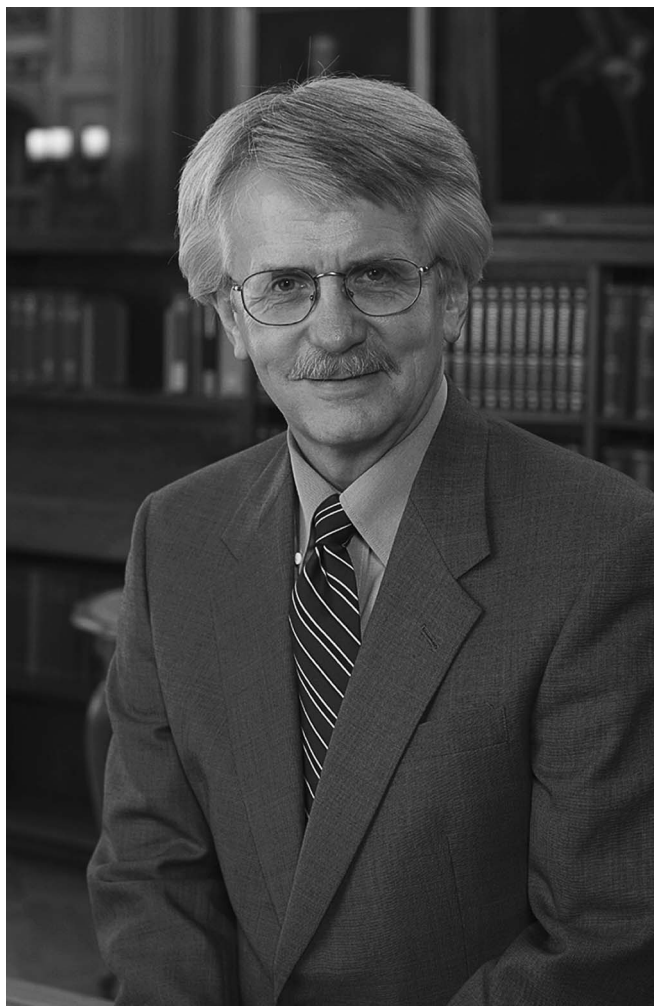


Mild Cognitive Impairment: Where Are We?

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Mild cognitive impairment (MCI) has become a prominent focus of research for many investigators in the field of aging and dementia. The construct of MCI has come to represent a transitional zone between the changes of normal aging and the very earliest clinical features of Alzheimer disease (AD), but this concept has not been without controversy.¹ Work on MCI has infiltrated many areas of aging and dementia

research including epidemiology, clinical diagnosis, neuropsychology, neuroimaging, neuropathology, mechanism of disease, and clinical trials.² Most of these areas of investigation have included a subject group with MCI characteristics in an attempt to study the earliest presentations of the AD process. As such, MCI has had a prominent influence on the direction of the field.

Research on aging and dementia at the Mayo Clinic began in a major fashion in 1986 under the direction of Leonard T. Kurland, MD, DrPH, and Emre Kokmen, MD, when the Mayo Alzheimer’s Disease Patient Registry was initially funded by the National Institute on Aging. I was fortunate to be included in that research effort at its inception and this work has formed the foundation of research on the boundary between aging and AD for more than two decades. The Alzheimer’s Disease Patient Registry project was a response to a request for applications from the National Institute on Aging to establish registries of persons with AD. Because the Mayo Clinic had a longstanding history of studying the population of Rochester, Minnesota, this project drew upon existing resources to evaluate a typical community in the upper Midwest that was aging in place. Through the establishment of this registry, a longitudinal cohort of subjects was established and continues to be followed to the present day. From its very inception, we had identified a group of individuals who appeared to have a memory impairment greater than what one would expect for age, yet the subjects did not meet clinical criteria for dementia. In the early years we had various labels for this group but we ultimately settled on the term, “mild cognitive impairment.” This term had been used previously in the literature and it was believed that this captured the cognitive difficulties these subjects were experiencing.³ As we codified our criteria for these individuals and followed them longitudinally, it became apparent that they progressed to clinically possible or probable AD at an accelerated rate.⁴ Although we had described the various features of these individuals in previous publications, it was not until 1999 that we specified the precise characteristics of this cohort and described their longitudinal outcome.⁵

The initial criteria for MCI focused on memory impairment and the likelihood of progression to clinically probable AD. Several other studies were appearing in the literature using similar criteria and also demonstrating that these individuals were at an increased risk of progressing to AD at a rapid rate.^{6–9} In 2001, the American Academy of Neurology published a practice parameter paper on the early detection of dementia and endorsed the construct of mild cognitive impairment as being clinically relevant because these individuals were at increased risk of progressing to dementia.¹⁰ Following this work, additional longitudinal studies were completed attesting to not only the increased risk of progressing but also to the variability in outcomes.^{11,12}

As such, the criteria for the diagnosis of MCI were modified to allow for clinical subtypes and variable outcomes depending upon the etiology of the underlying condition as is shown in Figure 1. The primary clinical distinction for subtypes revolved around the presence or absence of a prominent memory impairment and hence, the subtypes were characterized as amnesic MCI and non-amnesic MCI.¹³ As is shown in

		MCI Subtypes			
		Etiology			
		Degen- erative	Vascular	Psychiatric	Medical conditions
Clinical classification	Amnesic MCI	Single domain AD		Depr	
	Multiple domain AD		VaD	Depr	
Non- amnesic MCI	Single domain FTD				
	Multiple domain DLB		VaD		

FIGURE 1. The combination of clinical phenotype of mild cognitive impairment and suspected etiologies of the clinical syndrome. Modified from reference 1, with permission.

Figure 1, the amnesic MCI, when of a presumed degenerative etiology, progressed to AD at a greatly accelerated rate. However, depending upon other putative etiologies, the outcome of amnesic or non-amnesic MCI subjects could be quite variable as would be expected based on the presumed cause of the underlying symptoms.

As several studies have indicated, subjects with amnesic MCI are not only at greater risk of progressing to AD but also have a reduced survival.^{14,15} Thus, the condition was being better characterized with additional sophistication of the criteria and these refinements in the criteria have important implications for outcome.

The normal aging subjects and those with MCI at Mayo became the subject of many ancillary studies including neuroimaging, biomarker, and neuropathology studies. Dr. Clifford R. Jack, Jr. and colleagues have produced numerous structural MRI, MR spectroscopy, and functional MRI studies on subjects with MCI as well as the various subtypes.^{16–19} These studies have demonstrated that individuals with MCI are neither normal nor do they completely align with subjects with very mild AD. As such, the intermediate state of these individuals is well documented. Additionally, these investigations have demonstrated that MCI subjects have atrophic hippocampal formations and entorhinal cortices as well as greater total brain atrophy and enlarged ventricles relative to normal subjects. However, the degree of these volumetric changes has not been as extensive as seen in AD subjects again indicating that MCI subjects are intermediate between normal aging and AD. When MCI subjects are followed longitudinally using these neuroimaging measures, many of these measures have been important predictors of the rates of progression to AD and consequently, this work has translated into a potential biomarker for response to therapeutics. In fact, a great deal of this work has resulted in a major project, the Alzheimer’s Disease Neuroimaging Initiative, co-sponsored by the National Institute on Aging and industry, to investigate neuroimaging measures as markers for potential response to

therapeutic interventions in MCI. This project is being launched currently and focuses on this transitional state between aging and very early AD.

Ultimately, the work by my colleagues at Mayo has demonstrated the importance of characterizing individuals across the aging spectrum. A great deal of basic normative neuropsychology work has been conducted on the cohort in Rochester, Minnesota, as well as the neuroimaging work, biomarker studies, and neuropathology of these subjects.^{20,21} The goal of this work has been to move the diagnostic threshold back to an earlier stage to allow intervention as soon as possible in the course of neurodegenerative diseases.

From a neuropathology standpoint, similarly, subjects who come to autopsy while their clinical diagnosis is MCI do not meet criteria for the neuropathologic features of AD yet have more pathologic burden than is seen in normal aging.²² However, this is an area that needs further study because it is well known that many normal subjects also have pathologic features of AD.^{23–25} Most investigators agree that the subjects with MCI have partially developed the neuropathological substrate of AD, but, like many studies using other techniques (eg, neuroimaging and biomarkers), these individuals do not have the fully expressed features of AD. As such, this discussion has raised the semantic question of when one should designate a person as having AD: Is it when the clinical symptoms are present, or when the neuropathological markers appear in the brain? This is an issue that will continue to be debated.

In the past several years there have been many clinical trials undertaken to study subjects with MCI.²⁶ It has been realized that if one could intervene at an earlier stage, greater benefit might be derived from potential therapies. The primary study in this area was recently completed by the Alzheimer's Disease Cooperative Study (ADCS) and will be presented at this meeting.²⁷ The ADCS trial randomized amnesic MCI subjects to either high-dose vitamin E, donepezil, or placebo and followed the subjects for up to 3 years. This study demonstrated that donepezil reduced the likelihood of progressing from MCI to clinically possible or probable AD for the first 12 months of the 36-month study. These results were accentuated in the Apolipoprotein E4 carrier group. As such, this was the first study to demonstrate any ability to postpone the clinical diagnosis of AD. Although this is largely a symptomatic treatment, it does open the door for other therapeutic interventions to have a positive effect at an earlier stage than previously recognized.

This interest in MCI has been reflected in the scientific literature. As is shown in Figure 2, from 1990 through 1999, 176 scientific articles with MCI in the title or abstract were published. However, for the 5 years from 2000 through 2004, 991 articles have been published demonstrating the emerging interest in this area of research.

Finally, I would like to acknowledge many individuals who have been essential in the work done on MCI at Mayo. As previously mentioned, Drs. Leonard T. Kurland and Emre Kokmen were friends and mentors during the initial establishment of the Alzheimer's Disease Patient Registry and the Alzheimer's Disease Research Center. We have appreciated the support of the National Institute on Aging for over

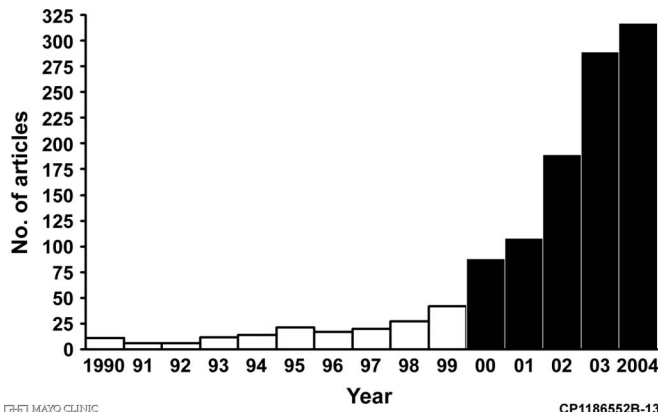


FIGURE 2. Published studies on mild cognitive impairment in the literature from 1990 through 2004 (with permission).

two decades as well as the Alzheimer's Association and the Robert H. and Clarice Smith and Abigail van Buren Alzheimer's Disease Research Program of the Mayo Clinic College of Medicine. We have been fortunate to have an extensive number of individuals in the Alzheimer's Disease Research Center in Rochester, MN, Jacksonville, FL, with support from our colleagues at Mayo Clinic Scottsdale. I would be remiss if I did not mention my family, my wife, Diane, daughter, Lindsay, and son, Matthew, for their support and encouragement over the years. It has been truly an honor to work with many colleagues at the Mayo Clinic and I owe a great deal of recognition to their support.

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