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# Mild cognitive impairment: Hope for stability, plan for progression

## ABSTRACT

Mild cognitive impairment (MCI) is a common heterogeneous syndrome that in some cases is transitional between normal age-related cognitive changes and dementia. Identifying it early may lead to prompt recognition of reversible causes and allows for timely future planning. This article describes definitions of MCI and its evaluation, differential diagnosis, and management.

## KEY POINTS

MCI that primarily involves memory or multiple domains has a higher risk of progressing to dementia.

Depression and the effects of anticholinergic medication can mimic MCI, and these should be looked for in patients presenting with cognitive loss.

Impaired functional status as reflected in activities of daily living is an important sign of progression from MCI to dementia.

Acetylcholinesterase inhibitors are not approved for treating MCI, have shown little efficacy in altering progression to dementia, and have multiple side effects.

Enhancing physical and mental health and developing strategies to compensate for deficits are key management approaches.

AS OUR POPULATION AGES, people are thinking more about preserving their quality of life, especially with regard to maintaining their cognitive and functional abilities. Older patients and caregivers often raise concerns about cognitive issues to their primary care providers: many patients have memory complaints, are worried about whether these are merely part of normal aging or symptoms of early dementia, and want strategies to forestall the progression of cognitive impairment.

Mild cognitive impairment (MCI) is a heterogeneous syndrome that in some cases represents a transition between normal aging and dementia. However, this condition is not yet well understood. Although some patients progress to dementia, others remain stable, or even improve. This article will review the current definitions and the underlying physiology of MCI, as well as diagnostic and management strategies.

*See related editorial, page 853*

## COGNITIVE CHANGES OCCUR WITH NORMAL AGING

Cognition is defined as a means of acquiring and processing information about ourselves and our world. It includes memory as well as other domains such as attention, visuospatial skills, mental processing speed, language, and executive function. Cognitive abilities typically peak between ages 30 and 40, plateau in our 50s and 60s, and decline in our late 70s.

With age come detectable changes in the brain: brain weight declines by 10% by age 80, blood flow diminishes, neurons are lost

TABLE 1

## Differentiating cognitive concerns

CONCERN	NORMAL AGING	MILD COGNITIVE IMPAIRMENT	DEMENCIA
<b>Complaints of memory loss</b>	Can remember details around issues as they relate to memory concern	With some delay, able to recall issues as they relate to memory concern	Not able to remember details around memory concern
<b>Short-term memory</b>	Preserved	Impaired in amnestic subtypes	Impaired
<b>Cognitive evaluation</b>	Normal	Normal or mildly impaired	Impaired
<b>Interpersonal social skills</b>	Preserved	Usually preserved	Impaired
<b>Activities of daily living</b>	Preserved	Preserved	Impaired
<b>Instrumental activities of daily living</b>	Preserved	Frequently impaired (especially managing finances)	Impaired

throughout life, and nerve conduction slows. Despite these changes, the brain has a great deal of functional reserve capacity.

TABLE 1 compares the signs of normal aging, MCI, and dementia. Normally, cognitive abilities decline gradually with age without affecting overall function or activities of daily living. Even in normal aging, the processing of new information (new learning) is reduced. Mental processing becomes less efficient and slower. Visuospatial skills gradually decline, recall slows, and ultimately, the speed of performance slows as well. Additionally, distractibility increases. On the other hand, normal aging does not affect recognition, intelligence, or long-term memory.<sup>1</sup>

The line between the normal effects of aging on cognition and true pathologic cognitive decline is blurry. In a busy clinical practice, it is often difficult to determine whether problems with memory and cognition that elderly patients and their family members describe represent true pathologic decline. In general, the clinical presentation of MCI is more profound than that of age-associated cognitive impairment: whereas normal aging may involve forgetting names and words and misplacing things, MCI frequently involves forgetting conversations, information that one would ordinarily remember, appointments, and planned events.

## BETWEEN NORMAL AGING AND DEMENCIA

MCI is a transitional state between normal cognition and dementia. But the course is not inevitably downward: on follow-up, patients with MCI may be better, stable, or worse (see **PROGNOSIS VARIES**, below).

On autopsy studies, the brains of people with MCI appear intermediate between normal brains and brains of people with Alzheimer-type dementia, which have neurofibrillary tangles, amyloid senile plaques, and neuronal degeneration.

## Definitions of MCI vary

True cognitive decline that is more profound than normal aging was named and defined differently in different studies, making comparisons difficult. The concept of MCI arose from the term “benign senescent forgetfulness,” used by Kral in 1962.<sup>2</sup> Other early terms include “cognitive impairment no dementia,” “memory impairment,” “mild cognitive disorder,” and “mild neurocognitive disorder.”<sup>3,4</sup>

MCI was first defined as a precursor to Alzheimer dementia. The term later described a sometimes reversible but abnormal state. It is a heterogeneous syndrome in terms of etiology, incidence, prevalence, presentation, and overall prognosis.

Normal aging involves forgetting names and words; MCI involves forgetting conversations

Most recently, MCI has been defined as<sup>5,6</sup>:

- Subjective memory complaints, preferably qualified by another person
- Memory impairment, with consideration for age and education
- Preserved general cognitive function
- Intact activities of daily living
- Absence of overt dementia.

MCI may arise from vascular, neurodegenerative, traumatic, metabolic, psychiatric, and other underlying medical disorders.<sup>7-9</sup>

The prevalence of MCI is difficult to determine because of the various definitions, populations studied (eg, clinic-based vs community-dwelling), and evaluation techniques. Published rates vary from 2% to 4% in all patients to 10% to 20% in the elderly. Incidence rates in the elderly vary from 14 to 75 per 1,000 patient-years.<sup>10-14</sup>

## EARLY RECOGNITION ALLOWS PROMPT EVALUATION AND PLANNING

Pathologic cognitive decline is best detected early, for many reasons. Early recognition and intervention may help delay further decline. Establishing a diagnosis can also lessen family and caregiver stress and misunderstanding. Education of caregivers is important so that they can prepare for likely behavioral changes and plan for future care. Advance care planning, including advance directives, power of attorney, and designation of proxy for decision-making, is extremely important and is best considered before cognitive impairment becomes severe.

The diagnosis of MCI also provides the opportunity to assess safety concerns related to driving, working, medication compliance, the home environment, and firearms. Because patients with MCI are still highly functional, these issues need not be fully evaluated and should be handled on a case-by-case basis, depending on concerns raised. For example, if depression is an active concern, firearms safety should be addressed.

## MEMORY LOSS MAY NOT BE THE PRIMARY CONCERN

MCI is categorized into two types based on

TABLE 2

### Functional assessments

#### Activities of daily living

Personal hygiene (bathing, oral care)

Dressing

Feeding self

Transferring

Toileting

Ambulating

#### Instrumental activities of daily living

Cooking

Housekeeping

Laundry

Transportation

Shopping

Using telephone

Medication management

Handling finances

whether memory loss is the primary cognitive deficit.

The **amnesic type** predominantly involves memory problems and is more common. Generally, several years elapse between initial memory concerns and a clinical diagnosis of MCI. Patients with amnesic MCI that progresses to dementia are more likely to develop Alzheimer disease.<sup>2,15</sup>

**Nonamnesic types** involve domains of cognition other than memory, such as executive function, attention, visuospatial ability, and language. Nonamnesic MCI can be subcategorized through extensive neuropsychological evaluation as involving single or multiple impaired domains.<sup>16,17</sup> Such categorization is particularly important in determining prognosis, as patients with involvement of multiple domains are at higher risk of progressing to dementia.

Patients with nonamnesic MCI who progress to dementia are more likely to have non-Alzheimer types of dementia, such as Lewy body dementia and frontotemporal dementias.<sup>10</sup>

**Advanced care planning is best made before cognitive impairment becomes severe**

TABLE 3

**Differential diagnosis of mild cognitive impairment (MCI)**

Delirium

Depression

Dementia

Potentially reversible conditions

Vitamin B<sub>12</sub> deficiency

Hypothyroidism

Anticholinergic medications

Sleep disorders

Central nervous system disorders (uncommon causes of MCI in absence of focal deficits)

Tumors

Stroke

Subdural hematoma

Normal pressure hydrocephalus

Epilepsy

Traumatic brain injury

Infectious conditions

HIV disease

**HISTORY SHOULD FOCUS ON FUNCTION, MEDICATIONS, AND DEPRESSION**

Cognitive impairment should be clinically evaluated within the context of cognition, function, and behavior. Clinicians should focus on the time course of cognitive concerns, the specifics of the concerns, and their impact on day-to-day living and functioning. In assessing functional capacity, it is important to determine the level of assistance the patient needs to perform specific activities of daily living and instrumental activities of daily living (ie, the more advanced skills needed to live independently) (TABLE 2).

A thorough history includes consideration of baseline education, intellect, and previous learning disabilities; sensory impairments with emphasis on sight and hearing impairments; uncontrolled pain; head trauma; sleep disorders; concurrent medical and psychosocial

illnesses such as depression and anxiety; substance abuse; and polypharmacy.

Depression, delirium, and the use of anticholinergic drugs are particularly important to evaluate, as these can result in cognitive deficits associated with MCI. The cognitive deficits may resolve with treatment or with stopping the drug.

Behavioral concerns such as wandering, agitation, and anger and sleep concerns, eating habits, and social etiquette are also important to evaluate.

**PHYSICAL EVALUATION: RULE OUT REVERSIBLE CONDITIONS**

The differential diagnosis of MCI includes delirium, depression, dementia, possibly reversible conditions affecting cognition (vitamin B<sub>12</sub> deficiency, hypothyroidism, effects of anticholinergic drugs), and uncommonly, central nervous system conditions (normal pressure hydrocephalus, subdural hematoma, tumor, stroke), and others (TABLE 3).<sup>18</sup>

A thorough physical examination should include neurologic, cardiovascular, hearing, and vision examinations, as well as an evaluation of functional status.

**Laboratory studies.** Although evidence is lacking to support a laboratory diagnostic workup for MCI, a selective evaluation including a comprehensive metabolic profile, complete blood count, thyroid studies, and a vitamin B<sub>12</sub> level can be useful. Occasionally, a treatable cause of impaired cognition such as vitamin B<sub>12</sub> deficiency or thyroid disease can be identified and resolved. A further comprehensive laboratory evaluation should be obtained if a patient progresses to dementia.

**Imaging** can be used in conjunction with other supportive evidence but should not be used solely to establish a diagnosis of MCI. Magnetic resonance imaging (MRI) can detect metastatic disease, normal pressure hydrocephalus, and subdural hematoma, in addition to traumatic, inflammatory, infectious, and vascular causes of cognitive impairment. MRI can also determine focal areas of atrophy; temporal lobe atrophy is a risk factor for progression to dementia.

**Other studies.** Structural MRI using techniques to evaluate the hippocampus, func-

Evaluation should focus on cognitive concerns and their impact on daily life

TABLE 4

### Characteristics of brief cognitive instruments

COGNITIVE INSTRUMENT	MINI-MENTAL STATE EXAM	MONTREAL COGNITIVE ASSESSMENT	SAINT LOUIS UNIVERSITY MENTAL STATUS
<b>Characteristics</b>	19 items; maximum score = 30	12 items; maximum score = 30	11 items; maximum score = 30
<b>Domains evaluated</b>			
Orientation	+	+	+
Registration	+	+	+
Short-term recall	+	+	+
Verbal fluency	+	+	
Abstraction		+	+
Attention	+	+	+
Executive function		+	+
<b>Average time to administer test</b>	10–15 minutes	10–15 minutes	7–10 minutes
<b>Bias</b>	Cultural	Educational	None

SOURCE: KANSAGARA D, FREEMAN M. A SYSTEMATIC REVIEW OF THE SIGNS AND SYMPTOMS OF DEMENTIA AND BRIEF COGNITIVE TESTS AVAILABLE IN VA. VA-ESP PROJECT #05-225; 2010.

tional imaging, genetic testing for ApoE4 alleles, and biomarkers in cerebrospinal fluid are currently under evaluation to identify those at risk of progression to dementia. Recently published guidelines by the Alzheimer's Association and the National Institute on Aging indicate that pathophysiologic findings in MCI that may predict future Alzheimer disease are meant to guide research and are not part of clinical practice at this time.<sup>19</sup>

#### COGNITIVE AND NEUROLOGIC TESTING IDENTIFIES DEFICITS

A number of global measures of cognition can be used in the office in clinical practice to help in evaluating significant cognitive concerns and to determine areas and severity of deficits at presentation. These include the Mini-Mental State Examination, the Montreal Cognitive Assessment, the Saint Louis University Mental Status, and many others (TABLE 4).<sup>20</sup>

Caveats about interpreting the results: each of these tests has different sensitivities

and specificities for detecting MCI. Also, we need to take into account the patient's level of education, as highly educated people tend to do better on these tests.<sup>21–23</sup> It is important to note that some patients with MCI have normal results or only minimally abnormal results on these tests.

Neuropsychological testing is reserved for patients needing further evaluation, eg, those with atypical or complex cases, and those in whom the specific domains of cognition involved need to be identified. It can also provide additional insight into the contribution of depression to cognitive deficits. Neuropsychological testing is usually very time-intensive and requires patients to be able to perform complicated cognitive tasks. Not all patients are good candidates for this testing; sensory and motor impairments must be considered to determine if patients can adequately participate in testing. The cost of neuropsychological testing for MCI may not be covered by insurance and should be discussed with patients before referral. Specific concerns about cognitive problems that need further eval-

**A treatable cause of cognitive impairment may be detected with vitamin B<sub>12</sub> and thyroid testing**

uation should be stated in the referral.

No one test should be used to make a diagnosis of MCI or dementia; clinical judgment is also necessary. The need for referral to a neurologist, geriatrician, or psychiatrist depends on the nature of the cognitive and behavioral concerns, the complexity of making a diagnosis, the need for further assessment of functional ability, and the need for evaluation of risk of progression to dementia.

### ■ MEDICATIONS HAVE LITTLE ROLE IN MANAGEMENT

No drug has yet been approved by the US Food and Drug Administration for treating MCI.

The acetylcholinesterase inhibitors donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon) have undergone clinical trials for treatment of MCI but have not been definitely shown to significantly reduce the risk of progression to dementia.<sup>24</sup>

On the other hand, Diniz et al<sup>25</sup> performed a meta-analysis of the use of cholinesterase inhibitors in patients with MCI as a means of delaying the progression to Alzheimer disease.<sup>25</sup> They calculated that 15.4% of patients who received these drugs progressed to dementia, compared with 20.4% of those who received placebo, for a relative risk of 0.75 (95% confidence interval 0.66–0.87,  $P < .001$ ). They concluded that the use of these drugs in patients with MCI “may attenuate the risk of progression” to Alzheimer disease and dementia.

In addition to not being approved for this indication and showing mixed evidence of efficacy, these drugs have well-known side effects such as diarrhea, nausea, vomiting, anorexia, and rhinitis, as well as significant but lesser-known side effects such as syncope, bradycardia, gastrointestinal bleeding, and vivid dreams.<sup>26</sup>

Nevertheless, some patients with MCI, particularly those at high risk with amnesic MCI, may still want to try these medications. In these cases, the risks and possible benefits (or lack of them) should be reviewed thoroughly with the patient and family, and the discussion should be documented before starting therapy. The lowest starting dose of acetylcholinesterase inhibitor should be used to determine tolerability; generally, the dose is increased after 4 weeks to a maintenance dosage, with particular

consideration of side effects.

Other agents have also been evaluated for MCI but have shown no evidence of benefit. Nonsteroidal anti-inflammatory drugs have not been found to either improve symptoms or delay progression to dementia. Ginkgo biloba has shown unclear benefit in achieving important treatment goals for MCI,<sup>27</sup> and it increases the risk of bleeding in the elderly. Vitamin E was evaluated in one study and did not slow progression to dementia.<sup>28</sup>

### ■ STAYING HEALTHY AND ACTIVE MAY HELP

We recommend optimizing vascular risk factors such as diabetes, blood pressure, smoking, and lipid levels in managing MCI, given that uncontrolled vascular risk factors may lead to progression to dementia. However, we can point to no research to support this recommendation.

Cognitive rehabilitation involves training in deficient domains and developing strategies to compensate for deficits. Different interventions are used, including computerized simulation exercises, memory aids, organizational techniques, personal digital assistants, crossword puzzles, mind games, and other mentally engaging activities.<sup>29</sup>

Increasing physical activity is another aspect of treatment. Some studies have shown that it improves cognitive performance in MCI, at least in the short term.<sup>30,31</sup>

Optimizing mood and emotions is also important. If present, depression should be identified and optimally treated. Social activity can be useful and leads to less emotional stress and to better coping mechanisms.

A multidisciplinary approach may help patients and may also help relieve the burden on the caregiver. Periodic reassessment of cognitive and functional symptoms may be warranted.

Maintaining disease-specific registries of patients who have MCI may be useful to longitudinally follow patients and ensure that they get the care they need.

### ■ PROGNOSIS VARIES

MCI is a heterogeneous condition that often does not predictably progress to dementia. Patients and families should be told that having

**No one test determines MCI or dementia; clinical judgment is necessary**



MCI does not mean that the patient will necessarily get dementia.

Several studies have shown that the annual risk of progression to dementia for patients with MCI is 5% to 10% in community-dwelling populations and up to 15% in specialty-clinic patients.<sup>24,32</sup> In comparison, the incidence of dementia in the general elderly population is 1% to 3% per year.

On the other hand, a number of studies show that MCI improves significantly in up to 15% to 40% of patients and sometimes reverts to a normal cognitive state.<sup>33,34</sup> But prospective studies of patients with clinically diagnosed MCI usually find a low rate of reversion to a normal state.<sup>35,36</sup> Many are short-term follow-up studies of different populations, making generalizations difficult.<sup>14</sup>

Patients with impairment in instrumental activities of daily living may be more likely to have nonreversible MCI and may be at higher risk of progressing to dementia.<sup>37</sup>

## PATIENT AND FAMILY EDUCATION AND FOLLOW-UP CONSIDERATIONS

Caregiver education and stress management are important components of managing pa-

tients with MCI. Formally assessing caregiver stress is useful. Steps to prevent caregiver burnout include making use of respite care, counseling, education, and community resources such as adult day care and those offered by the Alzheimer's Association.

Clinicians should follow patients with MCI closely to evaluate progression, address specific concerns, minimize risks, emphasize healthy habits, manage concurrent illnesses, and evaluate management.

Functional status, as demonstrated by activities of daily living, is the most important determinant of progression of MCI to dementia and should be evaluated at each visit. Repeat cognitive testing should be done on patients who have significant loss of functional status. Changes in work habits also warrant further attention.

Patients diagnosed with MCI or those who have persistent cognitive concerns should be considered for neuropsychological evaluation after 1 year to assess specific deficits and progression of cognitive impairment.

Finally, consideration should be given to current clinical research, and referrals should be made to research centers that focus on MCI management and treatment.

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