Mild Cognitive Impairment or Mild Neurocognitive Disorder: Implications for Clinical Practice

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AD is a Neurodegenerative Disease as Seen in the PET Scan and is Characterized by Amyloid Plaques and Neurofibrillary Tangles

Hypothesized Key Players in the Pathogenesis of AD

Risk Factors

Established Risk Factors
- Older age
- Family history of AD
- APOE-ε4 gene
- MCI (especially amnestic subtype)
- CV disease and associated CV risk factors (eg, smoking, diabetes, hyperlipidemia, hypertension, obesity)
- Less education
- Traumatic brain injury
- Elevated plasma homocysteine levels

Emerging Risk Factors
- Inflammation
- Chronic kidney disease
- Thyroid dysfunction
- Dietary factors and activity level
- Social isolation
- Depression

CV = cardiovascular; MCI = mild cognitive impairment.

Diagnosis of Mild Cognitive Impairment and Alzheimer’s Disease

SCI = subjective cognitive impairment.

Subjective Cognitive Impairment

- SCI, also referred to as “Senior Moments,” is not in the DSM-5
- SCI may represent a prodrome to Mild Neurocognitive Disorder (formerly called MCI)
### Terminology: An Update

**DSM-5**
- Delirium
- Mild Neurocognitive Disorder
- Major Neurocognitive Disorder
- Replaces DSM-IV "Delirium, Mild Cognitive Impairment, and Dementia"

**NIA/AA**
- Preclinical AD
- MCI
  - MCI due to AD
- All-cause dementia
  - AD dementia
    - Probable AD dementia
    - Possible AD dementia
  - Dementia unlikely to be due to AD

AA = Alzheimer’s Association; NIA = National Institute on Aging.

### DSM-5 Delirium
- Disturbance in attention and awareness
- Develops over short period of time, and tends to fluctuate in severity during the day
- An additional cognitive domain disturbance
- Physiologic consequence of a medical condition, substance intoxication or withdrawal, toxic exposure, or multiple etiologies
- The Confusion Assessment Method (CAM) is considered the best screening tool for delirium


### The Continuum of AD

![Image showing the Continuum of AD with stages Preclinical, MCI, and Dementia]


### Defining a Preclinical Stage of AD (NIA/AA)

#### Stage 1
- Asymptomatic amyloidosis
  - High PET amyloid tracer retention
  - Low CSF Ap42

#### Stage 2
- Amyloidosis + Neuronal dysfunction
  - Neuronal dysfunction on FDG-PET/fMRI
  - High CSF tau/p-tau
  - Cortical thinning/Hippocampal atrophy on sMRI

#### Stage 3
- Amyloidosis + Neuronal dysfunction + Subtle Cognitive Decline
  - Evidence of subtle change from baseline level of cognition
  - Poor performance on more challenging cognitive tests
  - Does not yet meet criteria for MCI

MCI = MCI due to AD
Dementia

CSF = cerebrospinal fluid; FDG = fluorodeoxyglucose; fMRI = functional magnetic resonance imaging; sMRI = structural MRI.

### Cognitive and Behavioral Domains That May Be Affected in MCI or Dementia

- **Attention**†
  - Sustained and divided attention, processing speed
- **Executive function/ability**†
  - Planning/decision making/judgment
  - Reasoning and handling of complex tasks
- **Learning and memory**†
  - Immediate and recent recall, free recall, cued recall and recognition
  - Ability to acquire and remember new information
- **Language**†
  - Expressive and receptive
  - Speaking, reading, writing
- **Visuococonstructional-perceptual activity/visuospatial abilities**†
- **Social cognition**
  - Emotions and behavioral regulation
- **Changes in personality, behavior, or comportment**†

\*DSM-5; †NIA/AA.


### Mild Neurocognitive Disorder/MCI

#### DSM-5
- Cognitive deficits do not occur exclusively in context of delirium
  - Both
  - Self- or informant-reported cognitive complaint
  - Objective cognitive impairment
  - Preserved functioning
  - No dementia

#### NIA/AA
- MCI due to AD
  - Exclusion of vascular, traumatic, medical causes of cognitive decline (when possible)
  - Evidence of longitudinal decline in cognition (when feasible)
  - History consistent with AD genetic factors (when relevant)

Estimates of duration of survival following diagnosis of AD range from 3 to 12 years.


Benefits of Early Diagnosis in AD

• Allows patient and family to learn about AD
• Allows time for future planning while patient still capable, eg, update will; health care proxy; POA
• Allows clinician to begin AD medications early and to educate patient and family about lifestyle interventions, which may slow disease progression or delay onset in family members
• Allows participation in clinical trials

POA = power of attorney.

Amyloid and Tau Biomarkers in SCI

• Amyloid and Tau biomarker profiles become increasingly abnormal from SCI to MCI to AD
• Amyloid and Tau biomarkers are unable to differentiate between SCI and healthy controls but may be able to differentiate between SCI patients who cognitively decline over time vs those who do not

FDG-PET and Neuropsychological Testing in SCI

• 24 women with SCI followed for 24 months
  • Changes in cognitive domain scores and regional cerebral metabolic rate of glucose measured
  • Significant reduction in executive functions found without changes in other cognitive domains
  • Declines in regional glucose metabolism found
  • Change in executive function was positively correlated with decreased glucose metabolism in the right posterior cingulate gyrus


Risk Factors for SCI

• APOE-ε4 genotype
  • Especially in those ≥ 70 years of age
  • Positive amyloid PET and/or Tau PET findings
  • Presence of anxiety or depression (may mimic SCI vs risk factor)


Predictors of Clinical Progression from SCI to MCI

• CREDOS study from South Korea enrolled 129 participants with SCI
  – Follow-up duration of 0.5 to 4.7 years
  – Median time to event was 3.64 years
• Predictors of conversion from SCI to MCI
  – Older age
  – Lower MMSE score
  – APOE-ε4 carrier
  – Lower verbal delayed recall score

CREDOS = Clinical Research Centers for Dementias of South Korea.

Predictors of Clinical Progression from SCI to MCI (continued)

• Presence of white matter hyperintensities
• Worried complainers
• Low general life satisfaction


Conversion from MCI to AD

• Not all MCI patients convert to AD
• Usually 50% of MCI patients convert to AD over 5 years
• Stress reduction (meditation, yoga), spiritual fitness, dietary modification, physical exercise, mental stimulation, and socialization may delay progression from MCI to AD


The 12 Years Preceding MCI Due to AD: The Temporal Emergence of Cognitive Decline

• Investigated the prodromal phase of MCI over a 12-year period in 27 initially healthy participants with subsequent MCI preceding AD (NC-MCI) vs 60 matched healthy individuals (NC-NC)
  – Sequence of cognitive decline
    • Began with verbal memory and savings: 8 years preceding MCI
    • Verbal episodic learning, visual memory, semantic memory (animal fluency): 4 years preceding MCI
    • Executive functioning, psychomotor speed, and informant-based reports: 2 years preceding MCI

Treatment of SCI/MCI

- No FDA approved therapies exist
- Recent SCI study using fish oil (EPA+DHA: 2.4 g/dL, n = 11) vs placebo (corn oil, n = 10) for 24 weeks
  - Results:
    - Increased RBC Omega-3 content
    - Improved working memory
    - Improved cortical blood oxygen level-dependent (BOLD) activity during working memory challenge

EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

Conclusion

- SCI is a prodrome to MCI, which is a prodrome to AD
- SCI is not listed in the DSM-5; however, a variety of biomarkers, as well as clinical features enable us to diagnose SCI
- There is growing evidence that anxiety and depression may mimic SCI
- There is growing evidence that lifestyle modification may slow progression from SCI to MCI to AD

Practical Take-Aways

- There is growing evidence that Mild Neurocognitive Disorder (MCI), especially of the amnestic type, is a risk factor/prodrome to AD
- Clinicians need to advise their at-risk patients to:
  1) Control any and all cardiovascular risk factors—including hypertension, hyperlipidemia, diabetes, obesity, smoking, lack of exercise
  2) Keep mentally, physically, socially and spiritually active
  3) Treat/avoid stress/anxiety/depression, eg, mindfulness/relaxation therapy
  4) Avoid head trauma (protect the brain)
  5) Adopt a Mediterranean Diet
- By following these guidelines, patients have a better chance of delaying/decreasing their risk of AD