• One patient can maintain more AD pathology than another but they appear clinically the same.

• Clinically Mild Cognitive Impairment may be accompanied by very minimal pathology, or, enough to meet pathologic criteria for AD.
Definitions

Mild Cognitive Dysfunction
M.C.D.

**Definition:** At least two of the following:
- getting lost travelling to unfamiliar location
- decline in work performance
- word and name deficits apparent
- relative little retention of material read
- difficulty remembering new names
- losing/misplacing objects
- concentration deficit upon clinical testing

(Reisberg et al., 1982, *American Journal of Psychiatry*)

Age Associated Memory Impairment
A.A.M.I.

**Definition:** - Complaint of Memory Impairment
- Memory function 1SD below young
- Age > 50 years
- Adequate intellectual functioning
- Absence of dementia (MMSE ≥ 24)
- Absence of memory affecting disease

(Crook et al., 1986, *Development Neuropsychology*)
Aging-associated Cognitive Decline  
A.A.C.D.

**Definition:**
- Subjective report of declining cognition
- Decline in one area of cognition for 6 months
- Difficulty in one: Memory and learning
  - Attention and concentration
  - Thinking
  - Language
  - Visuospatial function
- 1SD below mean by age & education on tests
- Exclusion criteria
  (Levy et al., 1994, *International Psychogeriatrics*)

Mild Cognitive Impairment  
M.C.I.

**Definition:**
- Memory complaint by patient, family, or physician
- Normal activities of daily living
- Normal global cognitive functioning
- Objective memory impairment by scores > 1.5SD
- CDR (clinical dementia rating) score 0.5
- Not demented
- Age between 60 and 89 years

Recognize and monitor for cognitive and functional decline due to their increased risk for subsequent dementia

International Working Group on Mild Cognitive Impairment


International Working Group on Mild Cognitive Impairment

- Recommend a clinical, rather than a psychometric definition of MCI
- “A wide range of cognitive functions appear to decline … including memory, attention, language, visuospatial skill, perceptual speed and executive functioning.”
- Entirely compatible with the original GDS Stage 3 MCI definition.
**Mild Neurocognitive Disorder**

**Definition:**
- Memory complaint by patient, family, or physician
- Normal activities of daily living
- Objective memory impairment by scores 1-2 SD
- Clinical Judgment with ‘bedside’ assessments
- Not demented
- Not related to delirium or other mental disorder

Recognize and monitor for cognitive and functional decline

**Sub-Types of M.C.I.**

**Cognitive domains specified**

**DSM-IV:**
- Memory impairment
- Aphasia
- Apraxia
- Agnosia
- Executive dysfunction
Mild cognitive impairment
Amnestic

Mild cognitive impairment
Multiple domains slightly impaired

Mild cognitive impairment
Single non-memory domain

Alzheimer’s disease

Alzheimer’s disease
? Normal aging

Frontotemporal Dementia
Lewy Body Dementia
Primary Progressive Aphasia
Parkinson’s Disease
Alzheimer’s Disease

Pathology of M.C.I.
Diagnosis

MARKERS IN AD

- Biomarkers of Aβ deposition
  * spinal fluid Aβ levels
  * PET amyloid imaging (Pittsburg Compound –B)
- Biomarkers of neuronal injury
  * spinal fluid tau levels
  * MRI looking at hippocampus, temporal lobe or whole brain (high-resolution T2 weighted)
  * FDG-PET (2-[18]fluoro-2-Deoxy-D-glucose )
  * SPECT(single-photon emission computed tomography)
- Genes (apolipoprotein E alleles,: others chromosome 14, presenilin-1, chromosome 1, presenilin-2, chromosome 21, APP )

Hippocampal atrophy

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<thead>
<tr>
<th></th>
<th>NC (N=114)</th>
<th>MCI (N=119)</th>
<th>AD (N=57)</th>
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BIOMARKERS IN AD

- Biomarkers of Aβ deposition
  * spinal fluid Aβ levels (low)
  * PET amyloid imaging
- Biomarkers of neuronal injury
  * spinal fluid tau levels
  * MRI looking at hippocampus, temporal lobe or whole brain
  * FDG-PET
  * SPECT
- Genes

CSF ABeta 42

- CSF levels of Total Abeta disappointing as CSF marker
- ABeta 42 is principal component of plaques
- Decreased ABeta 42 found in diverse CNS diseases including:
  - MSA
  - ALS
  - CJD

SPINAL FLUID (CSF) IN AD

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<th>Aβ42</th>
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BIOMARKERS IN AD

- Biomarkers of Aβ deposition
  * spinal fluid Aβ levels
  * PET amyloid imaging (high)
- Biomarkers of neuronal injury
  * spinal fluid tau levels
  * MRI looking at hippocampus, temporal lobe or whole brain
  * FDG-PET
  * SPECT
- Genes
BIOMARKERS IN AD

• Biomarkers of Aβ deposition
  * spinal fluid Aβ levels
  * PET amyloid imaging
• Biomarkers of neuronal injury
  * **spinal fluid tau levels (high)**
    * MRI looking at hippocampus, temporal lobe or whole brain
  * FDG-PET
  * SPECT
• Genes

CSF Total-Tau:

**Elevated in:**
• Head trauma
• Stroke
• Encephalitis
• Guillain-Barre
• ALS

**But Normal in:**
• Depression
• Parkinson’s Disease
• Alcohol overuse

Non-specific marker of neuronal destruction
Phospho-Tau

• Several Varieties found to be raised in AD
• ? Reflects abnormal phosphorylation in AD and not neuronal damage more generally?
  – P-Tau 18/231, 181, 199, 231, 396/404
• Not raised in
  – stroke or Creutzfeldt-Jakob dz
  – ALS, Parkinson’s
  – Depression
  – Vascular, frontotemporal, or Lewy Body Dementia

BIOMARKERS IN AD

• Biomarkers of Aβ deposition
  * spinal fluid Aβ levels
  * PET amyloid imaging
• Biomarkers of neuronal injury
  * spinal fluid tau levels
  * MRI looking at hippocampus, temporal lobe or whole brain (smaller)
  * FDG-PET
  * SPECT
• Genes

SPINAL FLUID (CSF) IN AD

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Hippocampal volume in Alzheimer’s disease

Dark lines cross the thinnest width of the hippocampus and arrowheads indicate hippocampal boundaries.
BIOMARKERS IN AD

- Biomarkers of Aβ deposition
  * spinal fluid Aβ levels
  * PET amyloid imaging
- Biomarkers of neuronal injury
  * spinal fluid tau levels
  * MRI looking at hippocampus, temporal lobe or whole brain
  * FDG-PET (areas of reduced metabolism)
  * SPECT
- Genes
MARKERS IN AD

- Biomarkers of Aβ deposition
  * spinal fluid Aβ levels
  * PET amyloid imaging
- Biomarkers of neuronal injury
  * spinal fluid tau levels
  * MRI looking at hippocampus, temporal lobe or whole brain
  * FDG-PET
  * SPECT
- Genes

Genes and Alzheimer’s disease
(60% - 80% of causation)
(all known genes relate to βamyloid)

- Familial AD (onset < 60 y/o) (<5%)
  - Presenilin I, II (ch 14, 1)
  - APP (ch 21)
- Non-familial (late onset)
  - APOE
    - Clinical studies suggest 40 – 50% due to ε4
    - If ε2 is considered, may be 95% of causation
    - Population studies suggest 10 – 20% cause
    - Evolution over last 300,000 to 200,000 years
  - At least 20 other genes

Conversion to Dementia

APOE 4 noncarrier
APOE 4 carrier
AD Progression

- Presymptomatic
- eMCI
- lMCI
- Dementia

Prevalence of M.C.I.

- Baseline MCI prevalence 34.8%
  - Amnestic MCI 10.5%
  - Amnestic multi-domain MCI 8.8%
  - Nonamnestic MCI 12.8%
  - Nonamnestic multi-domain MCI 2.7%

Sachdev et al. (2010). *International Psychogeriatrics, 22:8, 1248–1264*
Progression of M.C.I.

Mild Cognitive Impairment

Progression to Dementia

- Progression MCI to dementia = 12.8%\(^1\)
- Progression No Cognitive Impairment (NCI) to dementia = 1.8%\(^2\)
- 31-37%\(^4,5,6\) of those with MCI at baseline reverted to NCI at follow-up
- Multidomain subtypes more likely to progress to dementia (vs. NCI) than single domain

Importance of MCI as a prodromal syndrome

- MCI annual conversion rate to dementia approx 12%
- Normal controls: 1%-2% develop MCI/Dementia

- BUT not everyone progresses.......

Mild Cognitive Impairment

Normal MCI AD

CDR 0.5

GDS
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The Global Deterioration Scale (GDS)

**CDR – CLINICAL DEMENTIA RATE**

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GDS Stage 1

Healthy older persons

Free of subjective complaints of cognitive impairment

Free of objective evidence of cognitive impairment

GDS Stage 2

Subjective complaints of memory deficit.
  e.g., forgetting names one formerly knew well

Forgetting where one has placed familiar objects.

No objective evidence of memory deficit on clinical interview

No objective deficit in employment or social situations
SCI vs NCI: Prediction of Dementia

3.2 year F/U (MMSE ≥ 26) x3 risk for SCI

9.0 year F/U (MMSE = 29 or 30) x3 risk in high education group

After adjusting for age, gender, and depressive symptoms, SCI predicted dementia. 15% developed dementia in 5 yrs.

Mean Time to Decline

<table>
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<tr>
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<th>NCI</th>
<th>SCI</th>
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<tr>
<td>GDS Stage 1</td>
<td>8.8 years</td>
<td>5.3 years</td>
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<tr>
<td>GDS Stage 2</td>
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SCI persons have a ~ 4.5 x greater risk of decline to MCI or dementia than same gender, similarly aged and educated, non-SCI persons


Top Ten Warning Signs

*Alzheimer Association*

1. Recent memory loss affecting job
2. Difficulty performing familiar tasks
3. Problems with language
4. Disorientation to time or place
5. Poor or decreased judgment
6. Problems with abstract thinking
7. Misplacing things
8. Changes in mood or behavior
9. Changes in personality
10. Loss of initiative
Implications for Dementia Prevention

We are now in a position to address the prevention of AD in persons with complaints beginning >20 years before dementia develops.