Mild Cognitive Impairment: *An Overview*

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ABSTRACT

Mild cognitive impairment (MCI) refers to the transitional state between the cognitive changes of normal aging and very early dementia. MCI has generated a great deal of research from both clinical and research perspectives. Several population- and community-based studies have documented an accelerated rate of progression to dementia and Alzheimer's disease in individuals diagnosed with MCI. Clinical subtypes of MCI have been proposed to broaden the concept and include prodromal forms of a variety of dementias. An algorithm is presented to assist the clinician in identifying subjects and subclassifying them into the various types of MCI. Progression factors, including genetic, neuroimaging, biomarker, and clinical characteristics, are discussed. Neuropathological studies indicating an intermediate state between normal aging and early dementia in subjects with MCI are presented. The recently completed clinical trials as well as neuropsychological and nutritional interventions are discussed. Finally, the clinical utility of MCI, and directions for future research are proposed.

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Needs Assessment

Mild cognitive impairment represents a useful clinical entity. As therapeutic interventions become available, it is likely that these treatments may be applied to populations with various forms of mild cognitive impairment in an attempt to treat the disorders at an earlier point in the disease process.

Learning Objectives

At the end of this activity, the participant should be able to:

- Be familiar with the current criteria for making the diagnosis of mild cognitive impairment (MCI).
- Predict the outcome of patients diagnosed with MCI based on the suspected etiology of the underlying syndrome.
- Learn about the predictors of MCI.
- Understand the pathology of MCI.
- Understand current treatment options for MCI.

Target Audience: Neurologists and psychiatrists

CME Accreditation Statement

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Mount Sinai School of Medicine and MBL Communications, Inc. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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This activity has been peer-reviewed and approved by Eric Hollander, MD, chair at the Mount Sinai School of Medicine. Review date: December 14, 2007. Dr. Hollander does not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

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INTRODUCTION

With the increasing number of older adults, there is a growing interest in improving quality of life in old age. One important aspect of this

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endeavor is to identify individuals at an earlier point in the cognitive decline such that therapeutic interventions can be aimed at this juncture. Mild cognitive impairment (MCI) has been proposed as a condition of intermediate symptomatology between the cognitive changes of aging and fully developed symptoms of dementia, such as those seen in Alzheimer's disease. Given the overall aging of the world's population,[1] degenerative dementias hold the potential of an impending crisis. The rationale for the study of MCI is derived from the assumption that the sooner one intervenes in a degenerative process, the more likely the damage done to the central nervous system can be prevented. As such, early diagnosis becomes paramount in trying to prevent subsequent disability.

The concept of MCI has evolved considerably over the years. The first attempt to characterize cognitive changes at the normal tail-end of the continuum dates back to 1962, when Kral[2] used the term "benign senescent forgetfulness" to describe early memory concerns with aging. This was followed by a National Institute of Mental Health workgroup in 1986 that proposed the term "age-associated memory impairment" (AAMI) to refer to memory changes that were felt to be a variant of normal aging. Shortcomings of AAMI included restriction of impairment to the memory domain only and comparison of memory function in older adults to performance of young adults. As such, AAMI was unable to delineate individuals at risk of developing pathological conditions from those undergoing the processes of normal aging. The International Psychogeriatric Association coined the term "age-associated cognitive decline" in an effort to bypass many of the shortcomings recognized in AAMI.[4] The operational criteria for age-associated cognitive decline referenced a variety of cognitive domains presumed to decline in normal aging and included age- and education-adjusted normative values. Alternatively, the Canadian Study of Health and Aging[5] coined the term "cognitive impairment-no dementia" (CIND) to describe individuals with impaired cognitive function but not of sufficient severity to constitute dementia. In many respects these "in-between" persons resemble MCI subjects but the CIND label actually includes a broader subset of the population. The construct of CIND encompasses individuals with lifelong cognitive impairment, static encephalopathy, and learning disability. Recently, some investigators[6] have defined subsets of persons with CIND who more closely resemble MCI subjects.

The term MCI was initially used in the late 1980s by Reisberg and colleagues[7-9] to describe individuals with a Global Deterioration Scale (GDS) rating of 3. Another classification has used the Clinical Dementia Rating Scale (CDR) to identify individuals with CDR 0.5 stage of "questionable dementia."[10,11] While both GDS and CDR are useful scales for classification of individuals along the continuum of severity of cognitive impairment, they do not necessarily correspond to specific diagnoses; in fact, individuals with GDS 3 or CDR 0.5 may meet the criteria for MCI, mild dementia, or Alzheimer's disease; that is, the level of severity alone does not determine a specific diagnosis. Recently, MCI has emerged to represent a stage of impairment beyond what is considered normal for age, but not of sufficient magnitude as to warrant the diagnosis of dementia or Alzheimer's disease.[12]

CLINICAL PRESENTATION

Initial Study

The first major study focusing on the clinical characterization and outcome of MCI was published in 1999,[13] and this study demonstrated the feasibility of using MCI to identify individuals as high risk for further cognitive decline and progression to dementia of the Alzheimer-type. The results of this and other studies focusing on the use of MCI as a research tool led to the adoption of the American Academy of Neurology practice parameter on early detection of dementia in 2001.[14] The original criteria for MCI are outlined in the Table. These criteria were designed to characterize the early stages of an Alzheimer's-like process, and were thus centered on memory impairment.[13] With subsequent research, it

TABLE.
MCI Original Criteria

1. Memory complaint, preferably qualified by an informant
2. Memory impairment for age
3. Preserved general cognitive function
4. Intact activities of daily living
5. Not demented

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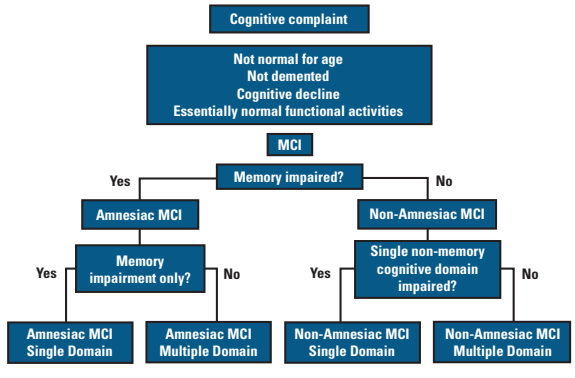
has become apparent that not all MCI subjects evolve to Alzheimer's disease. Therefore, the construct has recently been expanded to include impairments in other cognitive domains that may progress to non-Alzheimer's dementias. An international conference on diagnostic criteria was convened in Stockholm in 2003 to expand the criteria to include other forms of cognitive impairment.[15,16] Essentially, two subtypes emerged: amnestic (including memory impairment) and non-amnestic (non-memory cognitive domains impaired). This nomenclature is currently being using by the United States National Institute on Aging-sponsored Alzheimer's Disease Centers Program through their Uniform Data Set and by the Alzheimer's Disease Neuroimaging Initiative.[17]

Algorithm

Figure 1 depicts the diagnostic algorithm that can be used to arrive at a diagnosis of a particular subtype of MCI. This diagnostic process usually begins with a person, or an informant who knows the person well, expressing some complaint about the person's cognitive function. When presented with these complaints, the clinician should first establish whether this constitutes normal cognition or suspected dementia. This can be done by taking a history and performing a mental status exam, possibly complemented with neuropsychological testing.[18] If the clinician determines that the patient is neither normal for age nor demented, but has experienced a cognitive decline by history with functional activities largely preserved, then the patient can be described as having MCI.

FIGURE 1.
Current diagnostic algorithm for diagnosing and subtyping MCI



MCI=mild cognitive impairment.

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Once the diagnosis of MCI is established, the next task is to identify the clinical subtype. Here, the clinician should first determine whether memory is impaired, since memory impairment strongly predisposes the individual toward Alzheimer's disease. This can be determined by office memory tests usually involving an instrument with a delayed recall component or by more detailed neuropsychological testing. If memory is determined to be impaired for age and education, the clinician can assume that this is an amnestic subtype of MCI. If, on the other hand, memory is found to be relatively spared, but the person has impairment in other non-memory cognitive domains, such as language, executive function, or visuospatial skills, this constitutes a non-amnestic subtype of MCI.

Finally, the clinician should determine whether other cognitive domains are also impaired. This can also addressed using neuropsychological testing or other relatively brief office instruments. A diagnosis of amnestic MCI-single domain is assumed if the impairment involves only memory domain, whereas amnestic MCI-multiple domain pertains to impairments in the memory domain plus at least one other cognitive domain, such as language, executive function, or visuospatial skills. Likewise, a diagnosis of non-amnestic MCI-single domain is assumed if there is impairment in a single non-memory domain, whereas non-amnestic MCI-multiple domain refers to impairments in multiple non-memory domains. This exercise is typically what is done in clinical practice to determine the clinical phenotypes of diseases.

After the clinical characterization of the patient's symptoms has been determined, the next step involves determining the etiology of the symptoms. This is typically done based on the history from the patient and informant, laboratory testing for other causes of cognitive impairment and neuroimaging studies. Following these evaluations, the clinician then determines if the likely cause of the MCI syndrome is degenerative (gradual onset, insidious progression), vascular (abrupt onset, vascular risk factors, history of strokes, transient ischemic attacks), psychiatric (history of depression, depressed mood, or anxiety) or secondary to concomitant medical disorders (congestive heart

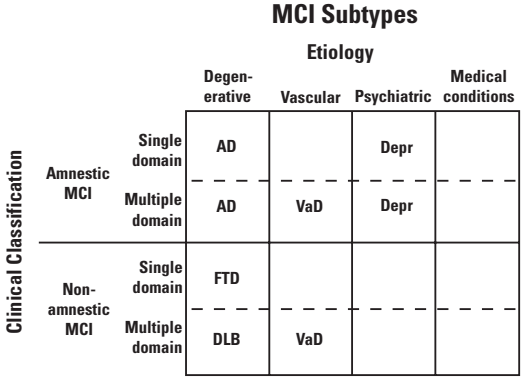
failure, diabetes mellitus, systemic cancer). As Figure 2 depicts, the single- and multiple-domain amnestic MCI subtypes with presumed degenerative etiology likely represent a prodromal form of Alzheimer's disease.[16] The non-amnestic subtypes that emphasize impairments in the non-memory domains may have a higher likelihood of progressing to non-Alzheimer's dementias, such as frontotemporal dementia and dementia with Lewy bodies.[19] Combining the clinical syndrome with putative etiologies can be useful in predicting the ultimate type of dementia to which these diseases will evolve.

Clinical Progression

Several population- and community-based studies have estimated the progression rate of MCI to dementia. Some variability exists in these estimates, which is perhaps most reflective of variability in diagnostic criteria.[20-22] The typical rate at which amnestic MCI patients progress to Alzheimer's disease is 10% to 15% per year.[23,24] Researchers from Harvard University have reported a lower conversion rate of 6% annually.[18] This lower rate, however, may have been due to recruitment strategy and selection of instrument, as participants in this study were recruited through media advertisement, and CDR was the sole instrument for evaluation. Although lower rates of progression have been described in some of the older epidemiologic studies, in a recent large prospectively designed trial from Germany,[25] MCI subjects diagnosed using the criteria in Table 1 progressed to dementia at rates of 7.2% to 10.2% per year. Some subjects improved from MCI to normal (~5% per year), but another subset initially improved and subsequently declined, implying instability in clinical course during progression to dementia. The vast majority of dementia cases were believed to represent Alzheimer's disease.

It is important to note that despite the variability in the precise rate of progression, all of these progression rates far exceed the population incidence figures for Alzheimer's disease of 1% to 2% per year. Thus, in counseling patients, a figure of 10% to 12% per year is probably a reasonably accurate prediction.

FIGURE 2.
Predicted outcome of MCI subtypes according to presumed etiology



MCI=mild cognitive impairment; AD=Alzheimer's disease; Depr=depression; VaD=vascular dementia; FTD=frontotemporal dementia; DLB=dementia with Lewy bodies.

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Progression Factors

The ability to predict which MCI subjects are more likely to progress to dementia or Alzheimer's disease more rapidly than others remains a major area of interest within the field of MCI research. Several potential candidates for predicting progression have emerged.

Apolipoprotein E-ε4 (ApoE4) carrier status is a well established risk factor for the development of Alzheimer's disease.[26] ApoE4 carrier status has been shown to be predictive of progression from MCI to Alzheimer's disease in several studies of various populations, including the Alzheimer's Disease Cooperative Study MCI Treatment Trial and the Religious Order Study.[27-29] It was also shown to correlate with more rapid progression of hippocampal atrophy on MRI in cognitively normal adults.[30] While this is an important adjunct to the clinical diagnosis of amnestic MCI in predicting the rate of progression, it is not yet recommended for clinical use for a variety of reasons.[31]

Clinical severity can also serve as a potential candidate for predicting progression; patients with more severe memory impairment are more likely to progress to Alzheimer's disease more rapidly than those with less memory impairment. This may account for some of the variability observed in the clinical trials to be discussed later. Furthermore, persons having amnestic MCI-multiple domain subtype will probably progress more rapidly than those having amnestic MCI-single domain. A recent study from the Mayo Clinic[32] reported that patients with amnestic MCI-multiple domain

subtype actually had poorer survival than patients with amnestic MCI-single domain.

Recently, the role of neuroimaging in predicting progression to Alzheimer's disease has gained a great deal of attention.[33-35] Jack and colleagues[36] has pioneered this effort and have shown that atrophy of the hippocampal formation predicts the rate of progression from amnestic MCI to Alzheimer's disease. Additional measures, such as whole-brain volume and ventricular volumes, have also been shown to predict progression to Alzheimer's disease, indicating that structural MRI is useful.[37] The role of FDG-PET in predicting progression has also been documented by some studies.[38-40]

Molecular imaging techniques that allow investigators to "visualize" the development of the pathologic process have also gained interest in recent years.[41,42] The Pittsburgh Compound B[41] is the most popular agent and labels fibrillar amyloid plaques. A second compound, developed at the University of California, Los Angeles, is FDDNP[42] and labels multiple neuritic elements including neuritic plaques and neurofibrillary tangles. These tracers, although in their infancy, are exciting new imaging techniques.

The possible utility of cerebrospinal fluid (CSF) biomarkers in predicting rapid progression to Alzheimer's disease has also gained attention. A recent large study[43] indicated that low CSF Aβ and high tau levels might predict which MCI subject are more likely to progress to Alzheimer's disease more rapidly than others. Ultimately, amnestic MCI subjects may be subclassified on ApoE4 carrier status, hippocampal volumes, fluorodeoxyglucose-positron emission tomography (FDG-PET) markers, CSF tau and Aβ levels and possibly molecular imaging tracers to identify a pure group of individuals who are highly likely to progress to Alzheimer's disease.

NEUROPATHOLOGY

The question arises as to whether persons with MCI actually have Alzheimer's disease at the time of their clinical diagnosis of MCI. This is a reasonable question since many of the biomarker and neuroimaging studies have implied that the Alzheimer's disease process is well underway even at the MCI clinical stage. A recent study from the University of Kentucky concluded that amnestic MCI subjects primarily had early Alzheimer's disease pathology.[44] These investigators acknowledged that their MCI subjects may have been more clinically advanced than in other studies and that the Alzheimer's disease population with which they were compared was in the early clinical stages of Alzheimer's disease.

Investigators from the Religious Order Study[45] have demonstrated an intermediate pathology between the neuropathologic changes of normal aging and very early Alzheimer's disease. These investigators acknowledge that there is likely a combination of findings, including neurodegeneration and vascular factors, contributing to the clinical picture.

Recently, two studies completed by investigators at the Mayo Clinic in Rochester, Minnesota have shed additional light on this topic. The first study[46] indicated that individuals who died while their clinical classification was amnestic MCI actually did not meet criteria for the neuropathologic diagnosis of Alzheimer's disease at that time. Rather, most of the subjects studied appeared to have transitional pathology implying that, had they lived longer, they would have developed the full neuropathologic picture of Alzheimer's disease. However, at this stage, there were insufficient data to conclude that they had Alzheimer's disease at this point in time. The most common characteristics of these subjects included neurofibrillary pathology in the medial temporal lobe and diffuse amyloid deposition in the neocortex. Most of the subjects did not have sufficient neuritic plaque pathology to constitute Alzheimer's disease neuropathologically. The other study from the Mayo Clinic[47] followed subjects who had previously been diagnosed with MCI and subsequently progressed on to dementia. This study reveals that, while most of the subjects with amnestic MCI went on to have Alzheimer's disease clinically and pathologically, >20% did not. This indicates that, while the amnestic MCI criteria are reasonably specific, they are not sufficiently so that the diagnosis of Alzheimer's disease can be made definitively at this clinical state. Some of the subjects went on to have other forms of dementia, such as dementia with Lewy bodies, frontotemporal dementia, or vascular dementia. This raises the issue of specificity of the clinical criteria, such that most subjects at the MCI stage are likely to progress to Alzheimer's disease but not all. Consequently, since it is important for the clinicians to be as accurate as possible and not mislabel subjects

with Alzheimer's disease, it is preferable to retain the diagnosis of MCI with its qualifications with regard to longitudinal outcome.

In summary, the actual pathologic substrate of most amnestic MCI subjects seems to be one of evolving Alzheimer's disease. That is, the full Alzheimer's disease neuropathologic spectrum is not present at the MCI stage, but many incipient features are evolving.

TREATMENT

As the focus of dementia research moves toward prevention, numerous clinical trials on MCI are being undertaken. Currently, there are no Food and Drug Administration-approved treatments for MCI. While one would not expect an overall treatment for MCI due to heterogeneity of the construct, treatments for amnestic MCI of a degenerative etiology that likely progress to Alzheimer's disease may be more feasible.[24,48-50] Over 5,000 subjects have been studied worldwide largely using therapies which have been proposed for Alzheimer's disease or were under consideration. A few trials were done to assess the impact on symptoms while most have been designed to have an impact on the rate of progression from MCI to Alzheimer's disease.[49]

The most promising trial was conducted by the Alzheimer's Disease Cooperative Study,[51] a consortium of Alzheimer's disease research centers in the US and Canada. A total of 769 subjects with amnestic MCI were randomly assigned to receive either donepezil, vitamin E, or placebo. Subjects were followed for 3 years; the primary endpoint was the clinical diagnosis of Alzheimer's disease and secondary endpoints included a variety of cognitive measures, quality-of-life indices, and pharamoeconomic measurements. The amnestic MCI subjects progressed to Alzheimer's disease at a rate of 16% per year. Over the 3 years of the study, there were no significant differences in the probability of progression to Alzheimer's disease among the three treatment groups. However, since assumptions of the primary-analysis model were not met, prespecified group comparisons were carried out at each of the 6-month evaluations. This analysis demonstrated that the donepezil group had a reduced risk of developing Alzheimer's disease for the first 12 months of the study. Subsequent analyses showed that the treatment effect was more prominent among ApoE4 carriers, with a reduction in risk apparent throughout the 36-month study. The results of the secondary analysis of cognitive and global measures supported the primary outcome results. This was the first study to show that donepezil treatment may delay the clinical diagnosis of Alzheimer's disease in MCI, and also demonstrated the feasibility of carrying out such large-scale studies in MCI.

Other trials have investigated the cholinesterase inhibitors, galantamine and rivastigmine, in MCI. Gold and colleagues[52] performed two international randomized, double-blind, placebo-controlled trials using their Alzheimer's disease compound, galantamine. The studies assessed the ability of galantamine to slow the progression from amnestic MCI (as measured by a CDR score of 0.5) to Alzheimer's disease (as measured by a CDR score of 1). There were a total of 2,048 subjects in both trials with a mean age of around 70 years. In neither trial did galantamine slow the progression of subjects from CDR scores from 0.5–1.0 by 24 months. There was a trend for a reduction in the rate of progression in both trials in favor of galantamine (13% galantamine vs 18% on placebo in one trial and 17% galantamine vs 21% placebo in the other trial), but the trials did not reach statistical significance. These studies showed a significantly higher rate of death in those who took galantamine, compared with those receiving placebo; a total of 13 subjects on galantamine (n=1,026) and one subject on placebo (n=1,022) died. About half of the deaths in the galantamine group were associated with various vascular causes (myocardial infarction, stroke, and sudden death).

Another large trial was conducted by Feldman and colleagues[53] using its acetylcholinesterase inhibitor, rivastigmine. This study involved 1,018 subjects and was designed to assess the rate of progression from amnestic MCI to Alzheimer's disease over the course of 2 years. However, due to an unexpectedly slow conversion rate, the study was extended to 4 years. Over that timeframe, 17.3% of the rivastigmine subjects progressed while 21.4% of the placebo subjects progressed, a difference which was not significant. There were essentially no changes over this timeframe in the composite cognitive battery.

The other large trial of amnestic MCI was conducted by Thal and colleagues[54] with their COX 2 inhibitor, rofecoxib. This was a randomized, placebo-controlled, double-blind study involving 1,457 subjects with amnestic MCI and also assessed the rate of progression to Alzheimer's

disease over 2 years. However, as in the rivastigmine trial, the progression rate was lower than expected and the trial had to be extended to 4 years. The annual conversion rate to Alzheimer's disease was 6.4% for the rofecoxib subjects and 4.5% for the placebo subjects and this treatment effect was statistically significant (*P*=.011) in favor of placebo, but the secondary cognitive measures did not corroborate this primary outcome. Hence, the investigators believed that this treatment difference was not clinically meaningful. Several factors led to a greater rate of progression to Alzheimer's disease, including a lower Mini-Mental State Exam score, ApoE4 carrier status, age, female gender, and prior use of ginkgo biloba. When these factors were used to analyze the primary outcome, the treatment effect in favor of placebo was no longer present.

Thus, while there are several clinical trials being conducted globally, currently, there are no pharmacologic interventions demonstrated to be efficacious in MCI. Nonetheless, as MCI is a rapidly evolving area of investigation, more effective treatment options are likely to be forthcoming.

PSYCHOSOCIAL AND NUTRITIONAL INTERVENTIONS

Recently, preventive approaches to treatment have also gained considerable attention. For instance, several studies have found that frequent participation in cognitively stimulating activities protect against cognitive decline and reduce the risk of Alzheimer's disease.[23,24] The construct of cognitive activity is generally operationalized through use of a number of scales that measure frequency of cognitive activities that are judged to primarily involve seeing or processing information.[25] These may include reading a book, playing a game such as chess or crosswords, or listening to a radio program. These studies have found that individuals who participate in cognitive activity and are engaged in their environment show the least decline in cognitive function compared with those with disengaged lifestyle.[24,26] Furthermore, a cognitively stimulating activity during childhood has been found to be associated with a higher cognitive function in old age.[27] Several studies have also found an association with incidence of Alzheimer's disease where individuals with lower participation in cognitively stimulating activities were at a higher risk of developing Alzheimer's disease compared to those reporting frequent cognitive activity.[23,28,29]

There is also evidence showing the link between nutrition and protection against cognitive decline. For example, studies that examined nutrition such as dietary fat consumption have found that low consumption of total fats, saturated fatty acids, and cholesterol was associated with less cognitive decline in aging.[18] Antioxidants, such as vitamins E and C, have also been associated with various benefits including cardiovascular health in old age.[19] The cumulative effects of such lifestyle factors have been shown in three large cohort studies: Health Professionals Follow-Up Survey, the Women's Health Initiative, and the Nurses Health Study; participants in these studies who did not smoke, exercised regularly (3–4 times per week), and adhered to a healthy diet (eg, high in fiber and ratio of polyunsaturated to saturated fats) experienced substantially lower risk of coronary heart disease and stroke.[20-22] Less is known with regards to the relation of such lifestyle factors to MCI and more work is needed in this area.

OUTLOOK

While the construct of MCI is a useful clinical entity, further refinements of the criteria and the prediction techniques may be necessary for prognosticating the outcomes. Further specificity of the criteria may result if certain biomarkers prove to be predictive of the ultimate outcome. For example, given the literature on the utility of volumetric magnetic resonance imaging (MRI) measures to predict the outcome of amnestic MCI subjects, volumetric measurements of the whole brain and hippocampal formations may lead to further refinement.[37] Several studies have indicated that ApoE4 carrier status further enhances the predictability of MCI subjects to progress to Alzheimer's disease.[55]

There are limited data indicating that FDG-PET may increase the sensitivity and the specificity of progressing to Alzheimer's disease.[40] Finally, recent studies on the possibility of the use of Pittsburgh Compound B, amyloid imaging, or FDDNP as a means of imaging the underlying pathologic process involved in evolving Alzheimer's disease may be useful.[41,42] Ultimately, it may take a combination of factors to enhance the predictive outcome of amnestic MCI.

One large multicenter trial, the Alzheimer's Disease Neuroimaging Initiative[17] is currently underway to assess the utility of some of these markers. The Alzheimer's Disease

Neuroimaging Initiative[17] is funded by the National Institute on Aging and industry in conjunction with the Alzheimer's Association and is enrolling 200 normal subjects, 400 subjects with amnestic MCI and 200 subjects with mild Alzheimer's disease. All of the individuals will be scanned with an MRI at 1.5 Tesla and 25% will be scanned with a 3 Tesla MRI. In addition, 50% of the cohort will receive FDG-PET and CSF for biomarkers will be obtained in at least 20% to 50% of the cohort. Blood and urine biomarkers will be obtained on all subjects and the participants will be clinically evaluated approximately every 6 months for the normal and MCI groups and will be followed for 3 years while the mild Alzheimer's disease subjects will be followed for 2 years. The study will be completed around the year 2010.

CONCLUSION

The construct of MCI is becoming in increasingly important clinical entity. MCI can be viewed as a precursor stage to many dementias, and its subtypes may predict specific dementia subtypes. Most literature pertains to the amnestic MCI subtype, which is useful for identifying individuals likely to develop Alzheimer's disease in the future. The American Academy of Neurology[56] has recently performed an evidenced-based medicine review of the literature and concluded that MCI is a useful clinical construct and that persons with MCI should be identified and monitored due to their increased likelihood of progressing to dementia. On the research side, the concept of MCI has influenced virtually all aspects of research on aging and dementia, including clinical aspects, neuropsychology, epidemiology, neuromaging, neuropathology, mechanisms of disease, and clinical trials. As such, the amnestic MCI subtype as a precursor of clinically Alzheimer's disease is being considered for inclusion in the next revision of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*[57] since it meets many of the diagnostic criteria for consideration. However, much discussion needs to ensue. ***CNS***

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