Mild Cognitive Impairment: The Current Status

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Rochester, MN

Updates on Dementia
Stanford University
June 4, 2008

Disclosures

- Elan Pharmaceuticals: Chair SMC
- GE Healthcare: Consultant

MILD COGNITIVE IMPAIRMENT

- Conceptual framework
- Epidemiology
- Clinical features
- Outcome
- Predictors
- Neuropathology
- Unresolved issues
- Clinical trials

Prevalence of Mild, Moderate/Severe and Total Cases of Alzheimer’s Disease in the United States 2000-2050


Time Course: AD Pathology (in situ) & Clinical Expression

Pathological progression
Cognitive function
Cognitive Continuum

Mild Cognitive Impairment

Alzheimer's Disease

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Clinical Features

MILD COGNITIVE IMPAIRMENT
Original Criteria

• Memory complaint
• Memory impaired for age
• Normal general cognitive function
• Normal activities of daily living
• Not demented

Case

83 y/o Retired Priest

• Word finding difficulties
• Mild memory concerns
• ADL’s preserved
83 Y/O PRIEST

- NEUROPSYCHOLOGY PROFILE
  - VIQ 140
  - PIQ 110
  - FSIQ 129
  - WORKING MEMORY 128
  - VeMI 92
  - ViMI 111

83 Y/O PRIEST

- LEARNING EFFIC 104
- DELAYED RECALL 71
- TRAILS A & B 50% ile
- BOSTON NAMING TEST 59/60
- FLUENCY 80% ile

34 months later

MILD COGNITIVE IMPAIRMENT

Original Criteria

- Memory complaint
- Memory impaired for age
- Normal general cognitive function
- Normal activities of daily living
- Not demented
Current Classification Scheme for MCI

Mild Cognitive Impairment

Mild Cognitive Impairment

Mild Cognitive Impairment

MCI Outcomes

MCI Outcomes
MILD COGNITIVE IMPAIRMENT

• Conceptual framework
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MOANS Change Scores

MCI Studies

MILD COGNITIVE IMPAIRMENT

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MILD COGNITIVE IMPAIRMENT

Predictors of Outcome

• Apo-E Status
  +E4
• Clinical severity
• Hippocampal volumes
• ? FDG-PET
• ? CSF Biomarkers
• ? Amyloid imaging
MCI: Conversion to Dementia

Atrophy and AD Stage

 Boundary Shift Integral
New Neuroimaging Research

Voxel-based Morphometry

VBM
Normal(43) vs AD (51)

VBM
Whitwell

MCI Converter vs Non-Converter

Voxel-wise methods capture time dependent progression from aMCI to AD \( n = 33 \)

3D Maps from Multiple MRI Illustrate Changing Atrophy Patterns as Subjects Progress from MCI to AD Whitwell, Jack, Brain 2007
Synapse Number and Volume Loss in CA1 in MCI


Total No. of Synapses
Total Volume

Molecular Neuroimaging

In vivo Amyloid Imaging with Pittsburgh Compound B (PIB)

Histology - Thioflavin T

PET Imaging - [11C]6-OH-BTA-1 (PIB)

FDG and PIB in Aging and AD

AD -FDG

AD-PIB

Normal Control - PIB

PIB in Controls, MCI, AD

Chet Mathis, U Pittsburgh

Control Subject  MCI Patients  MCI Patients  MCI Patients  AD Patient

Some MCI’s have control-like PIB retention, some have AD-like retention, and some have intermediate retention

PIB Idealized

Price et al., JCBFM 2005

Lopresti et al., J Nucl Med, in press
PIB Examples – full spectrum

Cerebrospinal Fluid

Progression to AD from MCI

Progression Normal to MCI

Predicting Progression to CDR >0

Alzheimer’s Disease Neuroimaging Initiative ADNI
ADNI

- Observational study of imaging and biomarkers
- Normals = 200
- MCI = 400
- AD = 200
- MRI, FDG PET, PiB, CSF, biomarkers
- 3 years

ADNI Demographics

<table>
<thead>
<tr>
<th></th>
<th>Normal controls (n=229)</th>
<th>MCI (n=398)</th>
<th>AD (n=192)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>76.4 (5.0)</td>
<td>75.3 (7.5)</td>
<td>75.8 (7.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>Female (%)</td>
<td>48.0</td>
<td>35.4</td>
<td>47.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Years of education, mean (SD)</td>
<td>15.6 (3.1)</td>
<td>16.0 (2.9)</td>
<td>14.7 (3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apolipoprotein E e4: Positive (%)</td>
<td>26.6</td>
<td>53.5</td>
<td>65.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ADNI Cognitive Function

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=229)</th>
<th>MCI (n=398)</th>
<th>AD (n=192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated premorbid verbal IQ</td>
<td>119.8 (9.0)</td>
<td>116.2 (9.7)</td>
<td>113.6 (9.9)</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auditory verbal learning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials 1-5 correct</td>
<td>43.3 (9.09)</td>
<td>30.7 (9.03)</td>
<td>23.2 (7.70)</td>
</tr>
<tr>
<td>Delayed recall (%)</td>
<td>65.8 (27.6)</td>
<td>32.1 (31.4)</td>
<td>11.3 (21.9)</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston Naming</td>
<td>27.9 (2.3)</td>
<td>25.5 (4.1)</td>
<td>22.3 (6.2)</td>
</tr>
<tr>
<td>Category fluency total</td>
<td>34.6 (8.1)</td>
<td>26.7 (7.5)</td>
<td>20.3 (7.5)</td>
</tr>
<tr>
<td>Executive function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail A time</td>
<td>36.5 (13.2)</td>
<td>44.8 (22.8)</td>
<td>68.2 (36.8)</td>
</tr>
<tr>
<td>Trail B time</td>
<td>89.2 (44.3)</td>
<td>130.5 (73.5)</td>
<td>199.6 (86.8)</td>
</tr>
<tr>
<td>Digit symbol correct</td>
<td>48.7 (19.2)</td>
<td>36.9 (11.1)</td>
<td>20.7 (12.9)</td>
</tr>
<tr>
<td>Visuospatial ability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clock draw: Copy</td>
<td>4.86 (0.43)</td>
<td>4.65 (0.68)</td>
<td>4.31 (1.00)</td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit span: Forward</td>
<td>8.78 (1.99)</td>
<td>8.22 (2.01)</td>
<td>7.54 (1.94)</td>
</tr>
<tr>
<td>Digit span: Backward</td>
<td>7.21 (2.16)</td>
<td>6.17 (2.2)</td>
<td>4.96 (1.83)</td>
</tr>
</tbody>
</table>

ADAS-Cog Baseline

<table>
<thead>
<tr>
<th></th>
<th>NC</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total11</td>
<td>20</td>
<td>25</td>
<td>30</td>
</tr>
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ADAS-Cog

<table>
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<tr>
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<td>20</td>
<td>25</td>
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</table>
Amnestic MCI
First 12-Month Change

<table>
<thead>
<tr>
<th>ADCS</th>
<th>ADNI</th>
<th>UDS</th>
<th>MCSA</th>
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</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>-0.8 (2.3)</td>
<td>-1.0 (2.0)</td>
<td>-0.6 (2.8)</td>
</tr>
<tr>
<td>CDR, SoB</td>
<td>+0.4 (1.3)</td>
<td>+0.7 (1.3)</td>
<td>+0.5 (1.4)</td>
</tr>
<tr>
<td>ADA-Cog</td>
<td>+0.6 (4.1)</td>
<td>+1.0 (4.5)</td>
<td>–</td>
</tr>
</tbody>
</table>

Breadth of MCI Research

- Epidemiology
- Clinical
- Imaging
- Biomarkers
- Mechanism of disease
- Neuropathology
- Clinical trials

Practice Parameter: Early Detection of Dementia: Mild Cognitive Impairment
(an Evidence-Based Review)
Report of the Quality Standards Subcommittee
of the American Academy of Neurology
Ronald C. Petersen, PhD, MD; J. C. Stevens, MD; M. Ganguli, MD, MPH; E. G. Tangalos, MD; J. L. Cummings, MD; and S. T. DeKosky, MD

AAN PRACTICE PARAMETER DETECTION SUMMARY RECOMMENDATIONS

- GUIDELINE
  - PATIENTS WITH A MILD COGNITIVE IMPAIRMENT SHOULD BE RECOGNIZED AND MONITORED FOR A COGNITIVE AND FUNCTIONAL DECLINE DUE TO THEIR INCREASED RISK FOR SUBSEQUENT DEMENTIA

Publications on MCI

Practice Parameter: Early Detection of Dementia: Mild Cognitive Impairment
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Ronald C. Petersen, PhD, MD; J. C. Stevens, MD; M. Ganguli, MD, MPH; E. G. Tangalos, MD; J. L. Cummings, MD; and S. T. DeKosky, MD
Mild Cognitive Impairment Should Be Considered for DSM-V

Ronald C. Petersen, Ph.D., M.D., and John O'Brien, M.D.

ABSTRACT

Mild cognitive impairment (MCI) is a term of great utility from both clinical and research perspectives. It represents a transition between normal aging and early dementia. The hallmark of MCI is the presence of memory symptoms that are severe enough to cause subjective concern and impairment in daily activities, but not to the extent of meeting the stricter criteria for dementia. MCI has been used as an endpoint in clinical trials of neuroprotective and neurotherapeutic agents. However, MCI can be confounded by several factors, including heterogeneous symptom presentation, overlap with normal aging, and shared risk factors with early dementia. Several strategies are proposed to address these limitations, including the development of a multidisciplinary approach that includes cognitive, neurobiological, and genetic assessments.
**Neuropathological**

- Braak 1
- Braak 2
- Braak 3
- Braak 4
- Braak 5
- Braak 6

**Neurofibrillary tangles**

- APP
- Oligo's
- Protofibrils
- Fibrils
- Plaques

**Amyloid**

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**Clinical**

- Normal
- Presymp
- MCI
- Dementia

**Pathological**

- Braak 1
- Braak 2
- Braak 3
- Braak 4
- Braak 5
- Braak 6

- Neurofibrillary tangles
- APP
- Oligo's
- Protofibrils
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**AD?**

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**MCI SUMMARY**

- USEFUL CONCEPT
- CRITERIA AVAILABLE
  - CLINICIAN INVOLVED
  - ALGORITHM
- OUTCOME DEPENDENT
- NEUROPATH TRANSITIONAL
- CLINICAL TRIALS FEASIBLE

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  - Eric Tangalos
  - Joe Parisi
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