Mild Cognitive Impairment Is Not a Clinical Entity and Should Not Be Treated

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THERE HAS BEEN GREAT progress in the diagnosis and treatment of Alzheimer disease (AD) and related dementias thanks to the availability of well-validated diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); National Institute of Neurological and Communicative Disorders and Stroke—the Alzheimer’s Disease and Related Disorders Association [NINCDS-ADRDA]); and a large number of randomized clinical trials using cholinesterase inhibitors (AChEIs) and Memantine. Work from specialized neurological clinics suggests that mild cognitive impairment (MCI) is an early stage of AD, and there is a temptation for neurologists to prescribe AChEIs in this population. On the other hand, there is epidemiological evidence that many subjects labeled as having MCI do not worsen over time and may revert to normal cognitive abilities. A diagnosis of MCI as a predementia stage of AD in such individuals would be inaccurate and carry a heavy personal and societal burden. Reversible causes of MCI may be found, such as depression, upper airway obstruction, and a variety of metabolic, nutritional, or sensory impairments. Since MCI does not constitute a homogeneous clinical syndrome, it is inappropriate to propose a specific drug treatment such as AChEIs, but the recognition that MCI is a risk state toward further cognitive decline is clinically relevant, and control of risk factors such as systolic hypertension, hypercholesterolemia, diabetes mellitus, atrial fibrillation, transient ischemic attacks, and strokes may delay progression to dementia.

GENERAL CONCEPT OF MCI

The concept of MCI is being widely used in epidemiological and clinical studies as an intermediate stage between normal cognition and dementia. A high number of persons have been found to have MCI in the population at large, and many are now being referred to memory clinics. There is an expectation that even larger numbers of individuals with memory complaints will be coming forward for assessment in the near future.

The heterogeneity of MCI has been recognized in a report of the Quality Standards Subcommittee of the American Academy of Neurology,1 where it has been recommended to qualify the term MCI with an appropriate modifier such as “amnestic,” which was defined operationally by Petersen et al2 in 1999 (Figure 1).

MCI IN SPECIALTY CLINICS

Specialized clinics in Rochester, Minn, and St Louis, Mo, have established that amnestic MCI is frequently a prodrome to AD or its first manifestation.3 Conversion rates from amnestic MCI to AD range from 12% to 15% per year.2 The heterogeneity within MCI has been noted and a new classification has been proposed, based predominantly on neuropsychological profiles, and includes amnestic or single memory MCI, multiple-domain MCI, and single nonmemory MCI.4

MCI IN POPULATION STUDIES

Estimates of prevalence of MCI in population-based epidemiological studies vary greatly depending on the definition in use and range from 3% to 16.8%.5 The former figure is obtained from specialized referral clinics using amnestic MCI criteria, whereas the latter figure has been documented in the Canadian Study of Health and Aging where the term cognitive impairment no dementia (CIND) was defined as various categories of impairment identified in a clinical examination and neuropsychological tests.5 The most common cause of CIND was circumscribed memory impairment, a close equivalent to amnestic MCI, with a prevalence of 5.3%.5 The follow-up of individuals from that cohort with MCI defined by different criteria led to a wide range of conversion to dementia (20.0%-50.9%), AD (11.6%-28.8%), and death (30.1%-42.4%).6

An epidemiological study based on a general practice research network in France revealed a prevalence of 3.2% for MCI, which was a poor predictor of dementia within a 3-year period, with an 11.1% conversion rate and many subjects reverting to normal cognition.7 Another cohort in France demonstrated a prevalence of 2.8% for MCI and an annual conversion rate of 8.3% across 5 years, but within 3 years more than 40% of subjects with MCI had reverted to normal cognition.8

Figure 1. Operational definition of amnestic mild cognitive impairment.
The Kungsholmen Project is another population study looking at MCI, where a distinction was made within CIND as mild, moderate, or severe based on Mini-Mental State Examination scores (mild, 1 SD lower than age-specific and education-specific mean scores; moderate, 1.5 SDs; severe, 2 SDs). Depression and cerebrovascular disease were more common in the CIND population compared with unimpaired subjects; similar proportions of subjects with CIND progressed to dementia, death, and cognitive improvement across 3 years.11 A community-based sample in a rural area of the United States showed that 3% to 4% of elderly persons without dementia met MCI criteria and had a higher risk of progressing to dementia across 10 years, but many remained stable or reverted to normal cognition during follow-up.12

### MCI IN RANDOMIZED CLINICAL TRIALS

The operational definition of amnestic MCI has made possible large-scale, placebo-controlled, randomized clinical trials to test the hypothesis that the treatment of MCI with AChEIs, such as donepezil hydrochloride, rivastigmine tartrate, or galantamine hydrobromide, can delay the diagnosis of AD and/or improve cognitive impairments. Different MCI populations are defined for each study15-17 (Figure 2).

Results of these studies are only partially analyzed and reported, but for the purpose of the arguments in this “Controversies” section, there was a wide range of rate of conversion to AD across 2 to 4 years. This variability is based on differences in the number of carriers of the apolipoprotein E4 genotype, variations in the memory impairment cutoff scores at entry, and the heterogeneity of MCI, even in the relatively pure amnestic subtype. Efficacy of AChEIs overall in improving cognition or delaying the conversion from MCI to AD have been disappointing so far.

### MCI AT HIGHER RISK OF CONVERSION TO DEMENTIA

There are patterns emerging from specialized neurological clinics, population studies, and randomized clinical trials for higher risks of progression to dementia. It is likely that models combining multiple risk factors, such as the ones listed in Figure 3, will be needed for predicting the risk of individuals with MCI for progression to dementia.

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**Table: Entry Criteria for Studies**

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<tr>
<th>Study</th>
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<tr>
<td><strong>Donepezil Hydrochloride Tocopherol Study</strong></td>
<td>- Memory complaint corroborated by an informant&lt;br&gt;- Abnormal memory function documented by delayed recall of 1 paragraph from the Logical Memory III subtest of the Wechsler Memory Scale-Revised, adjusted for age and education&lt;br&gt;- Normal general cognitive function as determined by a physician’s judgment based on the CDR and the MMSE&lt;br&gt;- No or minimal impairment in ADL&lt;br&gt;- No clinical dementia&lt;br&gt;- Age 55-90 y&lt;br&gt;- In good general health with no significant cerebrovascular disease, and Hachinski Ischemic score ≤4&lt;br&gt;- Not depressed, with a Hamilton Depression Rating Scale score ≤12&lt;br&gt;- No infection, infarction, or focal lesions on computed tomography or magnetic resonance imaging&lt;br&gt;- CDR global score of 0.5, with a score of at least 0.5 in the memory domain</td>
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<tr>
<td><strong>Rivastigmine Tartrate Study</strong></td>
<td>- Abnormal memory function documented by a delayed Recall Score ≤10 on the New York University Delayed Paragraph Recall Test&lt;br&gt;- Insufficient impairment on ADL to warrant a diagnosis of dementia&lt;br&gt;- Age ≥50 y&lt;br&gt;- CDR global score of 0.5, with a score of at least 0.5 in the memory domain</td>
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<tr>
<td><strong>Galantamine Hydrobromide Studies</strong></td>
<td>- Abnormal memory function documented by the New York University Delayed Paragraph Recall Test with a cutoff inclusion score &lt;9&lt;br&gt;- No clinical dementia&lt;br&gt;- Age 55-85 y&lt;br&gt;- Not depressed, with a Hamilton Depression Rating Scale score &lt;13, item 1 (depressed mood) score ≤1&lt;br&gt;- CDR global score of 0.5</td>
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**Figure 2.** Entry criteria for studies. ADL indicates activities of daily living; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination.

**Figure 3.** Mild cognitive impairment at higher risk of progression to dementia.
current limitations of the diagnostic criteria and to propose ways of addressing them.

FUTURE PERSPECTIVE ON MCI

A future perspective on dealing with MCI would be (1) defining MCI as a clinical syndrome with diagnostic criteria, (2) defining clinical subtypes of MCI, and (3) defining etiological subtypes of MCI and then treating accordingly.

For the first step, a set of clinical criteria based on a clinical approach may be preferred to a predominantly neuropsychological one. These criteria could be created and used in a way similar to DSM-IV or NINCDS-ADRDA criteria. As a starting point, we have made a proposal for new MCI criteria (Figure 4).22

A working group of health care professionals and epidemiologists proposed similar criteria for MCI20 based on 3 diagnostic features: (1) not normal, without dementia, (2) cognitive decline indicated by subject and/or informant report and objective cognitive tests, and (3) preserved basic activities of daily living with some minimal impairment in complex instrumental functions.

The second step in dealing with MCI will be the characterization of the different subtypes, which can be defined using primarily neuropsychological criteria or primarily clinical criteria, and determining their natural history.

The third step will be the characterization of the etiology of each clinical subtype and its specific treatments. It is possible that amnestic MCI will be the characterization of the etiology of each clinical subtype and its specific treatments. Wherever possible, these criteria could be created and used in a way similar to DSM-IV or NINCDS-ADRDA criteria. As a starting point, we have made a proposal for new MCI criteria (Figure 4).22

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CONCLUSIONS

Guidelines such as the ones developed by the American Academy of Neurology1 need to be updated as new evidence on the natural history of amnestic and other types of MCI become available. Until then, we argue that MCI is not a homogeneous clinical entity and, as such, cannot be treated with a specific therapy such as AChEIs. On the other hand, reversible causes of MCI may be found, such as depression, upper airway obstruction, and a variety of metabolic, nutritional, or sensory impairments, whereas control of vascular risk factors such as systolic hypertension, hypercholesterolemia, diabetes mellitus, atrial fibrillation, transient ischemic attacks, and strokes may delay progression to dementia.