Mild Cognitive Impairment: A Clinician’s Perspective

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Patients with mild cognitive impairment (MCI) are at high risk of progressing to dementia, thus they may benefit from potential interventions and therapies.

There is considerable debate about the definition of MCI and its pattern of progression, which creates difficulty in clinical practice.

There are no well-established preventative treatments shown to stave off dementia.

As clinicians, how can we best identify at-risk patients and clinically improve the lives of those with MCI?
Importance in Delaying AD

- Dementia: a decline in memory with aphasia, and/or apraxia, agnosia, or an impairment in executive functioning that together significantly compromise daily activities.
- Alzheimer’s Disease (AD) is the most common cause of dementia in the U.S.

Causes Of Dementia

- 62% Alzheimer's disease
- 17% Vascular dementia
- 10% mixed: Alzheimer's disease and vascular dementia
- 4% Lewy bodies
- 3% Other
- 2% Fronto-temporal
- 2% Parkinson's disease dementia

Importance of Delaying AD

- The number of patients with AD in the US is currently 5.4 million and is expected to be 14 million by 2050.
- Currently, the annual cost of care is $183 billion and rising.
- Mild cognitive impairment (MCI) is of clinical interest to best identify an at-risk population who may benefit from pharmacological or lifestyle interventions to delay or prevent AD.
- Clinical interventions that could delay AD by even as much as one year could provide significant healthcare savings and decrease morbidity and mortality.

MCI: A working definition

- MCI patients are neither demented nor normal, but are at high risk of progressing to dementia in the future when compared to age-matched cognitively normal individuals.

References:
MCI: A Working Definition

- The Petersen criteria includes:
  - Objective and subjective cognitive deficits greater than what would be expected for age.
  - No significant functional impairments or clinical dementia.

- Objective measure may include:
  - Scores more than 1.5 standard deviations below that of age appropriate norms in Neuropsychological testing.
  - A Clinical Dementia Rating (CDR) of 0.5 which has been suggested to be more sensitive in picking up cognitive impairment than neuropsychological testing. However, using the CDR is less accurate in predicting who will progress from MCI to dementia over time.

There is wide disagreement in classification and diagnostic criteria. No current consensus statements exist on the definition of MCI.

MCI: A Working Definition

- MCI patients are a heterogeneous group with some patients progressing to AD and some remaining stable or even improving. This diversity has caused researchers to look for subgroups that may have a higher risk of progression than others.

Epidemiology

- Prevalence depends on the definition of MCI.
- Lopez et al estimated in a large population-based study that approximately 19% of persons over the age of 75 meet criteria for MCI.
- MCI is about twice as prevalent as dementia.
- Rate of progression from MCI to AD is estimated at 6-25% per year.
- Risk factors may include depressive symptoms, increasing age, and lower levels of education.

Diagnosing MCI

- Multidimensional assessment is required
  - Patient and caregiver subjective rating of daily functioning
  - Psychiatric assessment
  - General medical assessment
  - Neuropsychological testing and Clinical Dementia Rating (CDR)
  - Neuroimaging
  - Biomarkers
Diagnosing MCI: Subjective Reporting and Clinician Assessment

- Caregiver and patient reports of daily functioning must be integrated.
- Clinicians must rule out functional deficits in activities of daily living which would indicate dementia.
  - Activities of daily living may include bill paying, housework, working, social interactions, hygiene, etc.

Diagnosing MCI: Psychiatric Assessment

- Must rule out psychiatric causes of cognitive deficits such as depression and anxiety.
- If depression is suspected, a trial of antidepressants is indicated before cognitive testing is done.
- General cognitive screening instruments such as the MMSE should be used in patients with suspected cognitive impairment.

Diagnosing MCI: Medical Assessment

- Must obtain a CBC, CMP and vitamin B12/folate levels in order to rule out somatic causes of cognitive deficits such as:
  - Metabolic abnormalities such as hypoglycemia, uremia, liver failure, hyper/hypothyroidism, hypernatremia, and hypercalcemia.
  - Infection
  - B12 or folate deficiencies
- Other tests such as CSF studies, HIV serology, syphilis screen or EEG to rule out seizure disorders can be ordered according to clinical judgment.

Diagnosing MCI: Neuropsychological Testing

- May assist in diagnosing MCI, but is not definitive.
- There is no current consensus on which battery of tests to perform, but common domains such as verbal and logical recall, attention, processing speed, visuo-constructional function, executive functioning and semantic fluency should be included.
- May allow for distinction of MCI subtypes.

Diagnosing MCI: Neuropsychological Testing

- **Memory**
  - WMS-R/III Logical Memory II [42, 43]
  - WMS-R/III Visual Reproduction II [42, 43]
  - California Verbal Learning Test I/II: long delay free recall [44, 45]
  - Rey Complex Figure Test: 3-minute delay recall [46]

- **Attention/processing speed**
  - WAIS-III Digit Span [47]
  - WAIS-III Digit Symbol [47]
  - Trail Making Test: part A [48]

- **Language**
  - Boston Naming Test [49]
  - Category Fluency: Animals [50]

- **Visuospatial**
  - WAIS-III Picture Completion [47]
  - WAIS-III Block Design [47]
  - Rey Complex Figure Test: Copy [46]

- **Frontal/executive function**
  - Controlled Oral Word Association Test: FAS [50]
  - Stroop Test: Color-Word Interference [51]
  - Trail Making Test: part B [48]
  - Wisconsin Card Sorting Test [52]

Diagnosing MCI: Clinical Subtypes

- Amnestic type—defined as 1.5 standard deviations below the mean on cognitive tests based on memory.
- Nonamnestic type—defined as 1.5 standard deviations below the mean on cognitive tests based on language, visuospatial skills, attention or executive functioning.
- Both amnestic and nonamnestic types can have cognitive deficits in a single or multiple domains.
- Impairment in both amnestic and nonamnestic domains, or impairment in more than one test in each area was associated with a greater likelihood of progression to dementia over time.

Diagnosing MCI: Clinical Dementia Rating (CDR)

- CDR is a numerical scale used to quantify the severity of dementia that uses a structured interview format to assess patients in six areas:
  - Memory
  - Orientation
  - Judgment and Problem Solving
  - Community Affairs
  - Home and Hobbies
  - Personal Care

- MCI is generally defined as a CDR rating of 0.5.
  - Mild dementia CDR=1
  - Moderate dementia CDR=2
  - Severe dementia CDR=3

Diagnosing MCI: Neuroimaging

- MRI may be used to rule out cerebral infarction, mass lesion, or subdural hematoma.
- Not currently definitive in diagnosing MCI, but may be more clinically useful in the future.
- Research has shown decreased medial temporal lobe volumes in patients with MCI, but this is not standardized for clinical use.

Diagnosing MCI: Neuroimaging

- PET scan may be useful to distinguish frontotemporal dementia from Alzheimer’s disease, but is not covered by Medicare in the absence of dementia.

- Decreased temporoparietal blood flow on SPECT may predict a higher rate of conversion from MCI to AD.

Diagnosing MCI: Biomarkers

- The presence of the APOE ε4 allele is associated with an 1.4x increased risk of developing MCI.
- This allele is also correlated with a more rapid rate of cognitive decline and increased rates of stroke.
- PET scans show differences between brains with the APOE ε4 allele and those without in patients with no cognitive complaints.
- It is currently not recommended to screen all patients for the APOE ε4 allele as there are no current treatment strategies in place.
- In the future, a brain scan and assessment of genetic risk could identify patients with greater risk of MCI and dementia before they become symptomatic, thus enabling them to receive treatments earlier.

Diagnosing MCI: Clinical Assimilation

- There is a great deal of disagreement about what constitutes “normal” cognitive decline of aging, making the diagnosis of MCI even more difficult.
  - Some studies use young normal patients as controls while others use age-related elderly patients with no co-morbid psychiatric or medical illnesses.

- While measures such as neuropsychological testing, neuroimaging and scales of daily functioning may be useful in identifying patients at risk for dementia, there is still no objective cutoffs or consensus for ultimately defining MCI.

- A clinical assimilation of data is necessary and clinicians must use their best judgment to diagnose a patient with MCI.

Predictors of Progression

_rates of progression from MCI to clinical dementia depend on the definitions used, but may be as high as 10%-15% annually._

*It is estimated that up to 50% of patients with MCI will transition to dementia in 5 years.*

*Some studies show that patients with MCI have neuropathological evidence of AD such as senile plaques on autopsy, thus MCI may not be a separate diagnosis, but rather early AD._

*Other studies show that there is improvement from MCI to normal functioning and cognition over time in the population._


Predictors of Progression

- Teng et al. showed that MCI patients with neuropsychiatric symptoms such as apathy and depression had higher rates of progression to AD after 25 months of follow-up.
  - Treating these depressive symptoms did not result in improved neuropsychological testing performance or delay progression to AD.
- Neuropsychological testing performance, functional, structural, neuroimaging and CSF biomarkers have shown differing amounts of promise in predicting who will progress from MCI to AD.
- MCI subjects with lower scores on the MMSE and subjects with amnestic MCI may be more likely to progress.

Talbert MH et al: Neuropsychological prediction of conversion to Alzheimer’s Disease in patients with mild cognitive impairment. Arch Gen Psychiatry 2006;63:916-924.
Clinical Follow-Up

- There are currently no definitive preventive interventions or treatments available for MCI.
- Office visits are recommended every 6-12 months for cognitive assessment, patient education, and evaluation of conversion to dementia.
- There are insufficient data to recommend the cognitive screening of asymptomatic individuals.

Clinical Follow-Up

- Full neuropsychological testing may be repeated every 1-2 years or when clinically required.
- Patients should be encouraged to adapt lifestyle changes that may be helpful.
- Physicians should educate families on the need for medical, legal and financial planning if dementia does occur.

Pharamacological Treatment

- There are currently no proven pharmacological treatments for MCI.
- Acetylcholinesterase inhibitors, NDMA antagonists, various vitamins, antioxidants, and certain anti-inflammatory drugs have failed to prevent the rate of progression of MCI to dementia.
- Acetylcholinesterase inhibitors and NDMA receptor antagonists have been approved for symptomatic treatment of dementia in AD, but have not been shown to alter the disease process itself.

Lifestyle Changes

- Exercise is associated with a lower risk of dementia.
  - Walking three times per week or other moderate exercise has shown this effect.
  - Protective effect seems to increase as activity increases.
- Mechanisms:
  - Increased synaptogenesis, plasticity and neural responses to stress through exercise-induced endorphins and other growth factors.
  - Exercise increases blood perfusion to the brain and may stimulate angiogenesis.

Lifestyle Changes

- Clinicians should aggressively manage cardiovascular risk factors such as hypertension, diabetes and hyperlipidemia.
- All elderly patients should be encouraged to eat a low-fat, high-fiber diet with plenty of fruits and vegetables.

Lifestyle Changes

- The Seattle Longitudinal Study found there may be a neuroprotective effect in higher levels of intellectual activity in the elderly, such as dancing, crossword puzzles, and volunteering, particularly those that involve language and social interaction.
- Cognitive training may improve mood as well as cognition.
- Social networking has been shown to be important.
  - Increased loneliness, decreased social networking and fewer social activities seem to be associated with a higher risk of progression to AD.

Further Questions

- “MCI is a syndrome of increased risk, not a definite diagnosis of a neurodegenerative disease.”—Rosenberg, Johnston and Lyketsos
- How do we best define MCI and identify patients who may benefit most from preventative treatment?
- How can neuroimaging and biomarkers be used clinically to identify at-risk populations?
- How can we find factors that delay the onset of MCI and dementia, slow the disease progression or prevent cognitive decline?
- What treatments, either pharmacological or lifestyle interventions are effective?