Mild Cognitive Impairment

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Outline of Presentation

• Clinical Context
• Definition and Classification of MCI
• Epidemiology of MCI
• Neuropsychiatry of MCI
• Biomarkers of MCI
• Lifestyle factors and MCI
• Conclusion & Acknowledgement
Clinical Context
Clinical context

- 77 years old, otherwise healthy male patient presents with a complaint of forgetfulness for recent events and future engagements. These symptoms were of insidious onset and gradual progression.
- Otherwise functions independently, including driving car, reading books, socializing and other daily routines.
- Denies being depressed or going through a major stressor. Denies excessive alcohol consumption. He has no history of traumatic brain injury.
- Bed side cognitive screening (MMSE) was normal except for 0 out of 3 on recall item.
- Physical examination is essentially normal.
- Lab tests were also normal including normal sTSH, B12 and folate level.

→ What is your clinical impression? What critical test would you order to clarify diagnosis? What additional test/s would you consider?
Volumetric MRI in MCI and Alzheimer’s Disease

70 y/o NORMAL  
72 y/o MCI  
74 y/o AD
Definition and Classification of MCI
Research Agenda of the Field of Aging and Dementia

- 1980s: Mainly preoccupied with the investigation of dementia (DSM-III-R, NINDS criteria)
- 1990s: Field increasingly preoccupied with identification of high risk states for dementia
- Recently: Emphasis on identification of presymptomatic phase of neurodegenerative disease such as AD (Dubois 2004; International expert group 2007; Alzheimer’s Association and National Institute on Aging 2011)
- Various terms were used to describe the grey zone between normal aging and dementia
Boundary conditions

Normal Aging

- Benign senescent forgetfulness (Kral 1962)
- Age-associated memory impairment (Crook et al. 1986)
- Age consistent memory impairment (LaRue et al. 1989)
- Age-associated cognitive decline (Levy 1994)

Abnormal State

- Malignant senescent forgetfulness (Kral 1962)
- Late-life forgetfulness (Blackford et al. 1989)
- Questionable dementia (Hughes et al. 1982; Devanand 1997)
- Mild cognitive impairment (Flicker et al. 1991; Petersen et al. 1999)
- Mild neurocognitive disorder (APA 1994; DSM-IV; DSM 5)
Cognitive Continuum

Normal

Mild Cognitive Impairment

Alzheimer's Dementia
Mild Cognitive Impairment Criteria

- Cognitive / Memory Complaint
- Normal General Cognitive Function
- Normal Activities of Daily Living
- Memory or other Cognitive Domains Impaired for Age and Education
- Not Demented

Petersen, 1999, 2004
Publications on MCI by year
NIA-AA Criteria:
Diagnosis of MCI due to AD

Core Clinical Criteria: designed to be used in all clinical settings

1) **Cognitive concern** reflecting a change in cognition reported by patient or informant or clinician

2) Objective evidence of **impairment in one or more cognitive domains**, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)

3) Preservation of **independence in functional abilities**

4) **Not demented**

**Examine etiology of MCI** (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)

# NIA-AA Criteria: Diagnosis of MCI due to AD

Clinical Research Criteria intended to be used only in research settings

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (tau, FDG, sMRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI—core clinical criteria</td>
<td>Uninformative</td>
<td>Conflicting/indeterminant/untested</td>
<td>Conflicting/indeterminant/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>Untested</td>
<td>Positive</td>
</tr>
<tr>
<td>MCI—unlikely due to AD</td>
<td>Lowest</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.

## MCI Subtypes

<table>
<thead>
<tr>
<th>Clinical classification</th>
<th>Etiology</th>
<th>Degenerative</th>
<th>Vascular</th>
<th>Psychiatric</th>
<th>Trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amnestic MCI</strong></td>
<td></td>
<td>AD</td>
<td></td>
<td>Depr</td>
<td></td>
</tr>
<tr>
<td>Single domain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple domain</td>
<td></td>
<td>AD</td>
<td></td>
<td>Depr</td>
<td></td>
</tr>
<tr>
<td><strong>Non-amnestic MCI</strong></td>
<td></td>
<td>FTD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single domain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple domain</td>
<td></td>
<td>DLB</td>
<td>VaD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MCI Cognitive Domains

- **MEMORY:**
  - Logical Memory II
  - Visual Reprod II

- **ATTENTION:**
  - TMT B
  - Digit Symbol Sub

- **LANGUAGE:**
  - Boston Naming Test
  - Letter Fluency

- **VISUOSPATIAL:**
  - Block Design
  - Picture Completion
Epidemiology of MCI
MCI Prevalence

- Population-based study estimated the prevalence of MCI in 6,921 subjects (mean age 71.6) to be at 6% (Moretti, Aging Ment Health, 2013)

- MCI prevalence estimates range from 3% to 22% per year

- The variability is due to sampling and measurement bias
Population-Based Prevalence of MCI and Dementia

- Normal cognition: 73.6%
- MCI: 16.5%
- Dementia: 9.9%
- Amnestic: 11.6%
- Non-amnestic: 4.9%

Estimates of MCI and dementia are age- and sex-adjusted to the Olmsted County, MN, population.
Incidence of MCI (Continued)

• The incidence of MCI ranged between 51 and 76.8 per 1,000 person-years in systematic review involving 9 studies (Luck et al. 2010)
  – amnestic MCI subtypes between 9.9 and 40.6 per 1,000 person-years
  – non-amnestic MCI subtypes between 28 and 36.3 per 1,000 person-years

• Higher risk of incident MCI for higher age, lower education and hypertension (Luck, Dement Geriatr Cogn Disord., 2010)

• Frequency of dementia is higher in women than men (Ref)

• Male sex is a risk factor for both prevalence (Petersen, Roberts, … Geda, Rocca JAMA Neurology 2010) and incident MCI (Roberts, Geda,… Petersen Neurology. 2012)
Incidence of MCI

- Population-based studies examining incidence of MCI showed that:
  - Incidence rates for NP-MCI and CDR=0.5 were 95 and 55 per 1,000 person-years respectively (N=1,982) (Ganguli et al., Neurology 2013)
  - Incidence rate of MCI was 63.6 (per 1,000 person-years) overall, was higher in men (72.4) than women (57.3) and for aMCI (37.7) than naMCI (14.7; N = 1,450) (Roberts et al., Neurology 2012)
Age- and Sex-Standardized Incidence Rates

- Few studies reported age-sex standardized incidence rates (Kunghsolmen Project, Leipzig Study and the Mayo Clinic Study of Aging).

- The incidence rate of aMCI was higher for men (43.9 per 1,000 person-years) than women (33.3), and for subjects with ≤12 years of education (42.6) than higher education (32.5).

- The risk of naMCI was also higher for men (20.0) than women (10.9) and for subjects with ≤12 years of education (20.3) than higher education (10.2) (Roberts et al., Neurology 2012).
Neuropsychiatry of MCI
Neuropsychiatry of MCI

- Neuropsychiatric symptoms are highly prevalent in patients with MCI (Lyketsos, JAMA 2002; Geda, General Arch Psychiatry 2008)

- A systematic review of neuropsychiatric symptoms (NPS) in MCI (involving 27 studies) showed that global prevalence of NPS ranged from 35% to 85%. (Monastero, J Alzheimers Dis 2009)

- The most common symptoms were apathy, depression, and irritability in both Cardiovascular Health Study (Lyketsos, JAMA 2002) and Mayo Clinic Study of Aging (Geda, General Arch Psychiatry 2008)
Depression significantly predicts progression from Normal Cognition to incident MCI

<table>
<thead>
<tr>
<th></th>
<th>CN</th>
<th>Incident MCI</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Depression</td>
<td>1255</td>
<td>229 (18.2)</td>
<td>1.00 (reference)</td>
<td>0.00</td>
</tr>
<tr>
<td>Depression</td>
<td>153</td>
<td>43 (28.1)</td>
<td>1.55 (1.11, 2.15)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Geda et al., General Arch Psychiatry 2008
Neuropsychiatry of MCI (Continued)

- NPS may increase probability of conversion from MCI to Alzheimer’s disease (Monastero et al., J Alzheimers Dis 2009)

- NPS increase the risk for incident dementia among individuals with MCI (Pink et al. Neurology 2015)
Biomarkers of MCI
## Biomarkers and MCI

MCSA: N = 126 subjects with aMCI  
ADNI: N = 58 subjects with aMCI

<table>
<thead>
<tr>
<th></th>
<th>MCSA N (%)</th>
<th>ADNI N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker negative</td>
<td>18 (14)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Amyloid deposition only</td>
<td>18 (14)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Amyloid deposition + neurodegeneration (MRI atrophy, FDG-PET hypometabolism or both)</td>
<td>54 (43)</td>
<td>32 (55)</td>
</tr>
<tr>
<td>Neurodegeneration only</td>
<td>36 (29)</td>
<td>10 (17)</td>
</tr>
</tbody>
</table>

(Petersen RC et al. Ann Neurol. 2013)
MRI

• Review including 19 studies found that hippocampal volume as measured by MRI predicted conversion to Alzheimer’s dementia among persons with MCI (Anstey KJ 2003).

• Quantitative MRI markers predict progression to incident MCI (Kantarci K et al. Neurology. 2013).

• White matter hyperintensities portend an increased risk of amnestic mild cognitive impairment and dementia (Debette S et al. Stroke. 2010).
FDG-PET and Amyloid Imaging

- Cognitively normal elderly individuals with abnormal levels of both beta-amyloid and brain injury biomarkers have higher rates of medial temporal neurodegeneration.
- Although preclinical AD is currently only a research topic, the description of its brain structural changes may be important for trials designed to prevent or delay dementia due to AD. (Knopman DS et al. JAMA Neurol. 2013)
Lifestyle Factors and MCI
Physical Exercise and MCI

- Systematic review involving 15 prospective studies (total N: 33,816 nondemented subjects) observed a robust protective effect of physical activity against cognitive decline. The effect was observed for both low-to-moderate as well as high level of physical activity (Sofi F et al. J Intern Med 2011).

- Observational studies also reported that physical exercise is associated with decreased risk of MCI (Verghese 2006; Wilson 2002; Geda 2010; Krell-Roesch 2015).
Mental Activities and MCI

• Engaging in cognitively stimulating activities is associated with a decreased risk of MCI (Verghese 2003; Wilson 2002; Geda 2011)

• Systematic review on healthy older adults and subjects with MCI based on 35 studies found that cognitive interventions can be effective in improving: memory performance, executive functioning, processing speed, attention, fluid intelligence, and subjective cognitive performance (Reijnders et al. 2013).
Conclusion

- The field of aging and dementia is increasingly emphasizing using biomarkers in establishing the presymptomatic phase of Alzheimer’s disease. However, these biomarkers are not yet validated (Sperling 2011).

- Therefore, obtaining history (including collateral history), conducting exams, and obtaining neuropsychological tests remain the cornerstones of defining and classifying MCI.
Acknowledgement

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