Appropriate Diagnosis of Mild Cognitive Impairment: Just What Is “Normal”?

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Research is needed to define clinical biomarkers and genetic screens that could be used to identify early stages of dementia and to link clinical syndromes with the later development of dementia.

The topic of appropriate diagnosis of mild cognitive impairment (MCI), which is the focus of the November 2011 issue of the American Journal of Geriatric Psychiatry, is timely given the recently proposed DSM-5 criteria for minor neurocognitive disorders that were tested in the Large Academic Sites Field trials performed by the American Psychiatric Association.1 This is the first time a cognitive diagnosis previously restricted to “pre-dementia populations” will be applied broadly to a variety of neuropsychiatric disorders.

It will be increasingly important to strengthen the definitions of what is “normal” to avoid the “pathologizing” of aging or of any individuals who experience temporary or continuous cognitive impairment. Defining “normal” memory is becoming increasingly important as the field understands the trajectory for individuals who progress beyond the expected age-associated memory loss and as effective treatments are developed to interrupt the neurodegenerative or cerebrovascular process and thereby improve outcomes. In the 1980s, “normal cognitive decline” had several names, including age-associated memory impairment, age-consistent memory impairment, and late-life forgetfulness. Many potential cognitive problems were dismissed as “senior moments.”1 Our understanding of what is “normal” cognition in the elderly has recently been refined. Considerable data support the validity of MCI, first described 20 years ago. MCI is of interest because subtypes have been shown to predict subsequent development of Alzheimer disease (AD) and other dementing illnesses. In fact, the probability of conversion from MCI to dementia is estimated to be approximately 15%. Estimates of the prevalence of MCI currently range from 5% to 29% and are climbing as the population ages.1

**MCI and its subgroups**

MCI is defined as cognitive decline that is greater than expected for an individual’s age and educational level, but that does not interfere notably with activities of daily life. The definition has been further characterized by Petersen and colleagues3 and the classification proposed by an international Work Group on MCI. That Work Group defined 4 subgroups:

- Amnestic MCI single cognitive domain
- Multiple cognitive domains (memory plus 1 or more non-memory domains)
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• Single non-amnestic (1 non-memory domain)
• Non-amnestic/multiple cognitive domains (more than 1 non-memory domain).

This classification system has been adopted by the NIH’s Alzheimer’s Disease Research Centers and provides a common definition for research and clinical care.

The amnestic and non-amnestic MCI subgroups have distinct etiologies and paths of cognitive decline. Recently, the diagnostic categories of MCI have been expanded to include both neuropsychiatric features as well as performance on complex functional activities. These changes are intended to incorporate data that support the mild changes in complex activities of daily living (ADLs) that often are the first signs of MCI. Complex activities or instrumental ADLs include financial management, housework, using a telephone, using public transportation, and shopping for groceries. Neuropsychiatric syndromes (apathy, depression, anxiety, irritability) have also been shown to be common features of MCI and are associated with an increased likelihood of developing AD.

In a comprehensive latent class analysis of 1655 patients enrolled in 29 NIH AD centers, Hanfelt and colleagues define 7 empirically based subgroups of MCI based on memory and functional and neuropsychiatric features: 3 are primarily cognitive (either memory problems alone, memory problems with other affected cognitive domains, or a non-amnestic subtype), 3 demonstrate prominent functional and neuropsychiatric disturbances (2 of these subgroups had prominent cognitive deficits and the third showed relatively normal cognitive performance), and 1 subgroup had minimal impairment.

This study reaffirmed that MCI is a heterogeneous syndrome and defines subtypes of MCI according to a common etiology. The authors found that cardiovascular disease (CVD) played an important role in psychopathology contributing to prominent functional deficits and neuropsychiatric symptoms. They hypothesize that CVD is related to neuropsychiatric symptoms based on previous research that CVD is associated with deficits in neuropsychiatric syndromes, including depression and apathy. Further, they hypothesized that patients in CVD subgroups would be more likely to progress to a vascular dementia.

Duara and associates move the bar even closer to normal cognition in defining a group of patients with pre-MCI. The criteria for pre-MCI are symptomatic cognitive and subtle functional impairment by history, without cognitive deficits confirmed on formal neuropsychological testing. The investigators find that more than 90% of patients who met criteria for pre-MCI showed neuropathology consistent with AD at autopsy; these patients had a conversion rate between that of normal controls and patients with MCI.

In this very ambitious study, the investigators compared the longitudinal course of 275 patients with pre-MCI, no cognitive impairment (NCI), non-amnestic MCI, amnestic MCI, or mild dementia over 2 to 3 years of follow-up and evaluated them on the basis of clinical, imaging, and neuropsychological characteristics. At baseline, the pre-MCI subjects could be distinguished from NCI subjects with subtle impairments on language and executive function diagnosed by experienced clinicians who interviewed them. These deficits were not apparent on neuropsychological testing; however, the patients did show higher apathy scores as well as smaller left hippocampal volumes. In support of pre-MCI as a harbinger for dementia, 28.6% of the pre-MCI subjects progressed to a formal diagnosis of MCI or dementia compared with 4.1% of community-dwelling elders. Compared with MCI patients, there were significantly fewer pre-MCI patients who progressed to dementia over the 2- to 3-year follow-up. Pre-MCI was therefore on the border of normal cognition and MCI.

Another common comorbidity of MCI is major depression, which is responsible for up to 50% of cases in the convenience samples with major depression. Yeh and associates explored MCI in patients in remission from late-life depression. They capitalized on the fact that mood disorders in late life are associated with both cognitive impairment and a higher rate of conversion to a dementing syndrome. As the investigators note, depression in elders is often accompanied by deficits in all major cognitive domains, including memory, executive function, and information-processing speed. Some cognitive problems may diminish with the successful treatment of the mood disorder. Often, however, residual deficits are detectable in individuals whose depression is in remission.

These investigators evaluated consecutive outpatients at a geriatric center in a university teaching hospital who were older than 59 years, who had no evidence of dementia or significant functional problems in ADLs, and who met criteria for major depressive episode currently in remission. Their results replicated those of earlier studies of cognitive impairment in patients in remission from late-life depression: more than half of their patients met criteria for MCI (52.3%): 28.5% had amnestic MCI and 23.8% had non-amnestic MCI. Patients with amnestic MCI had a later age of onset of depression and increased ventricular atrophy on MRI scans. Those in the non-amnestic MCI group had a significantly increased stroke risk.
Because late-life depression, ventricular atrophy, and amnestic MCI are all associated with AD, Yeh and colleagues hypothesize that those in the amnestic MCI subgroup have the highest risk of converting to AD. In comparison, those in the non-amnestic MCI group had a higher stroke risk and would be more likely to develop a vascular depression. Research is needed to define clinical biomarkers and genetic screens that could be used to identify early stages of dementia and to link clinical syndromes with the later development of dementia. An increased likelihood of developing dementia is associated with:

- Apolipoprotein E4 allele carrier status
- Decreased MRI volumetric measurements of the hippocampus and perihippocampal regions
- Cerebral hypometabolism on fluorodeoxyglucose PET scans in areas known to be affected in AD
- Elevated levels of τ protein and α/β amyloid ratios in the cerebrospinal fluid
- Elevated τ and amyloid biomarker levels in the neocortex on PET scans
- Abnormal activation patterns on functional MRI

These potential biomarkers can help identify preclinical populations who would benefit from comprehensive preventive interventions in an attempt to delay progression to dementia by reversing or halting neurodegenerative or cerebrovascular processes.

References:


For More Information

- Storandt M, Grant EA, Miller JP, Morris JC. Longitudinal course and neuropathologic outcomes in original vs revised MCI and in pre-MCI. Neurology. 2006;67:467-473.

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