A·D·R·C
for healthy brain aging

Mild Cognitive Impairment

Victor W. Henderson, MD, MS
Departments of Health Research & Policy (Epidemiology) and of Neurology & Neurological Sciences
Stanford University
Director, Stanford Alzheimer's Disease Research Center

Mild cognitive impairment (MCI) is a conceptually important way station between normal cognitive aging and dementia.

Cognitive aging and dementia

Cognitive aging represents typical changes in mental abilities that occur as people grow older. Dementia, in contrast, represents more drastic cognitive impairment. Dementia is the result of pathological change (change caused by disease) in the brains of some people as they age.

Cognitive aging has positive and negative effects on mental abilities. With time and experience, we gain new knowledge and skills. We become wiser. However, for most adults cognitive aging also brings slower mental processing, reduced mental flexibility, increased susceptibility to distraction, and more difficulty learning new things. As an example, the amount of detail recalled from a short story or the number of words recalled from a long list of words drops with age. This decline begins as early as age 20. Cognitive aging by itself does not lead to dementia.

Dementia is a general condition with many causes and two key features. Alzheimer's disease is the most common cause of dementia. The first key feature is cognitive decline that is not related to a temporary medical condition like medication toxicity. The second is an adverse impact on function or independence. Dementia is said to be present when cognitive decline interferes with independent function in usual, everyday activities, such as managing a household and paying the bills.

Mild Cognitive Impairment

MCI describes cognitive decline beyond what can be explained by age alone, but the decline has not affected function to an important extent. Through the years, various terms and definitions have been used for cognitive decline short of dementia.

Criteria for MCI were developed at the Mayo Clinic to describe people with memory loss but no dementia (Petersen et al., 1991). The goal was to identify people who seemed likely to develop Alzheimer's disease. The original criteria were (1) a memory complaint, (2) abnormal memory for age, (3) normal cognition apart from memory, (4) normal activities of daily living, and (5) no dementia. Neuropsychology tests were used to help determine normal general cognition and abnormal memory.

Five years later, an international working group expanded the concept of MCI to include deficits in mental domains other than memory (Winblad et al., 2004). It was thought that MCI should still represent cognitive decline short of dementia, but decline might be seen in ways other than memory (Table 1).

 Supported by the NIH (AG046366)

Table 1. General criteria for MCI

- Cognitive complaint
- Cognition not normal for age, but there is no dementia
- Cognitive decline by self-report or informant report and impairment on objective cognitive tasks, or evidence of decline over time on objective cognitive tasks, or both
- Essentially normal functional activities

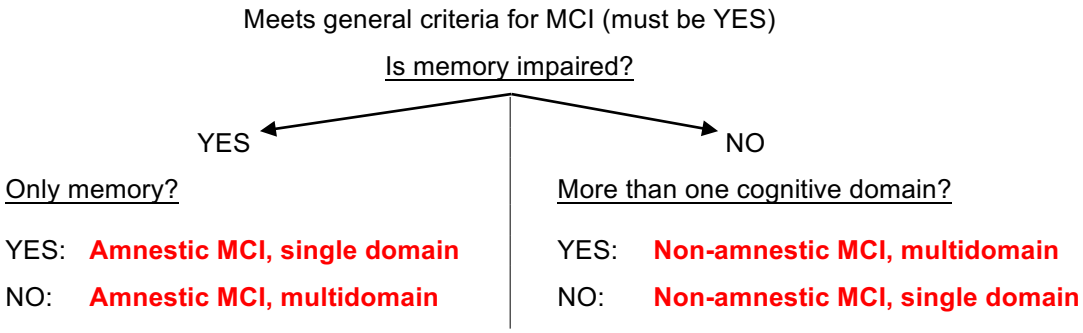
(after Winblad et al., 2004)

The proposal, which specified four varieties of MCI, was widely adopted and is used today (Figure 1). In this scheme, memory can be impaired by itself or memory can be impaired together with a deficit in one or more other cognitive areas. If memory is normal, an area of cognitive function other than memory can be impaired in isolation, or several areas of cognition can be impaired at the same time.

The word "amnestic" was used to describe the two varieties that involved memory and "non-amnestic" for the two varieties that did not. Amnestic MCI is about twice as common as non-amnestic MCI.

The four forms of MCI are conceived to represent the very early symptoms of a variety of dementing disorders, not just Alzheimer's disease. These other disorders include vascular dementia (caused by stroke and other processes affecting blood vessels and brain circulation), dementia with Lewy bodies or Parkinson's disease dementia, and frontotemporal dementia. In general, diseases that cause dementia are now well known. In a person with dementia, these diseases can be identified by a pathologist who examines the brain at the time of death.

Figure 1. Subtypes of Mild cognitive impairment (MCI)



(after Winblad, 2004)

When viewed in this way, dementia, MCI, and cognitive aging do *not* lie on a continuum (Table 2). Both dementia and MCI result from specific, identifiable pathological changes in the brain like, for example, the neuritic plaques and neurofibrillary tangles of Alzheimer's disease. Cognitive aging reflects other age-related changes that do not, by themselves, lead to dementia.

Table 2. Key characteristics of cognitive aging, MCI and dementia

Cognitive category	*Symptoms impair independence?*	*Symptoms due to dementia pathology?*
Cognitive aging	No	No
MCI	No	Yes
Dementia	Yes	Yes

(after Henderson, 2014)

Supported by the NIH (AG046366)

MCI due to Alzheimer's disease

Alzheimer's disease is the most common cause of dementia. Some researchers now refer to Alzheimer's disease in people without dementia, although in clinical practice Alzheimer's disease is understood to mean the presence of dementia.

A work group established by the National Institute on Aging and the Alzheimer's Association suggests that "MCI due to Alzheimer's disease" can be diagnosed in the presence of MCI when the medical history, physical examination, and laboratory tests fail to identify an alternative diagnosis other than Alzheimer's disease (Albert et al., 2011).

Biomarkers of MCI due to Alzheimer's disease

The work group suggested that a diagnosis of MCI due to Alzheimer's disease can be made with more assurance when spinal fluid tests or brain imaging tests provide additional evidence for Alzheimer changes in the brain (Albert et al., 2011). These tests are sometimes referred to as biomarkers, a laboratory measurement associated with the presence of a disease. Several broad categories of biomarkers are used to infer Alzheimer pathology in the brain. These are based on amyloid, tau, and nerve cell damage, and they are determined from cerebrospinal fluid measurements and from brain imaging studies (Albert et al., 2011; Jack et al., 2016).

Amyloid is an abnormal protein that aggregates and accumulates in brains of people with Alzheimer's disease. It is found in the core of the neuritic plaques. A low level of amyloid in the spinal fluid (the spinal fluid surrounds the brain) or a high level of amyloid on a brain scan provides biomarker support for Alzheimer change. Amyloid can be imaged by an amyloid-PET scan (PET stands for positron emission tomography). It is important to keep in mind that brain amyloid is a risk factor for Alzheimer's disease, but not everyone with this biomarker will go on to develop dementia.

Tau protein biomarkers are usually abnormal only after amyloid has begun to accumulate in the brain. Tau and phospho-tau levels are increased in the spinal fluid. (Phospho-tau is a modified form of tau protein, which is more specific — but not completely specific — for Alzheimer's disease). Tau-PET imaging may show increased amounts of tau in the brain. Like amyloid, phospho-tau accumulates in the brain in Alzheimer's disease, and it is the main component of the neurofibrillary tangles.

Other biomarkers assesses nerve cell injury inferred by brain shrinkage or by reduced brain metabolism. Computed tomography (CT) or magnetic resonance imaging (MRI) scans might show that the volume of the hippocampus or the entire brain is smaller than expected. (The hippocampus and nearby brain areas are involved in memory formation, and early microscopic changes of Alzheimer's disease affect this part of the brain.)

The brain can also be imaged with an FDG-PET scan, which provides a measure of metabolism in brain regions commonly affected by Alzheimer pathology. FDG-PET is based on the amount of blood sugar used by the brain. (FDG stands for fluorodeoxyglucose, a sugar-like molecule that can be labeled with a radioactive tracer.)

Tau and structural imaging (CT and MRI scans) biomarkers can be difficult to interpret in isolation, because other brain conditions damage neurons, not just Alzheimer's disease.

Assessment and treatment

The evaluation of MCI is similar to the evaluation of dementia but is in some ways more difficult. There is sometimes no clear distinction between cognitive problems due to MCI and problems due to cognitive aging on its own.

Physician evaluation

In most instances, a diagnosis of MCI should be made or confirmed by a geriatrician, neurologist, or geriatric psychiatrist. A neurologist is best qualified to recognize and diagnose early signs of neurological conditions that might cause MCI.

The physician's assessment includes a careful medical, neurological, and psychiatric history; a family history to see whether close family members have a similar or related disorder; a general physical examination; and a neurological examination. It is important for the physician to review prescription and over-the-counter medications. Many older adults take multiple drugs. A number of these impair mental function.

The physician should consider the possibility of underlying depression, sleep disorders like obstructive sleep apnea, excess alcohol consumption, and the presence of stressors that could affect mental abilities. These stressors might include work or financial problems, adjusting to retirement, marital problems, aging parents, difficult teenage and adult children, and many more.

The physician's evaluation includes tests of memory and other cognitive abilities. These can be supplemented when needed by more detailed testing by a neuropsychologist. The physician should consider the possibility of depression and look for evidence of anxiety.

Laboratory tests depend on the individual circumstances but usually include a screening blood test for kidney, liver, and related metabolic functions; a blood test for thyroid function; and a blood test to determine the level of vitamin B12. Brain imaging is performed if there is concern for an underlying brain disorder. Brain imaging with a CT (computed tomography) scan or MRI (magnetic resonance imaging) scan is used to evaluate brain structures and to help exclude stroke, tumor, and other less common neurological causes of cognitive impairment. None of these tests can prove the presence of early Alzheimer's disease.

Specialized biomarker testing (spinal fluid tests or PET scan imaging) is usually not needed, but it is useful for research can be considered when the added information may change treatment plans.

Clinical implications

MCI is a worrisome diagnosis, and people with MCI are at higher risk of dementia than someone without MCI.

Virtually everyone with dementia went through a stage of MCI. However, not everyone with MCI goes on to develop dementia. In a community setting, roughly 6% to 10% of older people with MCI develop dementia each year. Some people with MCI are later reclassified as normal.

At one time it was thought that amnestic forms of MCI would likely lead to Alzheimer's disease, whereas forms of MCI without memory impairment would more likely lead to dementia due to vascular disease

or some other disorder. However, Alzheimer changes may underlie most cases of MCI regardless of whether MCI is amnestic or non-amnestic. Conversely, some patients with amnestic MCI will turn out to have other dementia pathologies.

Treatment

The treatment of MCI depends on the underlying cause. There are specific treatments for disorders like depression, obstructive sleep apnea, and thyroid disease. Medication regimens can often be simplified or changed in ways less likely to affect cognition. Factors that increase the risk of stroke — like hypertension, diabetes, and high blood cholesterol — can be treated, and there are programs for cigarette smoking cessation.

There are no known effective drugs for MCI when the underlying cause is early changes of Alzheimer's disease or another neurodegenerative brain disorder. Drugs approved for treatment of dementia in Alzheimer's disease have not been shown to lower the risk of future dementia, and there is usually no improvement in cognitive symptoms.

Many physicians recommend regular physical exercise, mental stimulation, social engagement, and good nutrition for people with MCI. There is circumstantial evidence, but no proof, that these might help maintain cognitive abilities. If health permits, one target goal for aerobic exercise is brisk walking, about 150 minutes each week, divided into periods of about 30 minutes each, five days a week.

Mental activity is potentially important. People obtain mental stimulation through social interactions inside and outside the home, hobbies, computer tasks, card games and board games, and reading. There is no evidence that one form of mental stimulation — such as a set of computerized tasks — is better than another.

References

Albert, M.A., DeKosky, S.T., Dickson, D., et al. (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease. Alzheimers Dement. 7, 270-279.

Henderson, V.W. (2014) Three midlife strategies to prevent cognitive impairment due to Alzheimer's disease. Climacteric 17 (suppl. 2), 38-46.

Henderson, V.W. and Kerchner, G.A. (2014) Alzheimer's disease. Reference Module in Biomedical Sciences. Elsevier. doi: 10.1016/B978-0-12-801238-3.00017-9.

Jack, C.R. Jr., Bennett, D. A., Blennow, K., et al. (2016) A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology, 87, 539-547.

Petersen, R.C., Smith, G.E., Waring, S.C., et al. (1999) Mild cognitive impairment: clinical characterization and outcome. Arch. Neurol. 56, 303-308.

Winblad, B. Palmerm K. Kivipelto, M., et al. (2004) Mild cognitive impairment. Beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J. Intern. Med. 256, 240-246.

Resources

Alzheimer's Association
www.alz.org

National Institute on Aging, Alzheimer's Disease Centers
https://www.nia.nih.gov/research/dn/alzheimers-disease-centers

National Institute on Aging, Alzheimer's disease information resources
www.nihttps://www.nia.nih.gov/health/alzheimers

National Institute on Aging, Alzheimer's disease fact sheet
www.nia.nih.gov/alzheimers/publication/alzheimers-disease-fact-sheet

Stanford Alzheimer's Disease Research Center
adrc.stanford.edu

Stanford Center for Memory Disorders
https://stanfordhealthcare.org/medical-clinics/memory-disorders-center.html

Stanford Health Care Aging Adult Services
https://stanfordhealthcare.org/medical-clinics/aging-adult-services.html