The Mild Cognitive Impairment Spectrum

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Objectives

- Normal aging
- What is Mild Cognitive Impairment (MCI)?
- Risk factors for MCI
- MCI subtypes
- Multi-targeted treatment

Cognitive Aging is not a disease
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• Everyone is affected.
• Cognitive function can improve with aging.
• Intact adults can strengthen some cognitive abilities.

In normal aging intelligence is stable or improved

• Speed: always ↓
• Language: stable
• Memory: mild ↓

• Visuospatial: mild ↓
• Executive function: (cognitive flexibility, problem solving slowed but accuracy unchanged)

What does the term “dementia” mean??
Major neurocognitive disorder:
A neurodegenerative disease that causes a decline in thinking and function.


How is Mild Cognitive Impairment (MCI) different?


Mild Cognitive Impairment (MCI)
An acquired disturbance in cognition without impairment in daily functioning.


Who has MCI?

10-29% of those aged 65+ older may have MCI.

MCI is not just pre-Alzheimer's

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Our Minions
Does MCI always become AD?

- The annual conversion rate from MCI to any dementia subtype is 5-15%.
- MCI can remain stable, revert to normal or worsen.
- Some MCI types patients have up to 80% risk of having AD.
MCI subtypes

“Amnestic” MCI
- Memory impairment only
- Alzheimer’s disease
  - major subtype
  - (Vascular dementia)

“Nonamnestic” MCI
- Memory plus other domains impaired
- Frontotemporal dementias
  - Lewy body dementia
  - Primary progressive aphasia
  - Parkinson’s disease
  - (Alzheimer’s disease)
  - (Vascular dementia)

How can we detect MCI?

- Pre-Symptomatic
  - Amyloid imaging
  - CSF Ab42
- MCI
  - FDD-PET
  - FDG-PET
- Dementia
  - Function MRI
  - MRI Hippocampal Volume
  - Cognitive Performance

Courtesy of Paul Aisen, M.D., Alzheimer’s Disease Cooperative Study, UCSD, 2011
Biomarker: MCI due to AD

What is a biomarker?

- Neuropathology
- Structural Change
- Functional or metabolic change
- Biochemical Change


Structural change: medial temporal lobe atrophy

Normal

Alzheimer’s

T1 MRI coronal view

Functional change: glucose metabolism ¹⁸F-FDG positron emission tomography (PET)

Control

AD
Neuropathology: PET tracer binds amyloid

Debate over criteria: MCI due to AD

- International Workgroup (IWG) 1 prodromal AD
  - Amnestic MCI + 1 biomarker.
  - 35% prodromal AD; 3 year conversion to AD was 50%

- IWG 2 prodromal AD
  - MCI (all) plus CSF abnormalities in both amyloid and tau
  - 40% prodromal AD; 3 year conversion to AD was 61%.

- NIA-AA criteria for MCI due to AD
  - Several classifications
  - 46% high AD likelihood; 3 year conversion to AD was 59%.

Q: I am having new memory problems and an abnormal brain scan. I don’t have MCI. What does this mean?
What is pre-MCI?

- Cognitive and functional impairment evident on the history or examination.
- “Normal” neuropsychological testing.
  - May have impairment on testing, but not enough to meet criteria for MCI

Pre-MCI

- “Pre-MCI” are at risk for progression to AD if biomarkers suggestive of the presence of disease.
  - Approximately 3% of “normal” or pre-MCI progress to MCI or prodromal AD within 2-3 years.
  - Previously thought to be complainers, worried well, depressed or anxious.
Prodromal AD

• 1. Meets MCI criteria.
• 2. Must have a positive biomarker for AD-P (pathophysiological process).

• If meets criteria, MCI changed to prodromal AD.

Can we detect problems even before MCI?

What is Subjective memory impairment (SMI)?
**Subjective Memory Impairment (SMI)**

- **Memory complaints** without pathological results on neuropsychological test.
  - May have perfect testing or minimal errors.
  - Patients may seem depressed or anxious.
- May represent earliest stage of AD.
- **SMI findings:**
  - Brain atrophy pattern similar to aMCI.
  - Increased prevalence of an AD pattern in CSF.

**Does SMI lead to cognitive decline?**

- Drs. Jicha et al followed cognitively intact participants (73.2 ± 7.4) and asked about memory changes over ≈ 10 years.
- They reviewed those with autopsy data (n=243).

**Subjective memory impairment (SMI)**

- MCI occurred 9.2 years after memory complaints (SMI) were reported. AD occurred 2.9 after MCI.
- Participants with SMI and an APOE ε4 allele had double the odds of impairment, compared with people with memory complaints alone.
- **Smokers** with SMI converted to MCI quickly.
Can we prevent MCI?

MCI due to AD FIXED risk factors

- Age
- Family history 1° relatives
- Genetics
- Subjective memory impairment

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MCI due to AD FIXED risk factors

- Age
- *Family history 1° relatives*
- Genetics
- Subjective memory impairment

Apolipoprotein E (APOE)

You inherit one gene from mom and one from dad. Not everyone with APOE e4 genes develops AD.

APOE has three common forms:
- APOE e2 (least common) \( \downarrow \) risk of AD
- APOE e4: \( \uparrow \) risk of AD
- APOE e3: neutral.

AD runs in my family. What is my risk?

WRAP study followed 48 healthy adult children (ages 47-59) with a parent with AD.

Over time, the participants had more brain atrophy than those without a family history making them more susceptible to AD pathology.
Will we screen for AD like we screen for cancer?

Primary and secondary prevention
An Ounce of Prevention is Worth a Pound of Cure
- Benjamin Franklin -

MCI due to AD: 7 MODIFIABLE risk factors

- Lack of exercise
- Midlife obesity
- Low education
- Smoking
- High blood pressure
- Diabetes
- Depression

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1/3 of current AD cases are from these 7 factors

What % of AD is from Modifiable Risk Factors?

<table>
<thead>
<tr>
<th>RF</th>
<th>Prevalence</th>
<th>RELATIVE RISK (95% CI)</th>
<th>PAR% (CR)</th>
<th>NO. CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Activity</td>
<td>32.5%</td>
<td>1.82 [1.39, 2.78]</td>
<td>21.0% [5.8%, 36.6%]</td>
<td>1115 (308, 1942)</td>
</tr>
<tr>
<td>Depression</td>
<td>19.2%</td>
<td>1.40 [1.55, 2.33]</td>
<td>14.7% [9.6%, 20.3%]</td>
<td>781 (506, 1078)</td>
</tr>
<tr>
<td>Smoking</td>
<td>20.6%</td>
<td>1.59 [1.35, 2.06]</td>
<td>10.8% [3.0%, 19.8%]</td>
<td>574 (159, 1050)</td>
</tr>
<tr>
<td>HTN (midlife)</td>
<td>14.3%</td>
<td>1.61 [1.36, 2.24]</td>
<td>8.0% [2.2%, 15.1%]</td>
<td>425 (119, 798)</td>
</tr>
<tr>
<td>Obesity (midlife)</td>
<td>13.1%</td>
<td>1.60 [1.34, 1.92]</td>
<td>7.3% [4.3%, 10.8%]</td>
<td>386 (226, 570)</td>
</tr>
<tr>
<td>education</td>
<td>13.3%</td>
<td>1.59 [1.35, 1.86]</td>
<td>7.3% [4.4%, 10.3%]</td>
<td>386 (236, 544)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8.7%</td>
<td>1.39 [1.17, 1.66]</td>
<td>3.3% [1.5%, 5.4%]</td>
<td>174 (77, 288)</td>
</tr>
<tr>
<td>Combo of RF</td>
<td></td>
<td></td>
<td>2,866,951</td>
<td>2,866,951</td>
</tr>
</tbody>
</table>

Sleep apnea and Alzheimer’s

- Untreated sleep apnea affects spatial navigational memory.
- Untreated sleep apnea worsens cognitive impairment.


Magic pill?

“THEY TESTED SOME BRAIN BOOSTING PILLS ON ME AND NOW I’M SELLING MAPS. WANT TO BUY ONE?”

The magic brain pill... exercise?

- An exercise intervention in MCI may slow deterioration on testing as well as measured by functional neuroimaging (fMRI)
- Exercise may slow the progression of aMCI to overt AD.

What diet is good for the brain???

“After age 40, all food is bad for you. Learn to chew air and eat rocks.”

Food as an Alzheimer’s Drug?

• Systematic review of 11 prospective studies worldwide:
  – Mediterranean diet decreased AD risk by 50%

• Meta-analysis including 1.5 million people and 35 studies worldwide:
  – Mediterranean diet decreased risk of dementia death by 13%.

Mediterranean diet

• Fish, nuts, complex grains, olive oil, fresh produce and greens.
• Avoid red meat, fast food, fried food, packaged, processed foods and “diet” or “sugar-free” foods.
• Get plenty of omega-3 fats.
  – Sources include cold-water fish such as salmon, tuna, trout, sardines.
• Avoid refined carbohydrates
  – Sugary food, baked goods, white flour.
• Eat across the rainbow.
• Enjoy daily cups of tea or coffee.
Diabetes Mellitus (DM) and AD

- DM linked AD
  - DM + ApoE4 allele, 4 x higher risk of AD
  - Diabetes damages brain structure.
    - Reduced cortical grey matter volume, and increased microvascular lesions (alter function).

Protective factors to reduce MCI in older adults (median age 87.3 y)

- Art and crafts
- Socialization (volunteerism, church groups, group educational activities)
- Second language
- Musical instrument
- Computer activities (in late life only)

Galvin JE. Neurology 2014

Education as a protective factor

Image courtesy of Yaakov Stern Columbia 2002.
**Being bilingual may delay AD!**

- **Learning and speaking a second language** may delay the onset of cognitive impairment as suggested by Bialystok et al.
  - Bilingual speakers hold AD at bay for an extra 4 years on average compared with monoglots.
  - School-level language skills that you use while on vacation (i.e., going to France to practice French) may also improve brain function.

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**Dwindling evidence for Alcohol in improved health...**

**Study of 53K adults**

Light alcohol was only beneficial in younger men (50-64 yo) who consumed between 1/10 of serving to 1 serving daily and older women (> 65 yo) who consumed >5 servings weekly.


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**Dwindling evidence for Alcohol in improved health...**

**What does 1 FULL serving of wine look like?**

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Dwindling evidence for Alcohol in improved health...

One full serving of hard alcohol.

Why should diagnosis early?

1. Early diagnosis MCI due to Alzheimer's allows prompt treatment of reversible symptoms.
2. MCI is treatable.
3. Early intervention may modify or stop the disease.

“You are never too old to set another goal or to dream a new dream.”

C.S. Lewis