06 - 21.6 Mild Cognitive Impairment

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patients despite long-standing suppression of viremia. AIDS. 2010;24:1243. 21.6 Mild Cognitive Impairment The past decade has seen the emergence of a new concept, mild cognitive impairment (MCI), which is defined as the presence of mild cognitive decline not warranting the diagnosis of dementia but with preserved basic activities of daily living. In the DSM-5, MCI is classified as mild neurocognitive disorder due to multiple etiologies or unspecified neurocognitive disorder. It will most likely receive more attention in future revisions of the DSM. DEFINITION

Although the term mild cognitive impairment has been in use for more than 25 years, it was suggested as a diagnostic category designed to fill the gap between cognitive changes associated with aging and cognitive impairment suggestive of dementia. The criteria proposed by the Mayo Clinic Alzheimer's Disease Research Center (MCADRC) are (1) memory complaint, preferably qualified by an informant; (2) objective memory impairment for age and education; (3) preserved general cognitive function; (4) intact activities of daily living; and (5) not demented (Table 21.6-1). However, at this time there are no international diagnostic criteria for MCI. Table 21.6-1 Mild Cognitive Impairment Original Criteria Historical Perspective The imprecise border between normal aging-related cognitive decline and dementia-related cognitive impairment has been described for several decades. Thus, in 1962, Kral introduced the terms benign senescent forgetfulness (forgetfulness for less important facts and awareness of problems) and malignant senescent forgetfulness (memory problems for recent events and lack of awareness). In 1986, the National Institutes of Mental Health (NIMH) recommended the term age associated memory impairment for age-related normal memory changes. In 1994, the International Psychogeriatrics Association presented the concept of age-associated cognitive decline, which described cognitive deficits including but not limited to memory impairment in the absence of dementia or other affecting cognitive conditions. Cognitive impairment no dementia was introduced in 1997 by the Canadian Study of Health and Aging to describe the presence of nondemented cognitive impairment regardless of the underlying process (neurological, psychiatric, medical). Several other classifications, including age-consistent memory impairment and late life forgetfulness, are defined on the bases of performance on various cognitive tests. The exact place of MCI in the psychiatric nosology will be challenging. Based on the current definition of MCI, functional impairment is an exclusion criterion for MCI, but the same "functional impairment" is one of the standard criteria for defining psychiatric disorders. Further developments in finding biological markers for MCI will probably contribute to a more solid conceptualization and, hopefully, treatment of patients with prodromal dementia (Table 21.6-2). Table 21.6-2 Terms Related to Mild Cognitive Impairment

EPIDEMIOLOGY AND ETIOLOGY OF MCI The recognition that Alzheimer's disease pathology may exist in the brain long before the presence of clinical symptoms led to the focus on preclinical stages, with the purpose of characterizing initial impairments that are associated with an increased risk of progression to Alzheimer's disease. The clinical expression of MCI can be viewed as a result of the interaction among several risk factors and several protective factors. The most significant risk factors are related to the different types of neurodegeneration witnessed in dementias. These are clinically expressed in different subtypes of MCI, especially those associated with amnesia. Other risk factors include the APOE4 allele status and cerebrovascular events in the form of either cerebrovascular accident or lacunar disease. The role of chronic exposure to high levels of cortisol, as seen in late life depression, is also hypothesized to increase the risk for cognitive impairment through hippocampal volume reduction. The notion of "brain reserve" suggests that effects of brain size and neuron density may be protective against dementia despite the presence of

neurodegeneration (a larger number of neurons and a bigger brain volume would protect against clinical manifestations of Alzheimer's disease despite the presence of neurodegeneration) (Fig. 21.6-1).

FIGURE 21.6-1 Outcome of clinical phenotypes of mild cognitive impairment (MCI) according to presumed etiology. AD, Alzheimer's disease; Depr, depression; DLB, dementia with Lewy bodies; FRD, frontotemporal dementia; VaD, vascular dementia. (Adapted with permission from Petersen RC, ed. Mild Cognitive Impairment: Aging to Alzheimer's Disease. New York: Oxford University Press; 2003.) CLINICAL PRESENTATION The clinical picture of MCI is a function of the criteria used to define it. Memory impairment is necessary but has been difficult to quantify. One measure has been objective loss of memory or other cognitive domain that is more than 1.5 standard deviations below the mean for individuals of similar age and education. Some have suggested subjective complaints of memory loss be used as a marker, but this runs the risk of many false-positive diagnoses. Assessment Neuropsychological Assessment. Most experts agree that earlier deficits are noted in episodic (vs. semantic) memory. There is no consensus among experts with regard to which memory tests and which cutoffs to use. There is a lack of norms, test scores do not have normal distributions, and test performance is influenced by multiple demographic characteristics. Several experts have proposed that a scale such as the delayed recall task from the Consortium to Establish a Registry for Alzheimer's Disease might be useful in detecting Alzheimer's disease in the earliest stages. Brief mental status instruments (e.g., the Mini-Mental State Examination) are relatively insensitive for the detection of memory problems in MCI. Biomarkers. Several markers of progression from MCI to Alzheimer's disease have been studies in the past decade. Among these, apolipoprotein E4 (ApoE4) allele carrier status has been one of the most prominent variables. For the amnestic MCI, ApoE4 has been shown to be a risk factor for a more rapid progression to Alzheimer's disease. Several CSF markers have also been identified as possible predictors of disease progression: Pathological low concentrations of Aβ42 (the 42 amino acid form of βamyloid) as well as pathological high concentrations of total tau (t-tau) and phospho tau (p-tau) may differentiate early Alzheimer's disease from normal aging. Locating alterations in the expression of proteins involved in the pathogenetic pathways of Alzheimer's disease (proteomic approach) is another approach used to help early detection of Alzheimer's disease. Several proteins (cystatin C, β-2 microglobulin, and BEGF polypeptides) have been detected through new techniques, and currently there are a number of proteins from both CSF and blood that are implicated in Alzheimer's disease pathology.

Genetics. Because MCI is regarded as the prodromal stage for several disorders (Alzheimer's disease, frontotemporal or vascular dementia), different genes are probably related to MCI. Four genes have been described in relationship with Alzheimer's disease: the amyloid precursor protein (APP) gene, presenilin-1 (PSEN1), presenilin-2 (PSEN2), and the apolipoprotein E (APOE) gene. Because the first three genes are involved in rare autosomal dominant forms of Alzheimer's disease, screening for each of these mutations will have very limited value for the diagnosis of MCI in the general population. The APOE gene, a common genetic risk factor for early as well as for late-onset Alzheimer's disease, has been studied more thoroughly in relationship to MCI, but the results have been inconsistent. Because the etiology of MCI is heterogenous, it is likely that a very large number of different genes underlie the pathology of MCI. Most of these genes are yet to be discovered. Neuroimaging. Advances in neuroimaging studies aim to develop measures allowing the differentiation between MCI and healthy aging as well as within MCI among subjects who will

convert to Alzheimer's disease or will remain stable over time. Structural studies of volumetric MCI showed early changes in the medial temporal structures, including neuronal atrophy, decreased synaptic density, and overall neuronal loss. Atrophy of the hippocampal volume and entorhinal cortex has been described in MCI. Atrophy of the hippocampal formation was also reported to predict the rate of progression from MCI to Alzheimer's disease. Three-dimensional modeling techniques have localized shape alteration and specific regions of atrophy within the hippocampus. Other methods such as tensor-based morphometry allow tracking brain changes in detail, quantifying tissue growth or atrophy throughout the brain and indicating the local rate at which tissue is being lost. Other innovations in neuroimaging include MR relaxometry, imaging of iron deposition, diffusion tensor imaging, and high-field MRI scanning. Perhaps the most promising development has been the advent of PET tracer compounds that visualize amyloid plaques and neurofibrillary tangles. These new compounds—Pittsburgh Compound B (carbon-11-PIB) and fluorine-18-FDDNP—track pathology changes in the preclinical stages of Alzheimer's disease. These specific tracers allow investigators to visualize the pathological process and are also used to monitor progression from MCI to Alzheimer's disease. However, the burden of β-amyloid plaques does not always correlate with the clinical stages because some MCI subjects can present with minimal burden similar to healthy control participants, but others have amyloid burden comparable to Alzheimer's disease participants. A single biomarker will probably be insufficient to identify incipient Alzheimer's disease. Thus, the combination of several markers further increases the accuracy of the prediction and will probably become the norm as described by recent studies (combination of decreased parietal rCBF and CSF biomarkers as Aβ42, t-tau, and p-tau) (Fig. 21.6-2).

FIGURE 21.6-2 Positron emission tomography images obtained with the amyloid-imaging agent Pittsburgh Compound-B ([carbon-11]-PIB) in a normal individual with mild cognitive impairment (MCI; center images) and a patient with mild Alzheimer's disease (AD) (far right). Some MCI patients have control-like levels of amyloid, some have Alzheimer's disease– like levels of amyloid, and some have intermediate levels. (Courtesy of William E. Klunk, M.D., University of Pittsburgh, Department of Psychiatry, Pittsburgh, PA. All rights retained.) Diagnostic Differential The Cognitive Continuum. The cognitive continuum describes the subtle pathway from age-related cognitive decline to MCI to dementia. Per this model, there is an overlap at both ends of MCI, which indicates that it can be quite challenging to identify the transition points (Figure 21.6-3). In practice, differentiating MCI from agerelated cognitive decline resides mainly on neuropsychological testing, showing a cognitive decline more severe for age and less education. The main differentiation between MCI and Alzheimer's disease resides in the lack of functional impairment in MCI. FIGURE 21.6-3 Cognitive continuum showing the overlap in the boundary between normal aging and the mild cognitive impairment and Alzheimer's disease. (Reprinted with permission from Petersen RC, ed. Mild Cognitive Impairment: Aging to Alzheimer's Disease. New York:

Oxford University Press, 2003.) COURSE AND PROGNOSIS The typical rate at which MCI patients progress to Alzheimer's disease is 10 to 15 percent per year and is associated with progressive loss of function. However, several studies have indicated that the diagnosis is not stable in both directions; patients can either convert to Alzheimer's disease or revert back to normal. This variability in course is related to the heterogeneous source of the subjects (clinical vs. community) as well as to the heterogeneous definition criteria used by different studies. Amnestic MCI has been associated with increased morbidity compared with reference subjects. TREATMENT There are no

FDA-approved treatments for MCI at this time. MCI treatment involves adequate screening and diagnosis. Ideally, MCI treatment would also include improvement of memory loss together with prevention of further cognitive decline to dementia. Cognitive training programs have been reported as mildly beneficial for compensating memory difficulties in MCI. Controlling for vascular risk factors (high blood pressure, hypercholesterolemia, diabetes mellitus) may be a benefit preventive method for those MCI cases underlying vascular pathology. Currently, sensitive tools (imaging techniques or biomarkers) are not available for MCI screening in the general population. In primary care setting, clinicians should maintain a high suspicion for subjective cognitive complaints and should corroborate these complaints with collateral information whenever possible. Also, identifying reversible causes of cognitive impairment (hypothyroidism, vitamin B12 deficiency, medication-induced cognitive impairment, depression) can further benefit some of the prodromal dementia MCI cases. Currently, there is no evidence for long-term efficacy of pharmacotherapies in reversing MCI. Several epidemiological studies indicated a reduced risk of dementia in persons taking antihypertensive medications, cholesterol-lowering drugs, antioxidants, and anti-inflammatory and estrogen therapy, but no randomized controlled trials verify these data. With regard to cognitive enhancers, as of 2007, there have been seven trials designed for amnestic MCI, with ambiguous results (Table 21.6-3). Most of these studies were confronted with several problems, including (1) obtaining homogeneous samples and identifying potential beneficiaries of treatment; (2) treating a wider population, which led to large percentages of negative responses and problematic side effects; and (3) translation of the MCI construct into multiple cultures and languages and using Alzheimer’s disease diagnosis as the primary outcome, given the variability of this diagnosis in different countries. Table 21.6-3 Treatment Trials for Mild Cognitive Impairment

Advances in MCI detection will be paramount for early detection and treatment of patients with Alzheimer’s disease; experts agree that disease-modifying treatments for Alzheimer’s disease will focus on cognitively intact individuals at increased risk. The field of identifying sensitive and specific biomarkers (biological and neuroimaging markers) will probably witness exponential development in the coming years. REFERENCES Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Berry-Kravis E. The apolipoprotein E epsilon4 allele and incident Alzheimer’s disease in persons with mild cognitive impairment. Neurocase. 2005;11:3. Andreescu C, Aizenstein HJ. Amnestic disorders and mild cognitive impairment. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1198. Birks J, Flicker L. Donepezil for mild cognitive impairment. Cochrane Database Syst Rev. 2006;3:CD006104. Breitner JC. Mild cognitive impairment and progression to dementia New findings. Neurology. 2014;82(4):e34–e35. Doody RS, Ferris SH, Salloway S, Meuser TM, Murthy AK, Li C, Goldman R: Identifying amnestic mild cognitive impairment in primary care. Clin Drug Invest. 2011;31:483. Edwards ER, Spira AP, Barnes DE, Yaffe K. Neuropsychiatric symptoms in mild cognitive impairment: Differences by subtype and progression to dementia. Int J Geriatr Psychiatry. 2009;24:716. Gallagher D, Coen R, Kilroy D, Belinski K, Bruce I, Coakley D, Walsh B, Cunningham C, Lawlor BA. Anxiety and behavioural disturbance as markers of prodromal Alzheimer’s disease in patients with mild cognitive impairment. Int J Geriatr Psychiatry. 2011;26:166.

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Revision #1
Created 2026-01-04 19:51:20 UTC by Omar Ayman
Updated 2026-01-04 19:51:20 UTC by Omar Ayman