

# Mild Cognitive Impairment as a Clinical Entity and Treatment Target

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**M**ILD COGNITIVE impairment (MCI) has been actively investigated for the past decade.<sup>1,2</sup> The term was coined in the late 1980s by the New York University group to identify individuals who were not cognitively normal for age and yet did not have overt dementia, and their outcomes were described in an article examining predictors of dementia by Flicker et al<sup>3</sup> in the early 1990s. Flicker et al characterized MCI as equivalent to a Global Deterioration Scale rating of 3 and found that a diagnostic approach combining a careful, structured interview and the appropriate neuropsychological tests can discriminate those individuals with MCI likely to experience cognitive deterioration from those with a benign prognosis.<sup>3</sup>

Recently MCI has been given more specific criteria involving the features outlined in Figure 1 of the comments by Gauthier and Touchon<sup>4</sup> abstracted from Petersen et al.<sup>5</sup> In conjunction with increased attention to the early stages of development of Alzheimer disease (AD), these criteria served to catalyze intense interest in MCI as a possible prodromal stage of AD.<sup>6</sup> Sev-

eral studies on longitudinal populations were conducted, some retrofitting criteria to longitudinal studies of aging, and several others are either underway or completed and have demonstrated a progression from MCI to AD at an elevated rate over the base rate in the population.<sup>7-9</sup> Most of these studies examined the amnesic subtype of MCI, in which memory impairment is a key feature. However, other studies, often encompassing a broader definition of MCI, have demonstrated a reversion to normal in some subjects, implying a lack of stability for the construct over time.<sup>10-12</sup> This has led to a closer inspection of the underlying premises of MCI and a refinement of criteria to recognize that MCI is a heterogeneous condition.<sup>13</sup>

Several factors have emerged as contributing to the variability in the outcomes of several of these studies. Among these are the following factors: (1) criteria for MCI, (2) implementation of the criteria, (3) source of subjects, and (4) reference standards for normal performance. Each of these points deserves discussion as it pertains to the comments raised by Gauthier and Touchon.<sup>4</sup>

## CRITERIA FOR MCI

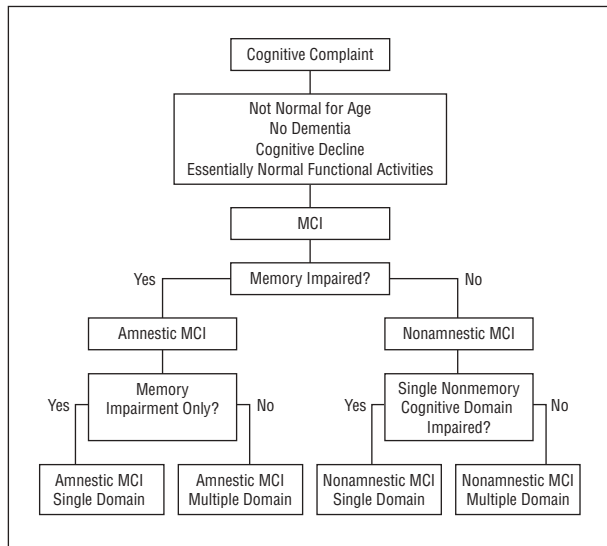
The criteria for amnesic MCI have been implemented in a variety of studies. In general, they characterize a subset of individuals with MCI who are likely to progress to clinically probable AD. In fact, many of the recently completed randomized clinical trials on MCI have used

these criteria and have been able to apply them on a multicenter basis, and in some cases, international basis, with good reliability.<sup>14,15</sup> The criteria have been reasonably specific as well. In the recently completed Alzheimer's Disease Cooperative Study Clinical Trial on MCI, 212 of the 214 subjects who progressed from MCI to dementia were characterized as having possible or probable AD, indicating that when rigorously applied, the criteria can be highly specific.<sup>14,16</sup>

However, subsequent work has also indicated that the amnesic MCI subtype (Figure 1 of the Gauthier and Touchon article) may not encompass all of the prodromal states of dementia. In fact, other syndromic subtypes of MCI can be postulated that likely lead to other dementias.<sup>13</sup> At a recent international conference on MCI in Stockholm, Sweden, a more general approach to the diagnosis of MCI was proposed, which included the consideration of multiple types of cognitive impairment in addition to the memory impairment that characterizes amnesic MCI.<sup>13,17</sup> As shown in **Figure 1**, an algorithm can be used to subdivide MCI into the major subdivisions of amnesic and nonamnesic MCI followed by further subclassification into single- or multiple-domain categories. This scheme is being implemented in several longitudinal studies of aging, including the newly initiated Alzheimer's Disease Neuroimaging Initiative sponsored by the National Institute on Aging (Bethesda, Md).

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**Figure 1.** Flowchart for diagnosis of mild cognitive impairment (MCI) subtypes.

Once the physician has made the delineation of the clinical subtype of MCI, the next step involves the determination of the proposed etiology of the syndrome as outlined in **Figure 2**. This approach is similar to that used in delineation of most neurological diagnoses, including dementia. If by history, examination, and laboratory testing, one concludes that the amnesic subtype is likely caused by a neurodegenerative process, then the probable outcome will be AD, as has been supported by progression to more severe stages of dementia and by neuropathological findings.<sup>18,19</sup> The insidious onset of symptoms that typifies AD suggests that virtually all affected individuals will experience MCI as the earliest clinical expression of the underlying AD process. Therefore, if a physician were interested in designing a randomized clinical trial for AD, the appropriate clinical subtype of MCI, amnesic MCI, could be combined with the suspected degenerative etiology and inclusion and exclusion criteria for the trial could be designed appropriately. This basic approach has been successful in characterizing a uniform group of individuals to participate in randomized clinical trials for MCI, using drugs that are purported to have a mechanism relevant to the underlying AD pathologic features.

It is likely that the lack of consideration of the etiology of the clinical

subtypes of MCI has led to some of the variability in the literature. Epidemiology studies characterize MCI subtypes clinically and evaluate the subjects longitudinally. However, as Figure 2 demonstrates, some etiologies of amnesic MCI (eg, major depression) would be expected to improve. Therefore, the general statement that MCI is “unstable” is inappropriate since it implies a problem with the construct of MCI. On the contrary, some types of MCI of certain etiologies should improve. However, if one were to restrict the discussion to the amnesic subtype of presumed degenerative etiology, then the predictive value of the construct as prodromal AD is borne out. It is only when the subtypes of MCI are discussed broadly without reference to the etiology that the confusion arises. The appreciation of this interpretation of the literature reflects increasing sophistication of the construct over the years.

#### IMPLEMENTATION OF CRITERIA

Some variability is introduced by the manner in which the criteria for MCI are used. Recently, the construct of cognitive domains has been introduced to subclassify the various types of MCI. Inherent in this notion is the definition of a domain and the instruments used to measure that domain. While there is some agreement on which domains are rel-

		Etiology				
		Degenerative	Vascular	Psychiatric	Medical Conditions	
Clinical Classification	Amnesic MCI	Single Domain	AD		Depr	
		Multiple Domain	AD	VaD	Depr	
	Nonamnesic MCI	Single Domain	FTD			
		Multiple Domain	DLB	VaD		

**Figure 2.** Scheme for combining clinical subtypes with presumed etiology. AD indicates Alzheimer disease; Depr, depression; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI, mild cognitive impairment; and VaD, vascular dementia.

evant, there is no consensus. However, this is not different from the application of the criteria for the diagnosis of dementia or AD.<sup>20</sup> These definitions also require impairment of memory and other cognitive domains (eg, attention, language, visuospatial skills), as well as a functional impairment. Therefore, the challenge is similar; the physician must determine what constitutes a given cognitive domain, such as memory, and use appropriate instruments for measuring that domain. There are no specific recommendations in the criteria for dementia or AD with respect to what constitutes specific domains or how the physician should measure them.

In addition to the definition of a domain, the physician must decide how to assess the domains. Does the physician use 1, 2, or more measures of memory, for example, to determine if memory is impaired? Clearly the more measures the physician uses, the more reliable the measurements will be. Some of the variability seen in the epidemiologic studies concerning MCI may relate to the tendency to use a single measure to assess a domain such as memory. If that domain forms the cornerstone for the definition of MCI and the subjects with MCI as a group are shown to be unstable over time, then the conclusion may be drawn that the construct of MCI is not reliable when, in reality, it may be the psychometric measure “instabil-

ity" that is responsible for the group variability over time.<sup>10</sup>

Another important aspect of the implementation of the criteria concerns the manner in which the criteria are applied. That is, do psychometric cutoff scores determine the diagnosis or are clinical methods used, including careful interviews with the subject and an informant? As mentioned earlier, to the extent that one relies on psychometric cutoff scores rather than clinically informed judgment, the reliability of the subsequent diagnoses may be compromised. Therefore, the physician needs to assess the literature on MCI from the perspective of the context in which the study was performed. If a physician believes that the study was derived from a setting that more closely simulates his or her practice, the data from research clinics might be more appropriate than those derived from the epidemiologic setting.

#### SOURCE OF SUBJECTS

A major source of variability among studies arises from the origin of the subjects for the study. There is less heterogeneity and hence less variability in studies arising from memory or dementia clinics than from community-based epidemiologic studies. The former often involve a group of individuals who are seeking help for a problem. Dementia clinics usually have inclusion and exclusion criteria that help to refine the subjects entering into the study, and the subjects typically will be more impaired at the time of initial examination. When unselected populations are approached through a random selection procedure, there is much more variability in both the syndromic symptoms and in the etiology of the clinical syndromes. The combination of these factors plus the practical requirement of performing less exhaustive evaluations and likely relying more heavily on psychometric criteria all contribute to the variability of the classifications and ultimate outcomes in the epidemiologic setting. This is not unreasonable since the 2 settings are likely addressing related but different questions. The dementia clinic is addressing clinical phenotypes and

predictors of outcome whereas the epidemiologic study focuses on rates of clinical conditions and progression.

#### REFERENCE GROUPS

Finally, the reference points for the comparison to normal can vary among studies. Variability can be introduced by reference standards for normal cognitive function, and these reference points can include age and education-based norms, comparison with performance of young individuals, and a change in performance over time, as well as other bases for comparison. None of these is perfect and each introduces a source of bias, yet these can be important. Since the most difficult clinical decision often involves the distinction between the cognitive changes of normal aging and MCI, this decision involves a recognized set of assumptions regarding normal cognition. This decision often is based on predetermined assumptions regarding performance in normal aging.

#### POTENTIAL TREATMENT

A difficult issue arises concerning potential treatments for patients with MCI. First, it must be recognized that no treatments have been approved by the Food and Drug Administration for the indication of MCI of any subtype. Nevertheless, if a person has the profile of amnesic MCI of a presumed neurodegenerative etiology, this subtype will progress to clinically probable AD with a high likelihood. Moreover, the neurobiological phenotype of this subset of MCI represents a biological substrate that is intermediate between physiological changes of aging and fully developed AD: overrepresentation of the apolipoprotein E4 allele,<sup>21,22</sup> volumetric loss in entorhinal cortex and hippocampus as measured by magnetic resonance imaging<sup>23,24</sup> neuronal counts in postmortem samples,<sup>25</sup> increased brain markers of oxidative stress,<sup>26</sup> and abnormalities of the cholinergic system.<sup>27</sup> Recognizing that broadly defined, MCI is heterogeneous and that not all individuals will progress to AD or other dementing illness,

nonetheless experienced physicians using a combination of clinical and neuropsychological methods increasingly and accurately detect the subset of MCI that very likely will progress to fully expressed symptomatic AD. The remaining discussion focuses on this subset alone.

All of the caveats regarding heterogeneity must be considered and physicians and patients alike must realize that MCI remains a research construct and that the uncertainties of outcome include the possibility of clinical stability. However, if the patient's clinical syndrome is considered likely to progress to clinical AD, then the patient can be counseled accordingly. For example, since individuals with MCI are quite competent and aware of their difficulties, they may want to engage in financial planning, retirement considerations, and other discussions regarding their futures. In addition, as noted in Figure 2, some etiologies of MCI may be reversible (eg, depression or medical comorbidities), and these conditions would need to be treated. Nonpharmacological interventions, such as cognitive rehabilitation, might be useful at this stage as well.

Some physicians may choose to use pharmacological interventions at this point. For example, if the treating physician is convinced that the clinical condition harbors the underlying pathophysiologic features of incipient AD, the physician may wish to discuss this with the patient from the perspective of initiating AD therapy early. Although there is no Food and Drug Administration approval for the use of symptomatic treatments for AD drugs prior to diagnosis, the physician may wish to consider the individualized use of cholinesterase inhibitors for potential symptomatic benefit at this point in the disease process. Memantine is also approved for AD treatment but for later stages of progression. There is no evidence that these medications have any impact on the underlying disease process or that they will postpone any clinically meaningful endpoints. The relative expense of treatment needs to be weighed against potential benefits. For individuals with MCI for whom their symp-

toms are judged clinically to be caused by AD, it may be reasonable to consider symptomatic treatment at this point in the overall course.

## SUMMARY

Mild cognitive impairment is an evolving construct. While appropriate questions have been raised concerning its definition, outcome, and potential treatments, considerable progress has been made. We agree with Gauthier and Touchon<sup>4</sup> that MCI is heterogeneous. The heterogeneity reflects a refinement of the entity rather than a weakness. Just as the construct of dementia has been refined over the years to reflect increasing sophistication in diagnostic skill, so has the characterization of MCI been refined. If the approach to classifying the syndrome of MCI into multiple subtypes is combined with the presumed etiology, much of the variability in the literature can be resolved.

The construct is useful both for clinical as well as research purposes. If used in a systematic fashion, it can help characterize the prodromal states of several types of dementia. If specific criteria are used including etiology, it can predict clinically probable AD with high specificity, and this provides physicians and investigators an opportunity to recognize, counsel, and ultimately treat the condition before it advances to fully expressed dementia. In essence, we have to be able to move the diagnostic threshold for these disorders back to earlier stages of impairment with the anticipation of developing appropriate therapies to intervene at these stages. Ideally, we would like to develop markers that predict the future development of dementia and intervene with safe and effective therapies to truly prevent AD and the other dementing disorders.

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