EDITORIAL

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Mild cognitive impairment: Challenges in research and in practice

THE INTEGRITY OF COGNITIVE FUNCTION is a reliable indicator of healthy aging. But the progression of cognitive changes from normal aging to dementia is often insidious and easily underrecognized. Consequently, mild cognitive impairment (MCI)—the entity that characterizes this transition—has become an area of intense research. Since 1999, the number of research publications related to MCI has exploded, with more than 1,000 peer-reviewed studies in 2010 alone.

Controversy remains over the definition, diagnosis, prognosis, and management of MCI. However, in an evidence-based review of the literature,[1] the American Academy of Neurology concluded that MCI is a useful clinical entity and that patients with MCI should be identified and monitored because of the increased risk of progression to dementia.

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Early studies appeared to indicate that patients with MCI were at high risk of further cognitive decline and progression to Alzheimer dementia.[1] But subsequent research found that not all were, leading to the recognition of two subtypes of MCI: amnestic, which mainly involves memory loss, and nonamnestic, which involves impairment of other cognitive domains. Patients with the amnestic type were determined to be more likely to eventually develop Alzheimer disease.[2] The amnestic subtype is being considered for inclusion in the next revision of the Diagnostic and Statistical Manual of Mental Disorders, ie, the fifth edition (DSM-V).[3]

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MCI varies with each person affected. Neither its clinical nor its neuropathologic course follows a predictable, linear path, making its study especially challenging. The pathologic and molecular mechanisms of MCI are not well established. In the amnestic type, the distribution of cortical amyloid deposits appears transitional to the pathologic changes seen in Alzheimer disease.[4] But postmortem brain tissues[5] and clinical imaging studies[6] reveal that some normal controls have a degree of amyloid deposition similar to that in patients with MCI. These findings limit the use of amyloid lesions as a robust pathologic marker for distinguishing normal aging from MCI.

MCI is diagnosed clinically, and clinicians should be able to diagnose most cases of MCI in the office. The first step is cognitive concern (ie, a change from the patient's baseline cognitive status) raised by the patient, by an informant, or by a clinician. Often, in amnestic MCI, the earliest symptom is memory loss. Once persistent memory loss is documented, the patient is assessed for the ability to perform activities of daily living. To fulfill the criteria for the diagnosis of MCI, patients need to have intact function in the activities of daily living and no features of neurologic and psychiatric diseases that affect cognition. Further office-based cognitive testing helps to determine whether MCI is the amnestic or the nonamnestic type. A brief neuropsychological test such as the Montreal Cognitive Assessment often supports the diagnosis of MCI, although accurate characterization of cognitive dysfunction is enhanced with thorough neuropsychological testing.

MCI is a useful clinical entity, and patients with MCI should be identified and monitored

MCI remains a clinical diagnosis with an imprecise prognosis. Although the amnestic

MCI criteria are reasonably specific, they do not always predict progression to Alzheimer disease. Growing evidence suggests that neuropsychiatric symptoms, including depression, apathy, and anxiety, are clinical predictors of the progression of MCI to Alzheimer disease, and that the added risk can be substantial. For example, in one study, the risk of incident dementia was seven times higher if apathy was present.[7] As such, a careful psychiatric evaluation of patients with MCI is strongly recommended and should be part of a comprehensive workup.

The study of MCI touches on almost all aspects of aging and dementia investigation. A great deal of research is focusing on the development of cerebrospinal fluid or imaging biomarkers of amyloid deposition, structural magnetic resonance imaging markers of neuronal loss, and genetic predisposition to detect the earliest signs of the disease in people who may be at risk. The rationale for the intense study of MCI is that the sooner the intervention in a degenerative process is started, the more likely that further cognitive and functional decline can be prevented: early diagnosis is paramount in trying to prevent subsequent disability. Clinical trials are needed to determine whether early detection of MCI or the detection of biomarkers in asymptomatic individuals alters the incidence of dementia or its prognosis.

Not all patients with MCI progress to Alzheimer disease, and some cases are reversible; thus, close follow-up is recommended

In this issue of the *Cleveland Clinic Journal of Medicine*, Patel and Holland[8] present a comprehensive overview of MCI and highlight the issues related to its diagnosis and management. The treatment of MCI is another area that is unclear. At this time, prescription of cognition-enhancing medications is not indicated. No pharmacologic agent is approved by the US Food and Drug Administration for treating MCI, although cholinesterase inhibitors have been studied. At the pathologic level, there is no clear consensus on whether presynaptic or postsynaptic (or both) cholinergic receptors are defective in MCI.[9] There is some evidence of increased choline acetyltransferase activity in the hippocampus and the superior frontal cortex.[10] Selected hippocampal and cortical cholinergic systems may be capable of compensatory responses in MCI. This may help explain why cholinesterase inhibitors are ineffective in preventing dementia in patients with MCI in therapeutic trials.

Patel and Holland recommend a reasonable multidisciplinary approach for managing MCI, although supporting evidence for such recommendations from clinical trials is lacking. Realizing that not all patients with MCI progress to Alzheimer disease and that some cases are reversible is cause for recommending close follow-up and monitoring of neuropsychiatric and cognitive symptoms in older patients.

MCI is now a clinical reality for all physicians dealing with older patients. Thus, MCI is of more than merely research interest to clinicians, who will come to recognize and diagnose this condition frequently in the aging population.

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