

Mild cognitive impairment

A way station along the road to Alzheimer's

By Ronald C. Petersen, MD, PhD

An unprecedented global shift toward an aging population has brought with it an increase in the occurrence of cognitive impairment such as Alzheimer's disease (AD). With the baby boom generation beginning to arrive at the age of risk, this issue may be approaching crisis proportions. If nothing is done to delay the onset or slow the progression of AD, experts at the Alzheimer's Association warn that this single disease entity may bankrupt the health care system as we know it. Consequently, a great deal of attention is being directed toward the assessment and prevention of cognitive impairment.

In the field of age-related dementia, there is likely a continuum from normal aging through an intermediate stage often called Mild Cognitive Impairment (MCI) on to dementia, including Alzheimer's disease. By cognitive impairment, we typically refer to a person's ability to remember, read, write, problem-solve, perform calculations, and navigate around the environment. The most common indicator of early Alzheimer's disease involves an insidious progression of forgetfulness. The challenge for clinicians lies in assessing the question: "How much forgetfulness is too much?" Some incidental episodes of forgetfulness—"Where are my car keys?" or "Where are my reading glasses?"—are likely common expressions of normal aging. However, when individuals begin to forget important information such as doctors' appointments and luncheon engagements with friends and, most importantly, when they do this on a repeated basis, there may be reason for concern about an evolving memory problem. Typically, when a person's friends and family begin to notice forgetfulness in the individual, it is time to seek medical attention.

How MCI relates to dementia

A great deal of research in aging and dementia is now focused on MCI. This is a clinical condition in which people are found to be more forgetful than they used to be and more forgetful than they ought to be. Research has shown that individuals who fit this profile have an increased risk of developing Alzheimer's disease in subsequent years. Often, these individuals are experiencing increasing forgetfulness despite having relatively preserved language abilities, visual perception of spatial relationships (such as the skills needed to put together a jigsaw puzzle), and problem-solving capacities. Their function around the community appears to be relatively normal and, to the casual observer, they look quite normal. However, when these individuals seek medical attention, the clinician finds that the degree of forgetfulness exceeds what would be expected for the patient's age and education.

At the Mayo Clinic in Rochester, investigators are pursuing these issues in the Mayo Clinic Study of Aging. This project, funded by the National Institute on Aging, is a study over time of a 2,000-person random sample of 70- to 89-year-olds in Olmsted County, Minnesota. Study participants undergo a three-part evaluation: 1) a thorough personal, medical and family history by a nurse or study coordinator; 2) a cognitive examination by a psychological measurement specialist and a neuropsychologist; and 3) a medical and neurologic examination by a physician. Each case is then judged by a consensus panel to determine if the individual is 1) functioning normally for his or her age and education; 2) meets criteria for MCI; or 3) meets criteria for dementia. The participants are evaluated annually. At each evaluation a great deal of additional information is acquired, including MRI scans, blood samples for DNA and plasma proteins, historical data on cognitive and intellectual activities, dietary information, a quantitative assessment of gait, and a measure of olfactory functioning, which can be associated with degree of dementia in AD.

The long-term goal of this project is to describe trajectories of successful aging, typical aging, and impaired aging from a cognitive perspective. Ultimately, we hope to identify a model that might be useful at predicting who is going to follow which of the three aging trajectories. When disease-modifying therapies become available, this model could help clinicians decide when and how to intervene with individual patients.

Findings so far

Thus far, the Mayo Clinic Study of Aging has demonstrated that between 13 percent and 15 percent of individuals between the ages of 70 and 89 have MCI. Another 10 percent to 11 percent have dementia. The remainder are cognitively normal. The study is also assessing the rates at which individuals progress from normal aging to MCI, and has found an alarmingly high rate of approximately 5.3 percent per year. In addition, subjects already diagnosed with MCI progress to dementia at a rate of about 10 percent per year. These numbers, when projected onto the general population of the United States, predict a particularly alarming increase in the numbers of cognitively impaired individuals in the future. It is therefore incumbent upon the research community to accelerate investigations to find effective disease-modifying therapies.

MCI is being investigated worldwide, and several international studies on its prevalence and incidence have alerted the wider clinical community to the importance of this condition. In general, these studies corroborate the figures described in Olmsted County. There appears to be a significant concern for many societies around the world, and data from Minnesota may very well have a significant impact on these projections and, hopefully, ultimate interventions.

No treatments yet for MCI

Currently, there are no therapies for MCI. There have been several international drug trials in recent years investigating the commonly used therapies for AD on MCI subjects. Unfortunately, none of these therapies has been effective at preventing the development of AD. One study co-sponsored by the National Institute on Aging and pharmaceutical companies Pfizer and Eisai, Inc., indicated that donepezil (Aricept) may be able to reduce the risk at which MCI individuals progress to AD for 12 months and, in a particular genetic subset of subjects, for up to 24 months. However, over the entire 36-month course of the study, no differences among the groups were observed at the end. The other treatment studied, high-dose vitamin E, was of no benefit. While the donepezil study was tantalizing in suggesting that it may someday be possible to delay the progression to AD, it is clear that better therapies need to be developed.

In general, research in aging and dementia is moving toward identifying the disease at its earliest point in the clinical spectrum. As in the Mayo Clinic Study of Aging, several efforts are under way evaluating the potential benefit of various imaging and chemical biomarkers at predicting who is going to get the disease in the future. One of these projects is sponsored by the state of Minnesota through the University of Minnesota–Mayo Clinic partnership. Investigators at the university are collaborating with counterparts at Mayo to develop new predictive tests to be used early in the clinical course.

A great deal of work is progressing on aging and cognitive impairment in society. This is a particularly important problem, and greater resources need to be expended to develop better analytical tools as well as intervention strategies. This is a high priority for the National Institute on Aging, and it may well be that studies performed in Minnesota will inform the worldwide community about this pending crisis.

Ronald C. Petersen, MD, PhD, is director of the Mayo Clinic's Alzheimer's Disease Research Center, one of 29 such centers across the country designated and funded by the National Institute on Aging of the National Institutes of Health.

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