with a staged approach should be done
Approach to the Patient with Memory Loss: An Update

Maria Kataki, MD, PhD
Assistant Professor of Neurology
Division of Cognitive Neurology
The Ohio State University Wexner Medical Center

Overview

- Challenges in the knowledge
- Updated diagnostic criteria for preclinical stages of Alzheimer's Disease
- Updated diagnostic criteria for Mild Cognitive Impairment
- Updated diagnostic criteria for Alzheimer's Disease
- Standard of care recommendations for evaluation and treatment of Alzheimer's disease.

Historical Data...

On a Peculiar Disease of the Cerebral Cortex;
A. Alzheimer (1907)

A woman, 51 years old, showed jealousy towards her husband... Soon, rapidly increasing loss of memory could be noticed... At times she would think that someone wanted to kill her...
She was totally disoriented to time and place...
Periodically, she was totally delirious...and seemed to have auditory hallucinations....
When reading, she went from one line into another, reading the letters or reading with senseless emphasis...
When talking she frequently used perplexing phrases and some paraphasic expressions (milk-pourer instead of cup)...
She seemed no longer to understand the use of some objects...
The generalized dementia progressed... After 4 1/2 years of the disease, death occurred.

Frequency of Stages of Alzheimer-Related Lesions in Different Age Categories

H Braak et al. Neurobiology of Aging, vol 18, No 4, pp 351-357, 1997
Revision of clinical criteria

- Lack of knowledge of distinguishing features of other dementing conditions
- Dementia with Lewy Bodies
- Vascular dementia
- Behavioral variant frontotemporal dementia
- Primary progressive aphasia


Revision of clinical criteria

- Proposed age cutoffs for the diagnosis of AD dementia.
- AD dementia in those aged <40 and >90 years is part of that same spectrum.
- Extreme heterogeneity of the "Possible" AD dementia category including a group of patients that would now be diagnosed as "Mild Cognitive Impairment"


Revision of clinical criteria

- No inclusion of results of Magnetic Resonance Imaging, Positron Emission Tomography (PET), and cerebrospinal fluid assays (CSF) (biomarkers)
- The implication that memory impairment is always the primary cognitive deficit in all patients with AD dementia
- Several non amnestic presentations of the pathopsysiological process


The continuum of Alzheimer's disease

Cognitive function

Preclinical

Aging

MCI

Dementia

Years


Hypothetical model of dynamic Biomarkers of the AD


Elevated CSF tau and low Ap42 is 95% specific and 60% sensitive for AD Mutter et al. Ann Neurol 1995;38:643-48

Jagust W. et al., ADNI-GO PET Core Team, 2011
FDG PET Neuroimaging

PET shows hypometabolism in bilateral parietal, temporal, and posterior cingulate cortex in AD subjects and in those who are asymptomatic but at increased risk for AD (those with Apo E 4).

Image provided courtesy of M. Mega, MD, PhD, Department of Neurology, UCLA School of Medicine.

Normal Brain

AD Brain

Summary of clinical and cognitive evaluation for MCI due to AD

- Memory complaint, preferably corroborated by an informant
- Objective memory impairment
- Normal general cognitive function
- Intact activities of daily living
- Not demented
- Examine etiology of MCI consistent with AD pathophysiological process.
- Rule out vascular, traumatic, medical causes of cognitive decline, where possible
- Provide evidence of longitudinal decline in cognition, when feasible.
- Report history consistent with AD genetic factors, where relevant.


Staging categories for preclinical AD research

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Aβ(PET or CSF)</th>
<th>Markers of neuronal injury (tau, FDG, sMRI)</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 +<em>downstream</em> 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>


Biomarkers under examination for AD

- Biomarkers of αβ deposition
  - CSF αβ42
  - PET amyloid imaging
- Biomarkers of neuronal injury
  - CSF tau/phosphorylated-tau
  - Hippocampal volume or medial temporal atrophy by volumetric measures or visual Rating.
- Rate of brain atrophy
- FDG-PET imaging
- SPECT perfusion imaging

### MCI criteria incorporating biomarkers

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarkers probability of AD etiology</th>
<th>Aβ(PET or CSF)</th>
<th>Neuronal injury (tau, FDG, sMRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC1-core clinical criteria</td>
<td>Uniformative</td>
<td>Conflicting/indeterminate/untested</td>
<td>Conflicting/indeterminate/untested</td>
</tr>
<tr>
<td>MCI due to AD-intermediate likelihood</td>
<td>Intermediate</td>
<td>Positive</td>
<td>Untested</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>


### Core Clinical Criteria Dementia

- The cognitive or behavioral impairment involves a minimum of two of the following domains:
- Impaired ability to acquire and remember new information-symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.


### Core Clinical Criteria Dementia

- Cognitive impairment is detected and diagnosed through a combination of:
  1. (1) history-taking from the patient and a knowledgeable informant and
  2. (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing.
- Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.


### Core Clinical Criteria Dementia

- Impaired reasoning and handling of complex tasks, poor judgment-symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
- Impaired visuospatial abilities-symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements or orient clothing to the body.

Core Clinical Criteria

Dementia

- Impaired language functions (speaking, reading, writing) - symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling and writing errors.
- Changes in personality, behavior, or comportment - symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive, or obsessive behaviors, socially unacceptable behaviors.


Core Clinical Criteria

- Probable AD is diagnosed when:
- Dementia
- Insidious onset
- Clear-cut history of worsening of cognition by report or observation and
- The initial and most prominent cognitive deficits are evident by history and examination in one of the following:
  - Amnestic presentations
  - Non Amnestic presentations (Language, Visuospatial presentation, executive dysfunction)


AD dementia incorporating biomarkers

<table>
<thead>
<tr>
<th>Diagnostic accuracy</th>
<th>Biomarker probability of AD etiology</th>
<th>AP(PET or CSF)</th>
<th>Neuronal injury (tau, FDG, structural MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD Dementia based on clinical criteria</td>
<td>Uninformative</td>
<td>Unavailable, conflicting, or indeterminate</td>
<td>Unavailable, conflicting, or indeterminate</td>
</tr>
<tr>
<td>With three levels of evidence of AD pathophysiological process</td>
<td>High</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Possible AD dementia (atypical clinical presentation) Based on clinical criteria</td>
<td>Uninformative</td>
<td>Unavailable, conflicting, or indeterminate</td>
<td>Unavailable, conflicting, or indeterminate</td>
</tr>
<tr>
<td>With evidence of AD pathophysiological process</td>
<td>High but does not rule out second etiology</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Dementia-unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Criteria for all cause dementia:
Core clinical criteria

- The core clinical criteria provide very good diagnostic accuracy and utility in most patients
- Biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process.

Pharmacologic treatment of AD

Practice recommendations
- Cholinesterase inhibitors (Standard), small average degree of benefit.
- Vitamin E (1000 I.U. PO BID) - slows progression of AD (Guideline).
- Selegiline (5 mg PO BID) - less favorable risk–benefit ratio (Practice Option). Doody et al, Neurology 56(9) May 8, 2001

Practice Recommendations
- Structural neuroimaging (Guideline).
- Depression (Guideline).
- B12 deficiency (Guideline).
- Hypothyroidism (Guideline).

Pharmacologic treatment of AD

- There is insufficient evidence
  - Antioxidants (Practice Option)
  - anti-inflammatories (Practice Option).
- Estrogen should not be prescribed (Standard).

Doody et al, Neurology 56(9) May 8, 2001
Conclusions

• Early diagnosis and treatment
• Early recognition of patients at high risk for developing AD will be extremely important for purposes of prevention.
• Reducing the mean age at onset of AD by 5 years will reduce the number of patients with AD dementia by 57% and will reduce the projected Medicare costs of AD from $627 to $344 billion dollars. (Hypothetical intervention).