Mild Cognitive Impairment

Ten Years Later

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In the past 10 years, there has been a virtual explosion in the literature concerning the construct of mild cognitive impairment. The interest in this topic demonstrates the increasing emphasis on the identification of the earliest features of cognitive disorders such as Alzheimer disease and other dementias. Mild cognitive impairment represents the earliest clinical features of these conditions and, hence, has become a focus of clinical, epidemiologic, neuroimaging, biomarker, neuropathological, disease mechanism, and clinical trials research. This review summarizes the progress that has been made while also recognizing the challenges that remain.

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During the past decade, a major transition in the clinical characterization of cognitive disorders has taken place. Many of the prodromal stages of conditions such as frontotemporal dementia and dementia with Lewy bodies have been recognized, and we can now make the clinical diagnosis at an earlier stage in the disease process. At the same time, there has been a growing interest in the predementia phase of these conditions because of suggestions that we may be able to identify the earliest clinical features of these illnesses before functional impairment is evident. Toward this end, the construct of mild cognitive impairment (MCI) has evolved to capture this predementia phase of cognitive dysfunction.

Most investigators believe that if we wait for functional impairment and perhaps even mild cognitive symptoms to emerge, it may be too late to treat the underlying disease process. Ideally, we would like to be able to prevent or postpone the disease process by intervening early. If a disease-modifying therapy or effective lifestyle intervention were available, we would want to intervene as soon as possible, but these treatments are not on the immediate horizon. As such, the construct of MCI serves a useful purpose as a clinical stage in which meaningful interventions can take place. Mild cognitive impairment may be an intermediate step on the way to primary prevention, but it remains important for formulating research hypotheses.

HISTORY

Mild cognitive impairment as a term was introduced into the literature in 1988 by Reisberg and colleagues, but at that time, it was intended to refer to stage 3 of the Global Deterioration Scale (GDS). In a similar vein, the Clinical Dementia Rating (CDR) scale has gained popularity as an instrument for characterizing either mild impairment or very early dementia, and both instruments have been catalysts for stimulating research on early impairment. As the field has advanced, however, we have realized that these severity scales do not adequately characterize the subtle differences between MCI and early dementia. Participants with MCI, as currently diagnosed, can be classified as GDS stage 2 or 3 and as having a CDR of 0 or 0.5. Therefore, a finer grain of diagnostic acumen was necessary to distinguish these prodromal conditions from the dementia stage beyond the granularity of the GDS and CDR instruments.
In a 1999 article published in the Archives of Neurology, a group of investigators from the Mayo Clinic described their experience with participants with MCI in a community cohort and put forth diagnostic criteria outlined in Table 1. These criteria have been the subject of a great deal of study, validation, and criticism, and there has been an explosion of interest in the literature, as characterized in Figure 1.

CRITERIA

The 1999 Archives article focused on MCI as a prodromal condition for Alzheimer disease (AD) and emphasized the importance of memory impairment for incipient AD. Subsequently, other investigators appropriately noted that not all forms of MCI may evolve into AD, and a broader conceptualization was necessary. In 2003, Winblad et al. convened a conference of international experts on MCI to revise criteria. From that conference, new, more expansive criteria for MCI were proposed, and these criteria now form the foundation for the National Institute on Aging-sponsored Alzheimer Disease Centers Program Uniform Data Set and the public-private neuroimaging/biomarker consortium, the Alzheimer Disease Neuroimaging Initiative (ADNI). These criteria depict the clinical phenotypes of amnestic MCI (aMCI) and nonamnestic MCI (naMCI) with the subtypes of single and multiple domain classifications (Figure 2). These clinical phenotypes are then combined with the presumed cause (Figure 3) as the next step in the diagnostic process. This is analogous to a physician diagnosing a particular syndrome and then searching for an etiologic explanation for the syndrome. This combination leads to the diagnostic impression of a possible outcome of the clinical entity of MCI. With this theoretical framework, many studies have been conducted to investigate the utility and prognostic outcome of the diagnoses.

EPIDEMIOLOGY

Numerous investigations worldwide have used these criteria as an infrastructure for estimating the frequency of MCI and its subtypes. Some studies have retrospectively applied MCI criteria to previously acquired data sets and have provided important insights. However, the most informative studies have been conducted prospectively to incorporate MCI criteria at the outset. These studies have captured the subtleties of the diagnosis in a prospective fashion and are consequently better able to address the clinical characterization and mild features of the construct.

The Mayo Clinic Study of Aging was designed as a population-based study in Olmsted County, Minnesota, involving a random sample of nearly 3000 participants, aged 70 through 89 years, who were nondemented and cognitively normal or who had MCI at entry. The prevalence of MCI from this study is estimated at approximately 15% of the nondemented population, with a 2:1 ratio of aMCI to naMCI. The most common putative cause

### Table 1. Original 1999 Mild Cognitive Impairment Criteria

<table>
<thead>
<tr>
<th>Criterion</th>
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<tr>
<td>Memory complaint, preferably corroborated by an informant</td>
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<tr>
<td>Memory impairment documented according to appropriate reference values</td>
</tr>
<tr>
<td>Essentially normal performance in nonmemory cognitive domains</td>
</tr>
<tr>
<td>Generally preserved activities of daily living</td>
</tr>
<tr>
<td>Not demented</td>
</tr>
</tbody>
</table>

*a Based on information from Petersen et al.*
is degenerative, and this cause predominates to a greater extent for aMCI than for nMCI.

Other studies\textsuperscript{12,13,17,19-27} have also addressed this issue and are summarized in \textbf{Table 2}. Although these studies incorporate a variety of tools to fulfill the diagnostic criteria for MCI, yielding some variability, there is a coalescence of prevalence rates from around the world.\textsuperscript{12,17} In general, the rates appear to converge in the 14% to 18% range for individuals aged 70 years and older.

\section*{OUTCOMES}

The next issue regarding MCI pertains to the participants’ outcomes following a diagnosis. A major factor in determining outcome depends on the source of participants being studied. In general, it appears that participants from referral sources, such as memory disorders clinics or AD centers, likely have a progression rate to dementia, particularly AD, of 10% to 15% per year.\textsuperscript{28} This is likely also true for some of the clinical trials on MCI, such as those designed to incorporate the protocols used by the Alzheimer’s Disease Cooperative Study and the ADNI.\textsuperscript{3} Particularly relevant for AD because apolipoprotein E \textsuperscript{4} carriers progressing more rapidly from MCI to dementia was published in \textit{JAMA}; since that time, there have been numerous replications.\textsuperscript{35,34} This finding is particularly relevant for AD because apolipoprotein E \textsuperscript{4} carrier status is a major genetic risk predictor of late-onset AD.\textsuperscript{35}

\section*{PREDICTORS}

Among those individuals who exhibit an elevated rate of progression from MCI to AD, can we predict who will progress more rapidly? A great deal of research on this issue has been generated in the past decade. \textbf{Table 4} lists the most common factors related to rate of progression.

\section*{SEVERITY OF COGNITIVE IMPAIRMENT}

As would be expected, those who are more impaired in the clinical spectrum, by virtue of degree of memory impairment or other cognitive deficits, are more likely to progress to dementia more rapidly.\textsuperscript{1} This factor has been demonstrated in several clinical studies and likely reflects the underlying extent of pathological involvement.

\section*{GENETIC CONSIDERATIONS}

In 1995, the initial report of the effect of apolipoprotein E \textsuperscript{4} carriers progressing more rapidly from MCI to dementia was published in \textit{JAMA}; since that time, there have been numerous replications.\textsuperscript{35,34} This finding is particularly relevant for AD because apolipoprotein E \textsuperscript{4} carrier status is a major genetic risk predictor of late-onset AD.\textsuperscript{35}

\section*{MAGNETIC RESONANCE IMAGING}

Quantitative magnetic resonance imaging (MRI) has perhaps been the most extensively studied imaging and biomarker entity in the context of MCI.\textsuperscript{36} Jack and colleagues at the Mayo Clinic\textsuperscript{37} have published the initial and many of the subsequent studies in this area. Following this lead, the National Institute on Aging–sponsored ADNI was designed to assess the utility of neuroimaging and chemical biomarkers in predicting prodromal AD and characterizing features that likely predict progression.\textsuperscript{11}

In general, structural MRI has been shown to predict progression from MCI to AD such that volumetric mea-
measurements of the hippocampal formation, entorhinal cortex, whole brain, and ventricular volumes are commonly used in clinical studies.\textsuperscript{38} This precision has been translated into a proposed design of clinical trials to reduce the sample size of the treatment groups for proposed therapies.\textsuperscript{39} The sample size for therapeutic interventions can be greatly reduced using volumetric indices gained from MRI as a stratifying variable.

In addition to structural MRI, other measures such as magnetic resonance spectroscopy, diffusion tensor imaging, and arterial spin labeling have been useful in differentiating among those participants with MCI and AD and those who are cognitively normal, and these measures may also be useful in predicting progression to dementia and AD.\textsuperscript{40} The breadth of useful measures involving MRI is impressive and clearly represents an advance in the field during the past decade.

**FLUDEXYLOSE F 18–POSITRON EMISSION TOMOGRAPHY**

A functional imaging modality that has been studied to a lesser extent than MRI includes the use of \(^{18}\text{FDG}\) PET (fludeoxyglucose F 18–positron emission tomography) scans. The available data suggest that many participants with the clinical syndrome of MCI exhibit the “AD pattern” of hypometabolism in the temporoparietal regions, which predicts progression to clinical AD.\textsuperscript{41} This imaging modality likely detects an aspect of neurodegeneration that perhaps reflects the loss of synaptic integrity and provides dynamic information on progression.

**CEREBROSPINAL FLUID**

One of the more active areas of biomarker prediction of progression has arisen in the area of cerebrospinal fluid (CSF) biomarkers,\textsuperscript{42} such as amyloid \(\beta_1\) to +2 peptide (\(\text{A}_{\beta_1+2}\)), total tau, and tau phosphorylated at threonine 181. An influential article in 2006 by Hansson and colleagues\textsuperscript{43} highlighted the finding that among those participants with MCI who possess the profile of AD, low \(\text{A}_{\beta_1+2}\) and elevated total tau or phosphorylated tau or the ratio of \(\text{A}_{\beta_1+2}\) to tau is predictive of progression from MCI to AD. A recent report of a group of 12 research centers from Europe involving
ing a large group of participants with MCI essentially replicated the findings from Hansson et al.\textsuperscript{44} A similar study from the ADNI recently reported the utility of CSF biomarkers in predicting progression, so there is a wealth of data now converging that CSF may provide useful information in predicting progression from MCI to AD.\textsuperscript{45} Because most of the participants in these studies have MCI of moderate severity, the real utility of these indices will reside in their ability to be accurate predictors in participants with less severe manifestations of disease.

MOLECULAR IMAGING

A recent advancement in imaging involves the use of molecular imaging of amyloid.\textsuperscript{46} The initial agent to address this issue was the carbon 11 compound known as Pittsburgh Compound B; this tracer has been the most widely studied in the world. However, since its introduction, several \textsuperscript{18}F compounds have been introduced, and some of these agents are likely to become commercial products; as such, new data are emerging. Early data from the University of Pittsburgh indicate that amyloid imaging may be important in selecting a subset of participants who are more likely to progress rapidly and perhaps in differentiating among those participants with aMCI and naMCI who might be appropriate for antiamyloid therapies.\textsuperscript{47}

COMBINATION OF MARKERS

In the final analysis, it is likely that the best prediction model will involve a combination of neuroimaging and chemical biomarker measures. Several recent studies have suggested that, depending on the stage in the clinical spectrum, certain neuroimaging and biomarker measures or their combinations may be quite informative.\textsuperscript{48} As shown in Figure 4, it is possible that a deposition of amyloid is the initial event, characterized by a low CSF A\textsubscript{β} level or a positive amyloid imaging scan, followed by measures of degeneration, such as seen on \textsuperscript{18}FDG PET or by CSF levels of total tau or phosphorylated tau, or, as the preponderance of evidence suggests, as characterized by structural changes on MRIs.\textsuperscript{49}

Then, as Figure 4 indicates, clinical changes become manifest typically as a change in memory function for early AD followed by other cognitive changes and eventually functional impairment. Certain neuroimaging and biomarker measures may be differentially sensitive and informative at different stages in the underlying progression of the diseases. No single measure will be uniformly predictive throughout the entire disease process. Toward that end, Jack and colleagues\textsuperscript{50} have proposed that amyloid deposition as depicted on amyloid imaging may set the stage for subsequent cognitive decline.

NEUROPATHOLOGICAL ANALYSIS

Relatively few neuropathological studies have been completed on participants during the MCI stage of AD. Some investigators contend that this stage of MCI is, in fact, AD but also indicate that these participants may be more clinically advanced than others in the literature.\textsuperscript{51,52} The Religious Orders Study has followed up a group of nuns and priests for many years and has an excellent autopsy rate. In general, they found that approximately 60\% of the participants with MCI have neuropathological evidence of AD, but they indicate that vascular disease also accounts for a significant degree of the neuropathological features.\textsuperscript{53} Other studies have highlighted the importance of neurofibrillary tangle density when accounting for the symptoms of MCI.\textsuperscript{54}

Two studies from the Mayo Clinic published in the Archives of Neurology shed additional light on these participants.\textsuperscript{55,56} One study evaluated participants who died while their clinical classification was MCI and found that most had a low probability of having the neuropathological features of AD at that point in time.\textsuperscript{55} However, it appeared as if the participants were in transition to greater degrees of pathological involvement. A second study observed participants who had been previously diagnosed with MCI and had progressed to dementia and characterized these participants as having the ultimate pathological characteristics.\textsuperscript{56} This study indicated that, while most of the participants with aMCI developed AD, a considerable proportion (20\%-30\%) developed another type of dementing disorder, indicating that, while the clinical criteria for aMCI likely predict AD, they are not absolutely specific.

CLINICAL TRIALS

In the past 10 years, there have been numerous clinical trials on aMCI that tested most of the current therapies available for AD.\textsuperscript{20,57,58} All of the acetylcholinesterase inhibitors have been evaluated, and, with one partial exception, results of all these analyses were negative\textsuperscript{29,57-60} (Table 5). Cumulatively, these trials have involved between 4000 and 5000 participants. One trial with rivastigmine, two with galantamine, and one with rofecoxib failed to achieve the anticipated rates of progression from MCI to AD and consequently had to be extended, resulting in a lack of power.\textsuperscript{57-59} The rivastigmine trial was
Conducted in multiple countries with multiple languages and likely recruited a heterogeneous group of participants with very mild disease.\(^6\) Hence, the rate of progression was lower.

Two trials involving galantamine used mild entry criteria and required a more advanced degree of “conversion” of CDR 1 rather than the clinical diagnosis of AD as an end point.\(^5\) Therefore, this criterion may have inadvertently required participants to remain in the MCI stage for a longer period, resulting in a lower rate of progression than anticipated. However, this trial almost achieved its anticipated rate and had a suggestion of a therapeutic response.\(^5\)

The rofecoxib trial initially required a more stringent degree of memory impairment and had to loosen the inclusion criteria to recruit enough participants. This may have contributed to its low rate of progression, necessitating an extension of the trial.\(^5\) Consequently, for a variety of reasons, all of these trials did not meet their anticipated therapeutic goals.

The Alzheimer’s Disease Cooperative Study conducted a therapeutic trial on participants with aMCI to test high-dose vitamin E and donepezil and achieved its anticipated progression rate of 16% per year.\(^2\) It is interesting to note that virtually the same recruitment techniques were used in the ADNI, and this study has achieved a virtually identical progression rate of 16% per year.\(^1\) The Alzheimer’s Disease Cooperative Study suggested a therapeutic effect of donepezil for the first 12 months in all participants with MCI and up to 24 months for the apolipoprotein E ε4 carriers. However, because the study was designed to assess effects over 36 months, the ultimate outcome was negative.\(^2\) A subsequent 48-week trial of donepezil alone failed to replicate the Alzheimer’s Disease Cooperative Study results, and hence no treatments have been approved for MCI.\(^6\)

### Table 5. Clinical Trials\(^a\)

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Sponsor</th>
<th>Duration</th>
<th>End Point</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petersen et al, (^29) 2005</td>
<td>Alzheimer’s Disease Cooperative Study</td>
<td>3 y</td>
<td>AD</td>
<td>Vitamin E, donepezil</td>
</tr>
<tr>
<td>Thal et al, (^14) 2005</td>
<td>Merck</td>
<td>3-4 y</td>
<td>AD</td>
<td>Rofecoxib</td>
</tr>
<tr>
<td>Feldman et al, (^7) 2007</td>
<td>Novartis</td>
<td>4 y</td>
<td>AD</td>
<td>Rivastigmine</td>
</tr>
<tr>
<td>Winblad et al, (^10) 2008</td>
<td>Johnson &amp; Johnson</td>
<td>2 y</td>
<td>CDR 1</td>
<td>Galantamine</td>
</tr>
<tr>
<td>Doody et al, (^26) 2009</td>
<td>Pfizer</td>
<td>48 wk</td>
<td>AD</td>
<td>Donepezil</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; CDR 1, Clinical Dementia Rating of 1.

\(^a\) All trials used the clinical diagnosis of AD as an end point.

### Table 6. Sources of Variability in MCI Studies

<table>
<thead>
<tr>
<th>Source of Variability</th>
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<tbody>
<tr>
<td>Sources of participants</td>
<td></td>
</tr>
<tr>
<td>Clinical heterogeneity</td>
<td></td>
</tr>
<tr>
<td>Variability in clinical outcomes</td>
<td></td>
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<tr>
<td>Vagueness of criteria related to cognitive function</td>
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<tr>
<td>Proactive vs retroactive application of criteria</td>
<td></td>
</tr>
<tr>
<td>Neuropsychological normative data</td>
<td></td>
</tr>
<tr>
<td>Blinded nature of evaluators on each visit</td>
<td></td>
</tr>
<tr>
<td>Is MCI a clinical entity, a pathological entity, or both?</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: MCI, mild cognitive impairment.

### IMPLICATIONS

From a clinical trials perspective, if we were designing a disease-modifying therapeutic trial involving participants at the MCI stage, we could consider aMCI criteria of a degenerative pathogenesis and require positive imaging and biomarker data to enrich the clinical population to enhance the likelihood of progression to clinical AD. This could very well be consistent with the presumed therapeutic target of the agent. That is, if we were testing an amyloid-specific agent, we could use aMCI clinical criteria and stratify participants according to their apolipoprotein E ε4 carrier status, amyloid imaging, or markers of CSF involving amyloid to create a subset of participants who are more likely to progress rapidly and harbor the underlying amyloid pathological substrate.

### CHALLENGES

While the construct of MCI has engendered a great deal of attention (Figure 1), it has also raised a great deal of controversy. Much of the concern about the construct pertains to its heterogeneity, lack of specific ability to predict outcome, and vagueness of the criteria, eg, the degree of cognitive impairment in nonmemory cognitive domains and the degree of functional impairment. Table 6 depicts many of the sources of variability in studies on MCI, and a few deserve mention.

The source of participants is a prominent aspect of variability in many of these studies. As mentioned earlier, participants from a referral clinic, memory disorders clinic, or AD center likely have a prior probability of having AD at the outset. On the contrary, participants who are recruited proactively through an epidemiologic procedure are likely more heterogeneous, have multiple medical comorbidities, and are “less pure” from an AD substrate perspective. These participants would cause more “noise” in the system if used in clinical trials but likely represent the reality of MCI in the population.

Several early studies retrospectively applied MCI criteria to previously collected data sets.\(^6\) This approach necessitates the use of an algorithmic model to retrofit previously acquired neuropsychological data.

An issue inherent in the discussion of neuropsychological test scores pertains to the use of normative data on neuropsychological instruments and cutoff scores. It is important to emphasize that MCI is not just a neuropsychological entity. Although findings from neuropsy-
chological testing constitute a cornerstone of the objective assessment, the ultimate diagnosis involves more than just a set of cognitive test scores.

Two other sources of variability merit discussion. In longitudinal studies, the blinding of the investigators to the previous clinical diagnoses is important. If the investigators know that the participants were previously classified as having MCI, they would be less likely to label them as being cognitively normal on a subsequent visit. This approach is not necessarily inappropriate because it may reflect the natural variability of the clinical course of these participants and may actually consider this in the diagnostic process. Hence, in a research setting, previous knowledge can confound the interpretation of the data. Hence, investigators in many studies are blinded to previous clinical classifications. These types of studies lead to higher degrees of “reversion” to normal.

Finally, we need to address the issues of MCI as a clinical or pathological entity along with constructs of sensitivity and specificity. That is, when we make the diagnosis of MCI, does this diagnosis refer to the clinical state of the patient or to the underlying pathophysiological features leading to the symptoms, or both? It might be most productive to keep these entities separate.

CLINICAL IMPLICATIONS

These studies, coupled with the neuropathological findings, suggest that the clinical criteria for aMCI may designate a mildly impaired set of participants, many of whom, but not all, have the underlying neuropathological features of AD. These findings have implications for the labeling of the clinical condition of MCI and the design of future trials. It may be inappropriate to label participants at the aMCI stages as having AD, or even incipient or prodromal AD, because many will not eventually evolve to AD. Hence, we cannot afford to mislabel all participants with MCI as having AD features because this is the only label that they will perceive. In other words, participants and families will only “hear” the AD part of the label, yet we will be incorrectly labeling some of them because not all will progress to AD. Therefore, it might be preferable to use an etiologically neutral term such as “MCI,” coupled with a suspected pathogenesis evidenced through history and ancillary testing, and explain to the participants the possibility that this term may imply development of AD in the future or might imply stability or, even less commonly, improvement in their clinical symptoms. This approach may be more consistent with the longitudinal data.

In 2001, the American Academy of Neurology published an evidence-based medicine practice parameter on MCI and recommended that physicians should identify and monitor patients with MCI because these persons had an increased risk of developing dementia.

SUMMARY

The construct of MCI has influenced the field of aging and dementia in several significant spheres. It has focused the attention of investigators on the earlier prodromal states of many cognitive disorders. Research programs ranging from epidemiologic studies to explorations of the mechanisms of disease have been influenced by the construct of MCI, and these investigations will hopefully lead to more effective therapies. This work has stimulated discussions regarding new clinical criteria for conditions such as AD and will likely have an effect on the development of international classification systems for cognitive disorders.

Ultimately, we hope that this work will lead to the development of imaging measures and biomarkers for assessing the asymptomatic stages of neurodegenerative diseases. By augmenting our knowledge of the role of imaging and biomarker measures in the MCI stage, we will be able to validate their utility when predicting the progression to more advanced stages of cognitive disorders and to suggest their further utility by being applied to the asymptomatic stages of these conditions. As such, MCI will have served an important role in advancing our understanding of disease mechanisms with the ultimate goal of finding preventive therapies.

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