Mild Cognitive Impairment in Geriatrics

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KEYWORDS

• MCI • Mild cognitive impairment • Biomarkers in Alzheimer disease • Cognition
• Functional impairment

KEY POINTS

- Mild cognitive impairment is an intermediate state between normal cognition and dementia. It is an important construct in understanding cognitive decline.
- Mild cognitive impairment is the most predominant form and is the best predictor of future dementia, including Alzheimer disease.
- Mild cognitive impairment has predictive value for conversion to Alzheimer disease. Biomarkers may have value in determining disease-modifying therapy.
- The genetics of Alzheimer disease apply to rates of conversion from mild cognitive impairment to Alzheimer disease. This link will benefit future tailored therapies.
- In long-term care settings the condition is common and it is particularly problematic in assisted living if a resident's cognitive capacity is not correctly identified.

INTRODUCTION

The concept of mild cognitive impairment (MCI) as an intermediate state between normal cognition and dementia entered into the vernacular of geriatric medicine more than 30 years ago. Geriatric fellowship programs teach to the condition and primary care providers all have a passing understand that somewhere between normal and dementia there resides a population that fits the definition. In long-term care settings, the condition is common and it is particularly problematic in assisted living if a resident's cognitive capacity is not correctly identified. Incorrect placement or movement to a higher level of care for additional services shortly after a move in destabilizes the resident and family all the more at a most critical time of transition.

MCI as a term was introduced into the literature in 1988 by Reisberg and colleagues,[1] but referred to a severity index of stage 3 as identified on the Global Deterioration Scale. Another instrument, the Clinical Dementia Rating scale sought to

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identify very early dementia given the possibility of identifying disease early and intervening as soon as possible.[2] By 1999, MCI had been proposed as a prodromal condition for Alzheimer disease with the focus on memory as a chief clinical complaint for incipient disease.[3] Not all forms of MCI evolve into Alzheimer disease.

Although a misclassification may be a disservice to the diagnosis of MCI, the greater disservice is to the patient. Geriatricians need to use the diagnosis appropriately for patient care, understand the treatment limitations, apply appropriate management strategies, and prepare for a biomarker approach to diagnosis that makes MCI a valuable construct at looking at the spectrum of Alzheimer disease.

A COMMON UNDERSTANDING

MCI refers to cognitive impairment that does not meet the criteria for dementia. Several criteria for, and subtypes of, MCI have been proposed.[4–6] For our purposes, there must be a measurable deficit in cognition in at least 1 domain, there cannot be a dementia diagnosis, and the individual should have no functional impairment in their activities of daily living.

MCI has a number of different clinical presentations and etiologies, although the prognosis and prevalence[6–8] varies depending on the starting point of decline. The usefulness of the diagnosis now allows extending the early detection of other dementias in their prodromal stages.[9–11] Current criteria were developed to encompass the cognitive domains most commonly affected in the disorders (eg, memory problems and Alzheimer disease).[11,12]

MCI fits between the cognitive changes of aging and the impact of dementia. Considerable judgment is required in making the distinction between impairments that are normal for the elderly population and, at the other extreme, do not represent dementia. What constitutes impairment in daily living is always contextual. Patients with spouses, good financial resources, or attentive families do better. They display fewer functional difficulties because of their socioeconomic environment. The astute geriatrician is well aware that changes in the living environment have great impact on revealing significant limitations. Subjective cognitive complaints and even activities of daily living have been challenged as criteria in establishing the diagnosis.[3,13,14]

Amnestic Mild Cognitive Impairment

Amnestic MCI (aMCI) is often thought of as a precursor to Alzheimer disease.[15] aMCI is the most common subtype, with a ratio of 2:1 compared with non-aMCI (naMCI), although relative prevalence of MCI subtypes has varied among studies.[16,17]

Initially, MCI was used to refer to the amnestic subtype, but other subtypes have since been recognized (see Nonamnestic Mild Cognitive Impairment).

- Single domain aMCI refers to those individuals with significantly impaired memory who do not meet the criteria for dementia. The criteria originally outlined for MCI are understood to identify specifically this type[4,9]:
  - Memory complaint, preferably corroborated by an informant;
  - Objective memory impairment (for age and education);
  - Preserved general cognitive function;
  - Intact activities of daily living; and
  - Not demented.

Memory impairments that qualify for MCI are generally represented by defects that are 1.5 standard deviations or more below age-corrected norms. This threshold is not absolute, however, because individuals can experience a significant loss of memory

without satisfying that criterion. Different tests of memory likely have different sensitivity and specificity and norms are not available for all populations; this lack further justifies the necessity of clinical judgment.[7]

Multiple Domains

Many individuals with aMCI complain only of memory loss; however, they may have additional subtle impairments in other cognitive domains that are revealed with careful neuropsychological testing.[10,18–20] Such persons may also manifest subtle problems with activities of daily living, but do not meet the criteria for a formal diagnosis of dementia.[8] The multiple domains are, by definition, only slightly impaired (ie, <0.5–1.0 standard deviations below age- and education-matched normal participants). These individuals often progress to meet criteria for Alzheimer disease dementia; in a minority of cases, the cognitive profile may simply reflect normal aging.[8] The prognostic usefulness of the multiple domain form of aMCI remains unclear, because some studies have identified this as the highest risk category for conversion to dementia, whereas others have exposed instability with some individuals returning to baseline level of function over time.[10,21,22] Much of this variability derives from different sources of subjects, for example, specialty clinics versus population cohorts.

Nonamnestic Mild Cognitive Impairment

Single domain

The concept of single domain naMCI is similar to aMCI, except that this form of MCI is characterized by a relatively isolated impairment in a single nonmemory domain, such as executive functioning, language, or visual spatial skills.[8] Depending on the domain, individuals with this subtype of MCI may progress to other syndromes, such as frontotemporal dementia (FTD), primary progressive aphasia, dementia with Lewy bodies, progressive supranuclear palsy, or corticobasal degeneration. Individuals within this group seem to be at less of a risk of conversion to dementia, although supporting evidence is limited.[12,23]

In certain disorders such as behavioral variant FTD, cognitive complaints are often preceded by significant alterations in behavior and comportment. Thus, some investigators have proposed the concept of mild behavioral impairment as a similar paradigm to recognize an additional group with increased risk of dementia.[24]

Multiple domains

Patients who meet these criteria are affected in multiple domains with a relative sparing of memory problems. The substrate of multidomain naMCI is felt to be that of degenerative disorders associated with tau, TAR DNA binding protein and alpha-synuclein such as FTD and dementia with Lewy bodies.[2,25] Other studies have linked MCI in multiple domains to other types of dementia.[26]

The *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* has included mild neurocognitive disorder since 2013.[27] Age-associated memory impairment and age-associated cognitive decline are also widely used terms but represent normal age-associated memory and cognitive changes in older adults as referenced to young normal adult individuals.[4,28,29] Age-associated cognitive decline was developed to better define the cognitive changes in elderly patients compared with age-adjusted norms, but has more recently been recognized as identifying a state of impairment similar to MCI.[30]

MAKING THE CASE

Cognitive impairment is prevalent in American nursing homes and assisted living facilities; 70% or more of residents have some type of cognitive impairment.[31–34] In both

settings, studies estimate that approximately 50% to 60% of all residents meet criteria for dementia[35–38] and approximately 20% to 25% of residents meet criteria for MCI.[33] The concept is now accepted for clinical care[39,40] and has been adopted in Europe. The ability to identify residents in long-term care settings with cognitive impairment is critical to effective care plans and interventions and can facilitate appropriate staff interactions so important to residents' quality of life.[41] There is ample evidence that, when cognitive impairment is not identified accurately, the management of medical conditions can be adversely affected.[42,43]

An International Association of Gerontology and Geriatrics–Global Aging Research Network consensus conference in St. Louis in early 2015 identified that cognitive impairment creates significant challenges for patients, their families and friends, and the clinicians who provide their health care. Early recognition allows for diagnosis and appropriate treatment, education, psychosocial support, and engagement in shared decision making regarding life planning, health care, involvement in research, and financial matters. The consensus panel examined the importance of early recognition of impaired cognitive health. Their major conclusion was that case finding by physicians and health professionals is an important step toward enhancing brain health for aging populations throughout the world. This conclusion is in keeping with the position of the United States' Centers for Medicare and Medicaid Services, which reimburses for the detection of cognitive impairment as part the of Medicare Annual Wellness Visit and with the international call for early detection of cognitive impairment as a patient's right. The panel agreed on the following specific findings:

1. Validated screening tests are available that take 3 to 7 minutes to administer;
2. A combination of patient- and informant-based screens is the most appropriate approach for identifying early cognitive impairment;
3. Early cognitive impairment may have treatable components; and
4. Emerging data support a combination of medical and lifestyle interventions as a potential way to delay or reduce cognitive decline.[44]

TOOLS OF THE TRADE

Currently, the Brief Interview for Mental Status[45] is the mandated cognitive assessment tool included in the Minimum Data Set 3.0 for skilled care nursing home residents. The Brief Interview for Mental Status is an efficient measure that has strong reliability and convergent validity, can be rapidly administered (average time is about 3 minutes), and is suitable for paraprofessional use.[46] The Brief Interview for Mental Status was never intended to be sensitive to the full cognitive continuum and does not stage dementia levels. The cut scores differentiating residents with and without cognitive impairments are based, in part, on the Modified Mini-Mental State Examination,[47] a measure that seems to have poor sensitivity to MCI.[48] Cut scores were not based on broader and potentially more powerful assessments, such as a neuropsychological battery, imaging analyses, or biomarkers. Consequently, reported test scores may be inaccurate. Memory is assessed using a simple word list (3 words), with no story recall component, and executive function is only addressed minimally.[33,49] The Brief Cognitive Assessment Tool has been proposed to address these shortcomings. The Brief Cognitive Assessment Tool is a 21-item instrument that can be administered in approximately 10 to 15 minutes by paraprofessionals and clinicians, contains a strong multilevel verbal memory component (inclusive of story recall items), and has a broadly complex executive function component. Another purported advantage of the Brief Cognitive Assessment Tool is that it has been shown to specifically differentiate between MCI and dementia.[31]

Geriatricians also have available to them a wide assortment of additional cognitive screens, including the informant-based AD8.[50–54] Each can have its place in a busy primary care practice to screen at-risk populations of patients, especially those who find themselves transitioning into some higher level of service with less independence. Assisted living and nursing homes come quickly to mind. The Mini Mental State Examination (MMSE), which was published in 1975[23] and the Kokmen Short Test of Mental Status[55] are now mostly relegated to research/drug protocols that rely on these baseline measures. All are validated, some have been translated into many languages (the AD8 is available in >100 languages), and each carries with it enough sensitivity and specificity when used in populations at risk to provide good stratification from normal to abnormal once the age and education is taken into account.

The Gerontological Society of America also looked at brief instruments that were nonproprietary. Their comprehensive toolkit is focused on the KAER model developed by the GSA Workgroup on Cognitive Impairment Detection and Earlier Diagnosis.[56] The workgroup identified valuable tools and resources to implement the 4 steps in the *KAER* model. The resulting toolkit provides options for each of the steps so that primary care providers, health plans and health care systems can select the approaches and tools that fit best with their existing primary care structure, organization, and procedures.

The toolkit is broken down by each section of the *KAER* model to allow quick and easy access:

- *Kickstart* the cognition conversation,
- *Assess* for cognitive impairment,
- *Evaluate* for dementia, and
- *Refer* for community resources.

THE AGING PATIENT

Although specific changes in cognition are frequently observed in normal aging, there is increasing evidence that some forms of cognitive impairment are recognizable as an early manifestation of dementia.[3] MCI is a heterogeneous syndrome and there remains controversy over aspects of the construct. However, the usefulness of this paradigm is the recognition that dementia is not a dichotomous state and thus refining our understanding of the layers of transition will improve the understanding of cognitive decline and ultimately benefit patients. Appropriate diagnosis lets us address our patient needs with the best available therapies, be they drug or nondrug interventions.

Unfortunately, all too often MCI is used to soften a diagnosis of what should really be dementia. In 2003, Winblad and colleagues[57] sought to expand and revise the criteria.[58] From that conference the criteria now used by the National Institute on Aging-sponsored Alzheimer Disease Centers Program Uniform Data Set and the Alzheimer Disease Neuroimaging Initiative[59] have helped us design protocols to improve our understanding of the dementing process. The clinical phenotypes as we have now discussed include aMCI and naMCI with the subtypes of single and multiple domain classifications.

In general, our shortcomings in approaching patients with cognitive decline have been to avoid a diagnosis and delay our interventions. The reasons are multiple, although taking the time to make a diagnosis means that much more time will be needed to explain the diagnosis and take action. Any assault on our independence with special concern regarding the loss of driving privileges plays poorly to the American mindset. We live in a land where our first right of passage is the driver's license and where all roads lead to the shopping mall. We do not live in walking communities

and the last thing we give up is our driver's license. There have also been financial disincentives in the past when clinicians used a psychiatric code to define cognitive disease though MCI and the dementing syndromes now can be classified with *International Classification of Diseases*-10 medical codes.

MCI has been studied more extensively in ambulatory patients, but both nursing homes and assisted living facilities have a high reported prevalence of cognitive impairment.[36,37] Questions remain regarding whether MCI subtypes found in community-dwelling patients are mirrored in long-term care settings and how selected impairment thresholds might impact probable diagnosis. The work by Mansbach and associates[60] identified 3 clear MCI subtypes in the long term care setting: amnestic, single domain; nonamnestic, single domain (executive); and amnestic, multidomain (memory and executive). A fourth category (undifferentiated) was identified in patients who did not meet the criteria for a distinct MCI subtype, but still had cognitive impairments.

Given the difficulty in identifying state by state assisted living facilities (conservative estimate of 1 million) as compared with skilled care (1.4 million, 2014 National Center for Health Statistics), the long-term care population should command the interest and respect of geriatricians. Generally, the only separation of these 2 populations is their functional impairment. Attempts have been made in assisted living to test the performance of various instruments given the high prevalence of disease. In a North Carolina sample of assisted living residents, 55 of 146 participants (38%) were diagnosed with probable dementia and 76 (52%) met criteria for MCI (most nonamnestic). Both the Mini-Cog and the MMSE showed high sensitivity and negative predictive value for dementia, but had relatively low sensitivity and negative predictive value for MCI. The Mini-Cog had low specificity and was less accurate as a dementia screen than either the MMSE or MMX. Reliability and validity data for testing the MMX, a 50-point test based on expanding selected MMSE items, were satisfactory and it performed better as a screening test for MCI than either the MMSE or Mini-Cog.[61] Additional studies have also indicated that amnestic and executive deficits are particularly common in long-term care patients,[36,62] whereas amnestic and executive subtypes have been identified in community samples of the elderly.[63]

FRAILTY AS A CONFOUNDER

Geriatricians may be confronted by those who are extremely old (90 in a male, 95 in a female) where sudden near complete failure includes a rapidly progressing dementia. It is unlikely that this is Alzheimer disease alone and there is rarely a classic presentation of MCI as prodromal. Cognitive frailty is a term that has recently emerged in the geriatrics literature, inspired by potential parallel links to and possible common underlying mechanisms with the physical frailty syndrome.

Physical frailty has been defined as "a medical syndrome with multiple causes and contributors that is, characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death."[64] Recently, it has been recognized that a subgroup of persons with cognitive impairment have a decreased resilience and functional decline that interacts with physical frailty. Converging evidence suggests that the cognitive status represents an important dimension of the frailty syndrome.

Epidemiologic studies have shown an association between frailty and late-life cognitive decline, incident MCI and Alzheimer disease, and non-Alzheimer disease dementias.[65] It has been suggested that cognitive frailty can be defined as a reduced cognitive function (Clinical Dementia Rating score of 0.5) with the cognitive impairment

being due to either physical or brain disease[2,66] or accelerated brain aging in the absence of evident brain disease. Physical frailty has to coexist to evoke the term cognitive frailty. It manifests commonly with executive dysfunction (frontal cortex) and less with pure amnestic defects (mesial temporal cortex). Others have suggested that the deficits in frail and prefrail patients in executive function and memory may be similar in size.[67]

There is some evidence that, even with normal aging, both cognitive decline and physical frailty often coexist.[68–70] Cross-sectional studies find a high level of coexistence between rates of cognitive impairment and dementia and physical frailty.[71] Frailty predicts cognitive decline and incident dementia[72,73] and cognitive impairment predicts frailty[74,75] in longitudinal studies. Loss of executive function and poor attention are particularly associated with slow gait.[76] There is increasing evidence that persons with white matter hyperintensities have poor balance, poor get up and go performance, slow gait speed, and increased falls.[77–79] White matter hyperintensities also predict functional decline.[80] In a Spanish study, fall risk factors did not hold a direct correlation with the level of cognitive impairment among elderly nursing home care residents.[81]

HOME-BASED AND COMMUNITY-BASED CARE

- The vast majority—80%—of elderly people receiving assistance, including many with several functional limitations, live in private homes in the community and not in institutions.[82]
- Elderly people with limitations in 3 or more activities of daily living who live in the community receive an average of 9 hours of assistance per day (counting both formal and informal sources of care) and people age 85 or older with that degree of impairment typically receive about 11 hours of assistance per day.[83]
- The trend toward community-based services as opposed to nursing home placement was formalized with the Olmstead Decision (July, 1999), a court case in which the Supreme Court upheld the right of individuals to receive care in the community as opposed to an institution whenever possible.
- The proportion of Americans aged 65 and over with disabilities who rely entirely on formal care for their personal assistance needs has increased to 9% in 1999 from 5% in 1984.
- Between 2000 and 2002, the number of licensed assisted living and board and care facilities increased from 32,886 to 36,399 nationally, reflecting the trend toward community-based care as opposed to nursing homes.[84] Most assisted living facilities, however, are unlicensed.
- Most assisted living facilities discharge residents whose cognitive impairments become moderate or severe or who need help with transfers (eg, moving from a wheelchair to a bed). This factor limits the ability of these populations to find appropriate services outside of nursing homes or other institutions.[85]

WHY DOES IT MATTER?

If we wait for functional decline to define dementia, it may be too late to treat the underlying disease process.[4] Moreover, because functional decline is in the definition of dementia, it is best to work with a construct that would allow intervention sooner rather than later. With this theoretic framework, many studies have been conducted to investigate the usefulness and prognostic outcome of the diagnoses.[4]

In addition, the concept of MCI plays extremely well as we design hypothesis-driven research, be it with regard to clinical markers, psychological assessment, neuroimaging,

biomarkers, or drug and nondrug interventions.[13] This point is perhaps equally as important as the clinical diagnosis and has generated research opportunities worldwide. The construct of MCI has been incorporated into research on aging from multiple perspectives including clinical research, epidemiology, neuroimaging, mechanisms of disease, clinical trials, and caregiving.[13]

Numerous investigations worldwide have used these criteria as an infrastructure for estimating the frequency of MCI and its subtypes.[5–8] Both prospective[5,9] and retrospective studies[10] have helped to define the subtleties of the diagnosis. A major factor in determining outcome depends on the source of the patient being studied. The closer one is to a community sample, the lower the annual rates of progression (6%–10%).[11] With referral-based studies, such as those that come from sampling a memory disorders clinic or Alzheimer disease center, the progression rates increases to 10% to 15% per year, particularly for Alzheimer disease.[12] These differences reflect the probability of having an underlying disorder such as MCI when a participant or concerned family member seeks treatment at a referral clinic. The same phenomenon occurs at dementia screening clinics that advertise their services and claim diagnostic rates approaching 50%. This finding is in the face of baseline incidence rates of dementia and Alzheimer disease of 1% to 2% per year.[3]

EPIDEMIOLOGY

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.[14] 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 is degenerative[86] and this cause predominates to a greater extent for aMCI than for naMCI. There is also strong evidence that these rates tend to hold up throughout the world at about 14% to 18% for individuals aged 70 and older.[13]

In early 2018, the American Academy of Neurology published its "Practice Guideline Update: Mild Cognitive Impairment."[86] The guideline focuses on the prevalence and treatment of MCI and finds that there is strong evidence that MCI prevalence is high in the general population, with prevalence increasing for every 4-year age group starting at the age of 60 years. Overall, in persons 65 and older, the pooled prevalence of MCI is about 15% to 20%, and that compares with a population prevalence of dementia of about 10% to 12%. Furthermore, strong evidence shows that the natural history for many MCI cases can progress to dementia so a thorough evaluation to determine the underlying cause is important because some causes are treatable (**Figs. 1** and **2**).

ASSESSING THE PATIENT

Patients with MCI, particularly the amnestic subtype, complain primarily of impaired memory, or at least their families make the case that there is a new problem. It is also likely that the changes have been progressive over time, subtle but taken as a whole a change from a former level of function. Subjective memory complaints have been demonstrated to predict cognitive decline, even when patients seems to be unimpaired on testing.[87–91] The 1 free pass, such as recalling names, is frequently reported by normal elderly patients. The patient that arrives worried and reports memory complaints can be found to have impaired concentration with a mood or affective disorder.[87,92] Some individuals who meet neuropsychological test criteria for MCI deny having any significant memory problems.[93]

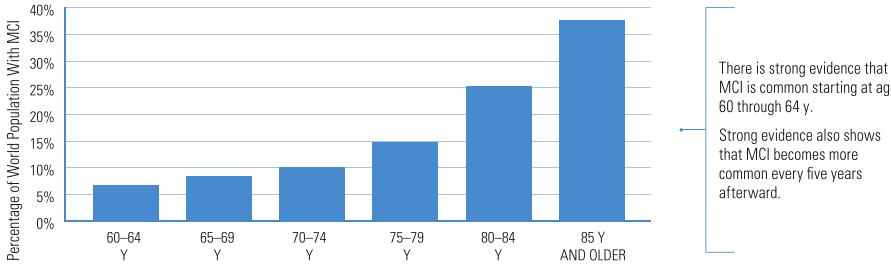

Fig. 1. Mild cognitive impairment (MCI) is common. (Practice guideline update: Mild cognitive impairment [patient summary]. Minneapolis, MN: American Academy of Neurology; Epub 2017 Dec 27. https://www.aan.com/Guidelines/Home/GetGuidelineContent/883. Accessed August 16, 2018. © 2017 American Academy of Neurology Institute. Reproduced with permission.)

In contrast with the impaired awareness of deficits commonly present in patients with Alzheimer disease, younger patients with MCI are often troubled by their symptoms.[89,94,95] However, as the patient ages and develops more overt disease, including Alzheimer disease, informant-reported symptoms over self-reported symptoms predominate.[96] As with dementia, mood and behavioral symptoms are more common in patients with MCI than in cognitively unimpaired, age-matched controls.[97–102] The prevalence of depression ranges from 25% to 40%[103]; other common symptoms include irritability, anxiety, aggression, and apathy.[99] Patients with MCI and behavioral symptoms may be more impaired on cognitive measures than those without behavioral symptoms.[99]

Population-based studies comparing MCI and patients with Alzheimer disease find a similar range of neuropsychiatric symptoms, with patients with Alzheimer disease having them in somewhat higher frequency and severity.[100,104,105] The end stage for nursing home patients is often the overt manifestation of behavioral symptoms, although this population continues to receive antidepressant therapy and treatment with atypical antipsychotics, although in lesser numbers and amounts than a decade ago.

Cognitive impairment may be a presenting symptom of depression, so-called pseudodementia. Depression may also be an early manifestation of cognitive impairment. A number of population-based studies have found an association between various measure of depression and the presence of MCI.[97,106,107] However, follow-up data have yielded somewhat mixed results:

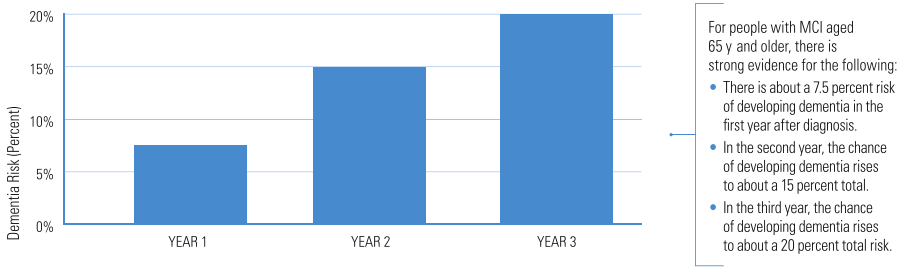

Fig. 2. Dementia risk in people with mild cognitive impairment (MCI). (Practice guideline update: Mild cognitive impairment [patient summary]. Minneapolis, MN: American Academy of Neurology; Epub 2017 Dec 27. https://www.aan.com/Guidelines/Home/GetGuidelineContent/883. Accessed August 16, 2018. © 2017 American Academy of Neurology Institute. Reproduced with permission.)

- Among 500 persons who were 85 years old, impaired cognition at baseline was associated with increasing depressive symptoms over 4 years of follow-up, but baseline depression was not associated with accelerated cognitive decline.[106]
- In contrast, other large cohort studies have found that depressed mood and/or anxiety are associated with increased risk of MCI in patients with normal cognition, and with progression to dementia in patients with MCI.[97,107–110]
- Finally, an analysis of MCI diagnostic criteria used in 6 clinical trials found that excluding patients with depression significantly decreased the sensitivity rates of MCI diagnosis for a future diagnosis of Alzheimer disease.[111]

ESTABLISHING THE DIAGNOSIS

A work group on diagnostic guidelines from the National Institute on Aging-Alzheimer's Association identified the following core clinical features that indicate MCI owing to Alzheimer disease.[112] These criteria only refer to the majority of MCI that is likely to progress to Alzheimer disease and not to MCI owing to other etiologies, for example, vascular disease, other neurodegenerative conditions, or psychiatric conditions.[58]

- Cognitive concern reflecting a change in cognition reported by patient or informant or observed by clinician;
- Objective evidence of impairment in 1 or more cognitive domains, typically including memory;
- Preservation of independence in functional abilities; and
- Not demented.

In addition, the etiology of MCI should be evaluated to identify the cause as most likely to be Alzheimer disease:

- Rule out vascular, traumatic, and medical causes of cognitive decline, where possible;
- Provide evidence of longitudinal decline in cognition, when feasible; and
- Report history consistent with Alzheimer disease genetic factors, where relevant.

As part of the MCI owing to Alzheimer disease criteria, biomarkers are used to augment clinical suspicions that the clinical syndrome of MCI is due to Alzheimer disease.[112] The geriatrician needs to be familiar with the concept of biomarkers. Future therapies will depend on the construct of prodromal MCI, MCI, and early Alzheimer disease and the vast array of testing now becoming available to segment the population for disease-modifying therapies based on genotype, amyloid or tau imaging on PET, and even cerebrospinal fluid evaluation.

One of the first biomarkers for MCI and Alzheimer disease was apolipoprotein E (APOE) genotypes. Generally, the E4 phenotype conveys a higher likelihood of disease, whereas the E2 genotype is somewhat protective.[113] The APOE e4 allele remains as an important predictor in MCI conversion to Alzheimer disease for patients with single domain MCI and multiple domains MCI from onset to disease progression. Among those with MCI, e4 carriers had the lowest level of plasma APOE as well (**Fig. 3**).[114]

The geriatrician must evaluate the patient for the potential of other conditions that can present with MCI:

- Depression or other disorders of mood that may present with cognitive complaints.
- Medications including anticholinergics, antihistamines, benzodiazepines, and the nonbenzodiazepine Z-class of sedative hypnotics.[115,116]

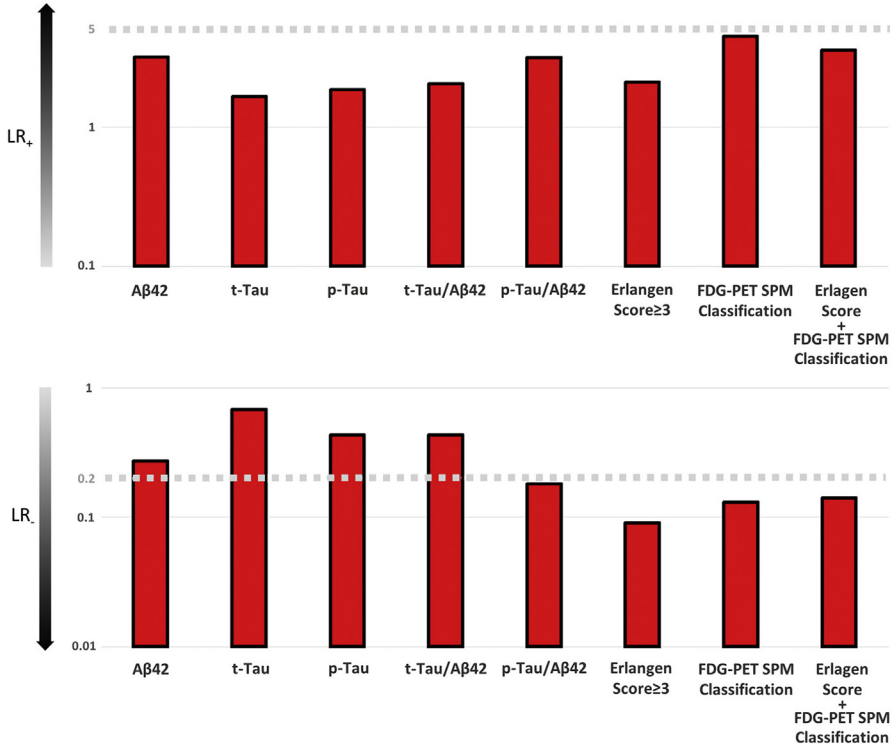

Fig. 3. Positive and negative likelihood ratio (LR_+ and LR_-) for correct classification or patients with mild cognitive impairment (MCI) converting to Alzheimer disease (AD) dementia. A LR_+ of greater than 5 indicates that the biomarker positive classification is associated with the disease occurrence. A LR_- of less than 0.2 indicates a relevant association between the negative biomarker classification and the absence of the dementia condition at follow-up. LR values are represented on a logarithmic scale. FDG, fludeoxyglucose F 18; SPM, statistical parametrical. (*From* Scarabino D, Broggio E, Gambina G, et al. Apolipoprotein E genotypes and plasma levels in mild cognitive impairment conversion to Alzheimer's disease: a follow-up study. Am J Med Genet B Neuropsychiatr Genet 2016;171(8):1135; with permission.)

- Vitamin B_{12} deficiency and hypothyroidism are always looked for and seldom found.
- Alcohol use and abuse and, as the boomers age, other recreational drug use as well.

In a community sample, patients with "cognitive impairment, no dementia" were diagnosed with depression and other psychiatric disease (10.2%), alcohol- and drug-related causes (6.9%), and delirium (1%).[117] Approximately one-quarter of patients had neurologic disease (brain tumor, Parkinson disease, multiple sclerosis, cerebrovascular disease, and epilepsy). Among the remaining 57.5% of patients, most (31.7%) had circumscribed memory impairment.

The story of beta amyloid is also intricately locked with our understanding of Alzheimer disease and, likewise, MCI. The role of beta amyloid in neurodegeneration has been thought to be seminal to the progression of disease. Unfortunately, all targeted therapies to date to clear beta amyloid, prevent its aggregation, or limit its impact on cellular function have not resulted in new drug interventions. Nonetheless, as a biomarker it clearly reflects disease progression (**Fig. 4**).[118]

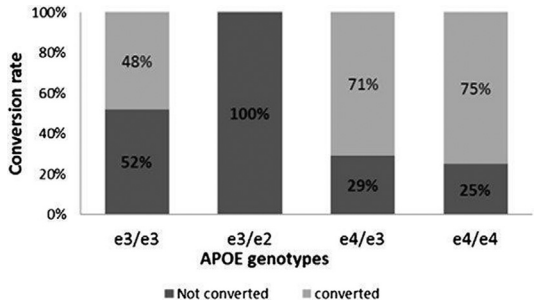

Fig. 4. Conversion rate of patients with mild cognitive impairment (MCI) according to apolipoprotein (APOE) genotypes. (*From* Doraiswamy PM, Sperling RA, Coleman RE, et al. Amyloid-beta assessed by florbetapir F 18 PET and 18-month cognitive decline: a multicenter study. Neurology 2012;79(16):1638; with permission.)

APPROACHING THE PATIENT AND THEIR CAREGIVER

The clinical history remains the mainstay in making a diagnosis of MCI. It is all about what insight the patient maintains in understanding their memory deficit. However, obtaining a history from both the patient and an informant may provide further support that a cognitive decline does exist.[21] Questions about cognition should address all major domains, including memory, attention–executive functioning, visuospatial skills, and language. Common memory symptoms include the tendency to repeat oneself or forgetfulness for recent events.

Patients with attention–executive functioning impairment may have problems in making decisions, planning activities, and multitasking. Visuospatial difficulties may be elicited by asking about a tendency to get lost while driving or an inability track the lines on a page while reading. Word finding difficulty, paraphasias, and/or anomia may indicate language dysfunction. The history taking should also focus on functional status, including the ability to drive, manage finances, and maintain basic activities of daily living. Possible neuropsychiatric, motor, and sleep issues should be addressed, because the presence of these symptoms may suggest a possible etiology of an MCI subtype.

Language difficulties, disinhibition, or socially inappropriate behavior may be seen in those with FTD; REM sleep behavior disorder, characterized by a tendency to act out dreams, has been associated with dementia with Lewy bodies. A past medical history may reveal cerebrovascular disease, seizures, head trauma, or systemic cancer or infections that may be contributing to the cognitive impairment.

The time course of symptoms is also important. A gradual, insidious progression of symptoms may suggest a degenerative cause, whereas a more acute onset may indicate a vascular, inflammatory, or infectious etiology. The loss of concentration may be a presenting symptom, but it is more often associated with depression than with cognitive impairment. Good screening tests for depression are readily available and the Patients Health Questionnaire (PHQ)-9 has found its way into many office practices.[22] The PHQ-9 is the 9-item depression scale of the Patient Health Questionnaire. It is a powerful tool for assisting primary care clinicians in diagnosing depression as well as selecting and monitoring treatment.

The primary care clinician and/or office staff should discuss with the patient the reasons for completing the questionnaire and how to fill it out. It can be done by intact patients or used as a survey instrument and done by just about anyone. After the patient has completed the PHQ-9 questionnaire, it is simply scored. There are 2 components of the PHQ-9: (1) assessing symptoms and functional impairment to make a

tentative depression diagnosis, and (2) deriving a severity score to help select and monitor treatment. It also responds to treatment initiatives with clinically validated changes in the patient's response.

After a history has been obtained that will also evaluate the impact of decline, a general neurologic examination should be performed. Any practitioner with appropriate experience can do the examination. Although the examination may be normal, abnormalities could suggest a potential etiology for the cognitive deficits. Parkinsonism may be seen with dementia with Lewy bodies as well as other neurodegenerative disorders, motor neuron signs may be associated with FTD, and focal deficits consistent with a specific vascular distribution may suggest a vascular cause for the cognitive impairment.

In addition to a general neurologic examination, a screening mental status examination, such as the MMSE, 3MS, or Kokmen Short Test of Mental Status, should be administered.[23–25] The severity of symptoms may be determined using assessments such as the Clinical Dementia Rating scale.[2] A formal neuropsychological battery also can be performed and should include tests that sufficiently challenge a patient in each cognitive domain.

After adjusting for age and education, scores below 1.0 to 1.5 standard deviations below the mean typically indicate cognitive impairment on neuropsychological testing.[26,119] Learning and recall tasks may differentiate subjects with MCI from those experiencing normal aging. On measures of general cognitive function such as the MMSE and full-scale IQ, the individual with MCI performs more similar to a normal elderly subject, whereas memory function on delayed verbal recall (Logical Memory II) and nonverbal delayed recall (Visual Reproductions II) more closely resembles mild Alzheimer disease.[3]

Although the screening mental status examination and neuropsychological battery may be useful, it is important to remember that these tests may not be sensitive to cognitive impairment. Individuals may score within the normal range, particularly those with high premorbid intellectual functioning. Despite normal scores, these patients may have MCI if the clinician determines that there has been a change from baseline functioning. In these circumstances, it is usually best to follow these patients clinically, with repeat evaluations at regular intervals.

Laboratory tests used in the evaluation of dementia may identify medical issues that could affect cognitive function.[120] Basic laboratory tests that look for reversible causes of cognitive impairment include a complete blood count, basic metabolic panel, thyroid function tests, vitamin B_{12} levels, and folate levels. Neuroimaging with MRI or computed tomography of the brain is also recommended to look for any structural abnormalities that may be contributing to symptoms.

Information from the history, screening mental status examination, neuropsychological testing, and ancillary studies should be used to determine if cognitive function is changing, normal, or impaired. Functional status can be obtained from the individual, the informant, or both. If the patient has experienced cognitive decline but has maintained most daily activities, then that individual can be given an MCI diagnosis. Once an individual has been diagnosed as having MCI, the clinician can determine the MCI subtype based on which cognitive domains are impaired. From this determination, the MCI subtype can be determined. If memory impairment is present, then the individual has an aMCI subtype. If memory is preserved but evidence of decline is seen in other cognitive domains, then the subtype is naMCI.

After indicating the subtype as aMCI or naMCI, the next step is to determine if 1 or more cognitive domains are affected. If memory is the only domain affected, then the subtype would be aMCI single domain; if at least 1 other cognitive domain is also

affected, then the subtype would be an aMCI multiple domain. If the impairment was isolated to one of the nonmemory domains, then the subtype would be naMCI single domain; if 2 or more nonmemory domains were affected, then the subtype would be naMCI multiple domains. Again, function must be essentially preserved to differentiate multiple domain MCI from dementia.

The goal of such subtyping in clinical practice is to accurately describe the individual's clinical syndrome and to determine the possible etiology of the patient's symptoms. Using the history, examination, and ancillary data, the clinician can begin to deduce whether the cause of impairment is degenerative, vascular, psychiatric, or secondary to concomitant medical disorders. Such deductions may assist in providing treatment options for each patient.

NATURAL PROGRESSION OF DISEASE AND OUTCOMES

Because MCI is considered to be a transitional state between normal aging and dementia, the etiologies for dementia theoretically could be applied to MCI. Although the construct has yet to be validated, aMCI owing to a degenerative etiology is thought to progress most likely to Alzheimer disease, an assertion that has been endorsed in a practice parameter from the American Academy of Neurology.[121]

Our earliest work in the Mayo Alzheimer's Disease Research Center taught us that even normal individuals change as they get older. Not only does reaction time slow, but on measures of Verbal IQ and measures of Performance IQ the things we do day in and day out are better preserved.[122–124] In all of our attempts at providing care to the elderly, these are the principles that shaped us early and continue to play out in the advice we give out every day. Overlearned behaviors, repetitive tasks, and rehearsed activities make it easy and comfortable for us to go about the routines of the day. The things we are confronted with that take an element of problem solving become all the more difficult as we age.

Although a diagnosis of MCI places an individual at higher risk for developing dementia, it does not indicate that the patient necessarily will progress to a dementia state. Although the majority of the patients with MCI in 1 large prospective trial progressed to Alzheimer disease at a rate of 7% to 10% per year, a small percentage of these individuals improved to normal.[5] Others have been known to remain clinically stable for many years and may not develop dementia.[125] These potential outcomes should be discussed with patients and their families after a diagnosis of MCI has been made.

Pathology

Studies of preclinical Alzheimer disease should be distinguished from studies of MCI.[126] In MCI studies, patients meet cognitive criteria for the diagnosis and are then followed prospectively to assess for conversion to Alzheimer disease. In contrast, preclinical Alzheimer disease refers to individuals with normal cognition who possess positive biomarkers for Alzheimer disease, such as a positive amyloid PET scan or evidence of Alzheimer disease biomarkers in the cerebrospinal fluid.[127]

The Religious Orders Study has followed a group of nuns and priests for many years and has an achieved high autopsy rates. The study reports that approximately 60% of the participants with MCI have neuropathologic evidence of Alzheimer disease, but that vascular disease also accounts for significant pathology.[15] Other studies have implicated the importance and the findings of neurofibrillary tangle density to account for the symptoms of MCI.[16,128] The best summary of outcomes after diagnosis of MCI was the results of a large autopsy series published in 2017. Of the 874 individuals ever diagnosed with MCI, final clinical diagnoses were varied: 39.2% died with an MCI

diagnosis, 46.8% with a dementia diagnosis, and 13.9% with intact cognition. The MCI diagnosis was usually associated with comorbid neuropathologies; fewer than one-quarter of MCI cases showed pure Alzheimer disease pathology.[128]

Two additional studies come from our own early investigations. We evaluated participants who died while their clinical classification was MCI and found that most had a low probability of having the neuropathologic features of Alzheimer disease at that point in time.[17] A second study observed participants who had been previously diagnosed with MCI and had progressed to dementia, and characterized these participants as having diagnostic pathology. This study indicated that, although most of the participants with aMCI developed Alzheimer disease, another sizable group (20%–30%) developed another type of dementing disorder.[18] These studies remain in contrast with opinions that the discoverable pathology of MCI, albeit more advanced MCI, is only Alzheimer disease.[19,20]

PET with fludeoxyglucose F 18 and cerebrospinal fluid biomarkers also play a role in predicting conversion to different dementias in patients with MCI. Even in prodromal MCI (before clinical relevance), the array of diagnostic tools will help us in determining whether to use cerebrospinal fluid biomarkers or the expanding array of biomarker images to help us predict what therapy might work best with what precondition (**Fig. 5**).[129]

Erlangen scores refers to an algorithm that divides cerebrospinal fluid biomarker patterns into 5 groups, covering all possible cerebrospinal fluid result combinations based on the presence of pathologic tau and/or amyloid-β cerebrospinal fluid values. The PET with fludeoxyglucose F 18 statistical parametrical classification uses statistical parametrical maps to normalize how scans are read and thus interpreted from one research center to another.

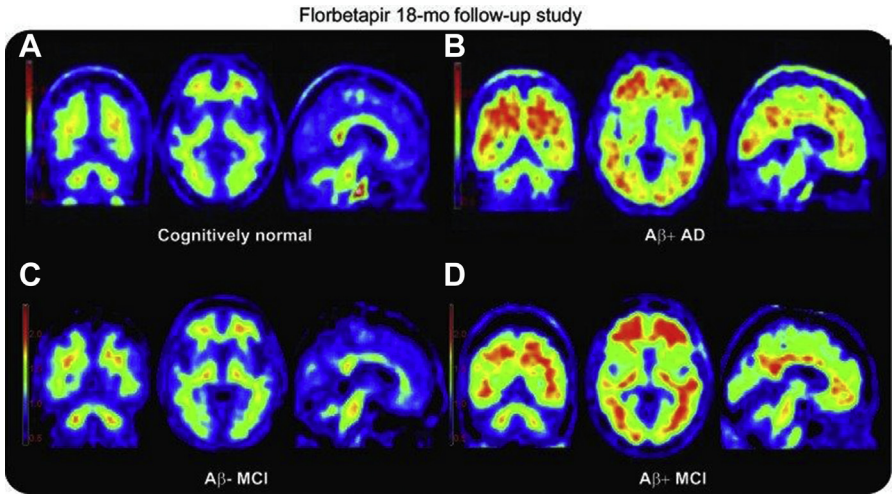

Fig. 5. Florbetapir PET scans in controls, patients with mild cognitive impairment (MCI), and patients with Alzheimer disease. Florbetapir PET images for an amyloid-negative Aβ− cognitively normal subject (*A*), an amyloid-positive (Aβ+) patient with Alzheimer disease (AD) (*B*), an amyloid-negative (Aβ−) patient with MCI (*C*), and an Aβ+ patient with MCI who converted to dementia during the course of this study (*D*). Aβ+ was determined per the majority of 3 raters. Color scale is shown in standardized uptake value ratio (SUVr) units. (*From* Caminiti SP, Ballarini T, Sala A, et al. FDG-PET and CSF biomarker accuracy in prediction of conversion to different dementias in a large multicentre MCI cohort. Neuroimage Clin 2018;18:173; with permission.)

Most likely, aMCI owing to a degenerative cause has similar features to clinically probable Alzheimer disease, with risk factors such as age, hypertension, and diabetes.[27–29] APOE4 carrier status is a recognized genetic risk factor for the development of Alzheimer disease,[30] but its value for detecting progression to cognitive impairment is less clear. It has been a consistent predictor but has not found a useful way into clinical practice.

Some studies have suggested that APOE4 carrier status may have assist in predicting those more likely to convert from MCI to Alzheimer disease[126,127,130] and a synergistic effect with depression has been seen in cognitively normal individuals at risk for developing MCI. APOE4 carrier status also may be associated both with hippocampal atrophy in patients with MCI and with higher rates of cognitive decline in cognitively normal adults.[131,132] However, others have shown that APOE4 carrier status itself has not been shown to predict cognitive decline or conversion to Alzheimer disease[133] and its routine use is not recommended[134]; the diagnosis of MCI is made clinically.

Suspected non-Alzheimer disease pathology MCI is a term that is increasingly used in research studies to denote individuals who meet the clinical criteria for MCI and show no evidence of amyloid pathology based on cerebrospinal fluid biomarker and/or amyloid PET imaging, but have evidence of neuronal injury as measured by either medial temporal lobe atrophy or hypometabolism on PET with fludeoxyglucose F 18.[130,131] In MCI with suspected non-Alzheimer disease pathology, low APOE e4 and high APOE e2 carrier prevalence may account for differences in neurodegeneration patterns when measuring beta amyloid peptide load using florbetpir F-18 PET scanning and hippocampal volume determined by MRI.[135]

TREATMENT

The early detection of cognitive decline theoretically may lead to the implementation of therapies that slow the progression of impairment. However, there currently is no treatment approved by the US Food and Drug Administration for MCI likely owing to Alzheimer disease. Because the etiologies of MCI can be heterogeneous, medications targeting a neurodegenerative cause theoretically would be different than those targeting cognitive impairment owing to vascular, psychiatric, or other medical disorders. Clinical trials nevertheless have focused on the aMCI subtype, with the goal of slowing the progression to Alzheimer disease.

The evidence is low that targeted cognitive interventions, taken as a group, may help to improve performance on some cognitive measures but with no evidence of functional benefit. The concept has further expanded to include a population of patients where the condition may be reversible owing to a combination of disease, medical stressors, and acute illness. An Italian study evaluated the proportion of MCI subjects who revert to normal cognition in a memory clinic context, focusing on the role of comorbidities. Between 2004 and 2013, 374 patients with MCI were recruited. During a mean time of 32 $\pm$ 25.5 months, 21 (5.6%) reverted to normal control. Subjects who reverted to normal cognition were younger ($P = .0001$), more educated ($P = .0001$), had a better global cognition ($P = .0001$), as assessed by the MMSE, and suffered from more comorbidities ($P = .002$), as assessed by Cumulative Illness Rating Scale than those who developed dementia.[136] There remain no known pharmacologic therapies for which evidence of lasting benefit has been demonstrated in well-designed studies for patients with static or progressive conditions. Moderate evidence shows that people diagnosed with MCI can benefit from regular physical exercise. Conceivably, if MCI were due to depression, it could also be treated with a drug.

A number of studies have targeted medications used in the symptomatic treatment of clinically probable Alzheimer disease. These medications have included 3 of the cholinesterase inhibitors, namely, donepezil, galantamine, and rivastigmine.[137–139] Additionally, vitamin E and rofecoxib have been studied,[137,140] because both oxidative damage and inflammation have been implicated in the pathophysiology of Alzheimer disease.[141–144] Unfortunately, none of these interventions have shown a significant decrease in conversion rates of aMCI to Alzheimer disease, ranging from 6% to 17% in the medication arms versus 4% to 21% with placebo. However, 1 study did find that donepezil reduced the progression risk for 12 months in those with aMCI, an effect that persisted for up to 24 months in APOE4 carriers.[137]

Despite the results of clinical trial data, these studies do support the construct of MCI as a transitional state between normal cognition and Alzheimer disease. The overall progression rates for MCI in these studies ranged from 5% to 16%, which are higher than the incidence rate for Alzheimer disease in the general population.[3,137] These rates suggest that patients who meet MCI criteria are at a higher risk of developing Alzheimer disease. Because not all of those with MCI develop Alzheimer disease pathology, more accurate identification of these subjects is essential. Incorporating potential predictive biomarkers in clinical trials may assist in testing compounds that target the underlying disease process of Alzheimer disease.[145]

A variety of nondrug interventions has also been tried on this population. Not surprisingly, cognitive training has been the most studied.[86] There may even be some benefit from exercise.[86] The environment of care has been addressed and lifestyle management has been included. Interventions range from individualized therapy to group programs that additionally address activity planning, self-assertiveness training, relaxation techniques, stress management, use of external memory aids, and motor exercise. Multicomponent interventions seem to benefit activities of daily living, mood, and memory performance. A standardized cognitive training manual has been proposed as well further studies using a larger sample size and more robust experimental designs.[146–148]

Although no symptomatic or disease-modifying drug therapies are available for MCI owing to Alzheimer disease, there is much that can be done. The domains of cognition, function, and behavior define this population and where they reside in the spectrum of disease. Their preserved abilities can also serve as markers for how the disease is progressing and how well they are living within a defined environment. Even without a drug treatment for MCI, understanding the environment that surrounds every one of these patients and how they function within their universe is most important. Overlearned behaviors and an environment that limits or prohibits excess disabilities should be stressed, even for patients with MCI. Much can be done and running toward a diagnosis is better than running away from it.

ADVANCE CARE PLANNING

Cognitive impairment, be it MCI or dementia, can still be defined by the capacities that are preserved and the capacities that are lost. This is where the issue of driving comes into play, although the concept applies to all kinds of tasks and opportunities. We counsel that a diagnosis is not an all or none phenomenon and many individuals with MCI or even early dementia sit on advisory boards to provide a patient voice in better understanding the needs of the patient. Unfortunately, explaining these concepts and what is both retained and what is lost takes time, especially for the primary care provider.

As our understanding of disease advances, the triad of cognition, function, and behavior not only defines the type of care that may be appropriate, but also contributes to our understanding of where the best site of care might be. Our ability to address the environment early in the care of patients with MCI or other age-dependent deficiencies may improve the quality of life for our patients, avoid common pitfalls and provide for more cost-effective and successful management of the person, and not just the disease they may have. A goal set by the Alzheimer's Association back in 1987 was to create an environment where a person can function with minimal failure and maximal use of retained abilities. There is even more opportunity today to create this success with earlier diagnosis and earlier intervention.

Patients and families should be aware that those who have aMCI owing to a degenerative cause may have a 10% to 15% chance of developing dementia; however, it also should be noted that MCI is heterogeneous with a number of potential outcomes.[125] Although some patients may not develop dementia, the label of "mild cognitive impairment" nevertheless may lead to psychological consequences, such as a feeling of uncertainty or concerns of becoming burdensome to others.[149] Neuropsychiatric symptoms such as depression, anxiety, apathy, and/or irritability also may be seen in those with MCI and may be associated with progression to Alzheimer disease.[104]

Encouraging patients and their families and caregivers to consider decisions about advance directives, future planning, and finances is essential, especially if the cognitive impairment is thought to be due to a degenerative cause. Although preventative strategies remain elusive, patients should be encouraged to follow a heart healthy diet, control for diabetes mellitus and hypertension, remain physically active, and engage intellectually and socially without frustration. Participation in a cognitive rehabilitation program also may be useful in patients with MCI, with improvements in activities of daily living, mood, and memory. Although these modifications may improve their overall quality of life, there has not been enough research to support that a decreased progression from aMCI to Alzheimer disease.

SUMMARY

The MCI construct implies an intermediate state between normal cognition and dementia. Individuals with MCI have (a) a subjective cognitive complaint that is usually corroborated by an informant, (b) preserved general cognitive functioning, (c) impairment in 1 or more of the cognitive domains (memory, attention–executive function, visuospatial skills, and/or language), and (d) essentially normal activities of daily living. Once the diagnosis of MCI has been made, the specific subtype can be determined, with aMCI referring to the presence of memory impairment and naMCI referring to the presence of impairment in 1 or more of the other domains with relative preservation of memory.

MCI remains a clinical diagnosis, aided by a thorough history, neurologic examination, screening mental status examination, and formal neuropsychological testing. Although an individual with high premorbid intellectual functioning may score within the normal range on bedside and formal testing, that patient may still be considered to have MCI based on the judgment of the clinician. Because there is subjectivity in the clinical diagnosis, creating an operational definition for clinical trials has been a challenge. In addition, a number of etiologies can be associated with MCI, including degenerative and vascular processes, psychiatric causes, and comorbid medical conditions. Treatable medical conditions may also present as MCI and have reversible outcomes.

Our goal with the geriatric patient remains the preservation of function and the amelioration of symptoms. Accurate diagnosis of MCI allows us to advise patients

and families regarding placement, level of care needs, and quite possibly predict the future. Limiting transitions is in the best interest of all parties and allows for the maximal use of retained abilities while limiting the frustrations that accrue with cognitive and functional decline. We urge practitioners, providers, patients, and their family to be as precise as possible in evaluating cognitive and memory complaints given the wealth of information and diagnostic testing available regarding MCI. The accuracy of the diagnosis affects the outcome and experience of each individual and family that seek our opinion.

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