Mild Cognitive Impairment

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 70-year-old woman has been noticing increasing forgetfulness over the past 6 to 12 months. Although she has always had some difficulty recalling the names of acquaintances, she is now finding it difficult to keep track of appointments and recent telephone calls, but the process has been insidious. She lives independently in the community; she drives a car, pays her bills, and is normal in appearance. A mental status examination revealed slight difficulty on delayed recall of four words, but the results were otherwise normal. Does the patient have mild cognitive impairment? How should her case be managed?

THE CLINICAL PROBLEM

Mild cognitive impairment represents an intermediate state of cognitive function between the changes seen in aging and those fulfilling the criteria for dementia and often Alzheimer's disease.[1] Most people undergo a gradual cognitive decline, typically with regard to memory, over their life span; the decline is usually minor, and although it may be a nuisance, it does not compromise the ability to function. A minority of people, perhaps 1 in 100, go through life with virtually no cognitive decline and are regarded as aging successfully. However, another trajectory of aging is characterized by a decline in cognitive function beyond that associated with typical aging; the decline is often recognized by those experiencing it and occasionally by those around them. Known as "mild cognitive impairment," this entity has been receiving considerable attention in clinical practice and research settings.[2]

Mild cognitive impairment is classified into two subtypes: amnestic and nonamnestic.[3] Amnestic mild cognitive impairment is clinically significant memory impairment that does not meet the criteria for dementia. Typically, patients and their families are aware of the increasing forgetfulness. However, other cognitive capacities, such as executive function, use of language, and visuospatial skills, are relatively preserved, and functional activities are intact, except perhaps for some mild inefficiencies. Nonamnestic mild cognitive impairment is characterized by a subtle decline in functions not related to memory, affecting attention, use of language, or visuospatial skills (Fig. 1). The nonamnestic type of mild cognitive impairment is probably less common than the amnestic type and may be the forerunner of dementias that are not related to Alzheimer's disease, such as frontotemporal lobar degeneration or dementia with Lewy bodies.[4] In clinical trials involving patients with amnestic mild cognitive impairment, more than 90% of those with progression to dementia had clinical signs of Alzheimer's disease.[5]

The estimated prevalence of mild cognitive impairment in population-based studies ranges from 10 to 20% in persons older than 65 years of age.[6-10] In the Mayo Clinic Study of Aging, a prospective, population-based study of persons without dementia who were between 70 and 89 years of age at enrollment, the
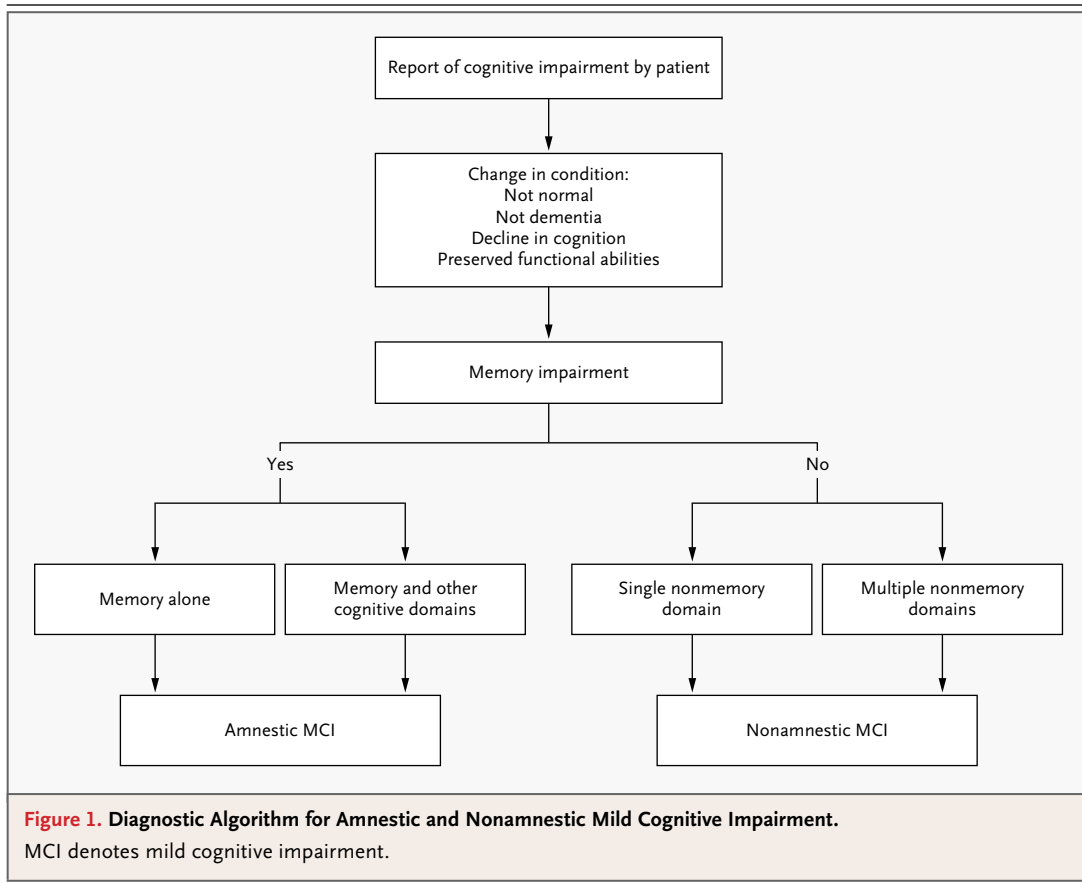
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Figure 1. Diagnostic Algorithm for Amnestic and Nonamnestic Mild Cognitive Impairment.

MCI denotes mild cognitive impairment.

prevalence of amnestic mild cognitive impairment was 11.1% and that of nonamnestic mild cognitive impairment was 4.9%.[11]

Several longitudinal studies have shown that most persons with mild cognitive impairment are at increased risk for the development of dementia.[6,8-10] As compared with the incidence of dementia in the general U.S. population, which is 1 to 2% per year, the incidence among patients with mild cognitive impairment is significantly higher, with an annual rate of 5 to 10% in community-based populations[12] and 10 to 15% among those in specialty clinics (the latter rates reflecting the fact that cognitive impairment is typically more advanced by the time a person seeks medical attention).[12,13] Although some data suggest that the rate of reversion to normal cognition may be as high as 25 to 30%, recent prospective studies have shown lower rates.[9] Moreover, reversion to normal cognition at the time of short-term follow-up does not preclude later progression. Longer periods of follow-up in community-based studies are needed to determine whether reported rates of progression are consistent over a prolonged period.

STRATEGIES AND EVIDENCE

EVALUATION

For the clinician, making the distinction between mild cognitive impairment and normal aging can be a challenge. Subtle forgetfulness, such as misplacing objects and having difficulty recalling words, can plague persons as they age and probably represents normal aging. The memory loss that occurs in persons with amnestic mild cognitive impairment is more prominent. Typically, they start to forget important information that they previously would have remembered easily, such as appointments, telephone conversations, or recent events that would normally interest them (e.g., for a sports fan, outcomes of sporting events). However, virtually all other aspects of function are preserved. The forgetfulness is generally apparent to those close to the person but not to the casual observer.

The patient's history typically raises the suspicion of a decline in cognition, usually memory, and neuropsychological testing may be necessary to corroborate the decline, especially for cases in

which the deficits are particularly subtle. Neuropsychological testing may be helpful to distinguish particularly mild cases from normal aging, but testing is not routinely needed to make the clinical diagnosis. A brief mental status examination in the physician's office, such as the Mini–Mental State Examination, is often insensitive to early impairment; more useful measures include the Short Test of Mental Status and the Montreal Cognitive Assessment[14,15] (both provided in the Supplementary Appendix, available with the full text of this article at NEJM.org). At times, the so-called worried well can provide a convincing history of memory loss, but neuropsychological testing reveals normal performance. A reversible form of mild cognitive impairment may result from other conditions, such as depression, or from the side effects of medication; these possibilities should be assessed in the process of obtaining the patient history.

Differentiating mild cognitive impairment from dementia is generally not difficult. Typically, in patients with dementia, cognitive deficits are affecting daily functioning to the extent that there is loss of independence in the community; this information may be provided by the patient or by a family member. A diagnosis of dementia can be supported with the use of instruments such as the Functional Activities Questionnaire, which can be administered in a primary care setting and characterizes impairment in function that is within the range of dementia[16] (this questionnaire is available in the Supplementary Appendix). However, a careful history taking is often sufficient to make this determination.

PREDICTION AND RISK FACTORS

A question commonly raised by patients with mild cognitive impairment and their family members concerns the likelihood and time course of progression to dementia. Although the general rate of progression among those with a diagnosis of mild cognitive impairment is estimated at 10% per year, certain factors predict a more rapid progression. The degree of cognitive impairment at presentation is a clinical predictor of progression, which is likely to be more rapid in patients with greater impairment at baseline,[17,18] probably because these patients are closer to the threshold for the diagnosis of dementia. Longitudinal data have shown that progression to dementia is more rapid among carriers of the apolipoprotein (APOE) ε4 allele than among noncarriers,[5] although
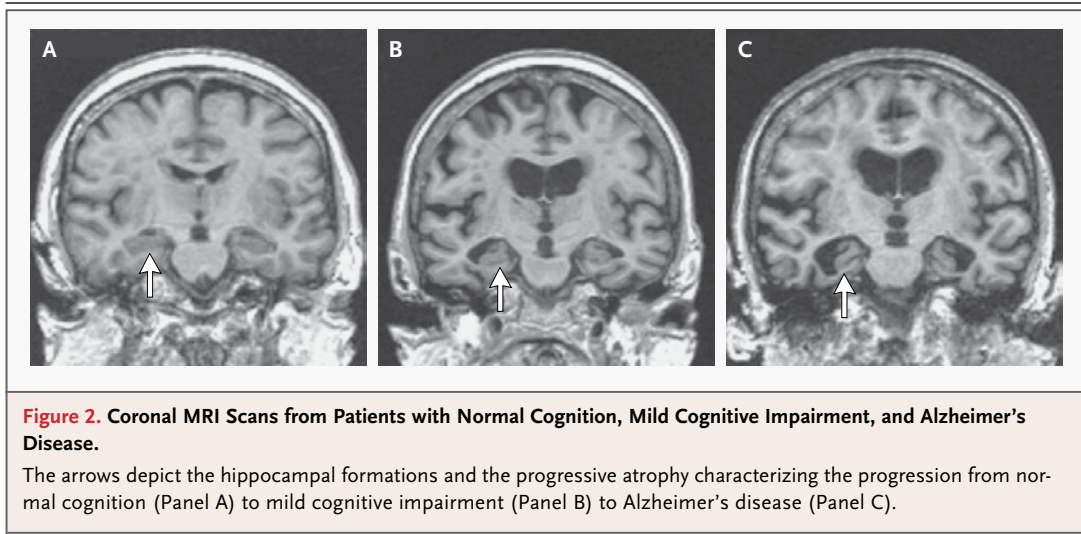
testing for the presence of the allele is not currently recommended in routine practice.

Various findings on imaging and tests for biomarkers may identify persons at risk for more rapid progression to dementia.[19] Although these measures are promising, they should not yet be used in routine clinical care, given the current lack of standardization among the techniques and the uncertainty regarding the optimal cutoff points for identifying high-risk groups.

The most extensively studied means of predicting progression of mild cognitive impairment to dementia is structural magnetic resonance imaging (MRI)[19,20] (Fig. 2). A recent community-based study showed that among persons with amnestic mild cognitive impairment, those with volumetric measurements of the hippocampus that fell at or below the 25th percentile for age and sex had a risk of progression to dementia over a 2-year period that was two to three times as high as the risk among persons whose hippocampal measurements were at or above the 75th percentile.[21] Other quantitative measures, such as larger ventricular volumes, have also been reported to predict progression.[22] However, at this time there are no accepted criteria for hippocampal atrophy or other proposed markers of progression on MRI. More data are needed to define these measures and to develop guidelines for their appropriate clinical use.[23]

Functional imaging techniques, such as ^{18}F-fluorodeoxyglucose positron-emission tomography ([18]FDG-PET), which provide an index of synaptic integrity, have also been evaluated as predictors of progression to dementia. Studies indicate that patients with a pattern of hypometabolism in the temporal and parietal regions of the brain on [18]FDG-PET, which is suggestive of Alzheimer's disease, may be at increased risk for rapid progression from mild cognitive impairment to Alzheimer's disease as compared with patients without this pattern.[24,25,26] The Alzheimer's Disease Neuroimaging Initiative (ADNI; ClinicalTrials.gov number, NCT01231971), a multicenter longitudinal study, showed that for subjects with mild cognitive impairment who had this pattern of hypometabolism on [18]FDG-PET, the risk of progression to Alzheimer's disease during the next 2 years was 11 times the risk among subjects who did not have this pattern.[24]

Analysis of markers in the cerebrospinal fluid has also been proposed as a means of assessing the risk of progression to Alzheimer's disease.[27]

Figure 2. Coronal MRI Scans from Patients with Normal Cognition, Mild Cognitive Impairment, and Alzheimer's Disease.

The arrows depict the hippocampal formations and the progressive atrophy characterizing the progression from normal cognition (Panel A) to mild cognitive impairment (Panel B) to Alzheimer's disease (Panel C).

A Swedish study showed that subjects with mild cognitive impairment who had low levels of β-amyloid peptide 42 (Aβ42) and elevated levels of tau protein in cerebrospinal fluid were significantly more likely to undergo progression to Alzheimer's disease than subjects without this profile (hazard ratio, 17.7; 95% confidence interval, 5.3 to 58.9); a similar relative risk of progression was associated with a low ratio of Aβ42 to tau in the cerebrospinal fluid.[28] An international multicenter study of 750 subjects with mild cognitive impairment corroborated these general findings[29,30] but used different cutoff points for abnormal findings. The reliability of these markers is highly variable across laboratories; standardization will be needed before they are considered for incorporation into routine care.

The use of molecular imaging, particularly of amyloid plaques in the brain (Fig. 3), has also been studied as a possible approach to risk stratification.[31-33] In several studies, subjects with mild cognitive impairment in whom amyloid was detected on positron-emission tomography (PET) with the use of the amyloid-binding carbon 11–labeled Pittsburgh compound B had more rapid progression to Alzheimer's disease than did subjects in whom amyloid was not detected.[34] The rationale for using this technique to predict disease progression is that the presence of amyloid in a patient with mild cognitive impairment is likely to indicate that the patient has early Alzheimer's disease; however, amyloid has been detected on autopsy in clinically normal persons, indicating that the predictive value of this measure requires further study.[35]

MANAGEMENT

From a clinical perspective, patients with mild cognitive impairment should not be labeled as having early Alzheimer's disease, prodromal Alzheimer's disease, or mild cognitive impairment of the Alzheimer's disease type, since the patient and family are likely to hear only "Alzheimer's disease" and not appreciate the uncertainty of the association with Alzheimer's disease.[36] Clinicians should make it clear that mild cognitive impairment is an abnormal condition but that the precise outcome is not certain.

At present, no medication intended for the treatment of mild cognitive impairment has been approved by the Food and Drug Administration (FDA). In several placebo-controlled clinical trials, there was no significant reduction in rates of progression to dementia among patients with mild cognitive impairment who were treated with agents used to treat Alzheimer's disease (donepezil, galantamine, and rivastigmine, administered at standard doses for Alzheimer's disease for 2 to 4 years).[5,37-40] In one trial evaluating the effects of high-dose vitamin E (2000 IU daily) or donepezil in persons with mild cognitive impairment, donepezil significantly reduced the risk of progression to Alzheimer's disease for the first 12 months of the study (and for up to 24 months in the subgroup of subjects who were carriers of APOE ε4) but had no significant effect on the risk of Alzheimer's disease at 36 months, which was the primary study outcome; vitamin E did not significantly reduce the risk of progression at any time point assessed.[5]
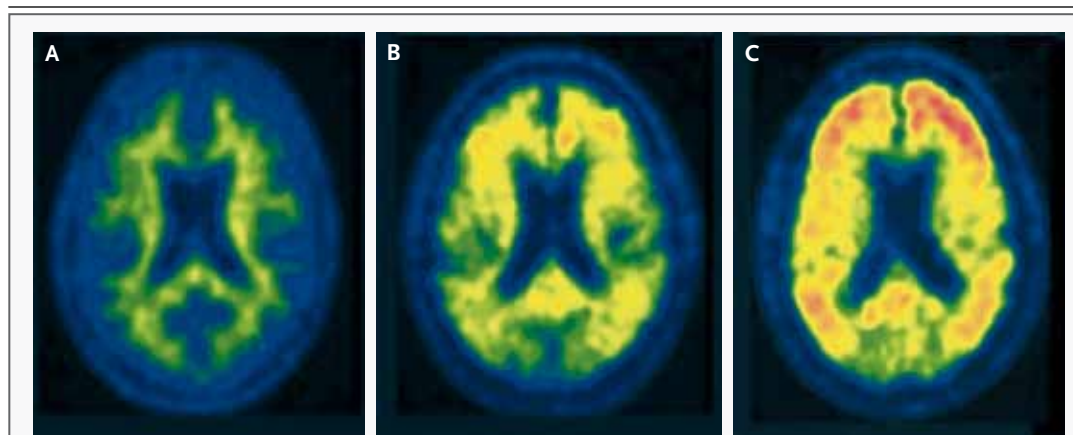
Figure 3. Axial Scans of the Brain Obtained with Positron-Emission Tomography and the Use of Amyloid-Binding Carbon 11–Labeled Pittsburgh Compound B.

The yellow and red areas indicate retention of the amyloid-binding tracer, reflecting amyloid deposits. The patient with normal cognition (Panel A) has no tracer retention, whereas the patient with amnestic mild cognitive impairment has an intermediate amount of tracer retention (Panel B) and the patient with Alzheimer's disease has prominent tracer retention (Panel C).

One potential explanation for the apparent lack of efficacy in the clinical trials of interventions in persons with mild cognitive impairment — other than a true absence of drug efficacy — concerns the heterogeneity of the subjects. As the diagnostic threshold moves to an earlier point in the clinical spectrum of cognitive impairment, the subtle changes in cognition could be due to a variety of causes other than a degenerative brain disease, making it difficult to determine whether an intervention has had a significant effect.

There is some evidence of a potential benefit from cognitive rehabilitation, including the use of mnemonics, association strategies, and computer-assisted training programs.[41,42] A recent systematic review of the literature on cognitive rehabilitation programs for persons with mild cognitive impairment, including some data from randomized clinical trials, showed significant improvement in cognitive function at the end of training.[42]

Observational data have shown associations between the presence of cardiovascular risk factors in patients with mild cognitive impairment and an increased risk of progression to dementia.[7] Such risk factors should be addressed, although there is no definitive evidence that modification of risk factors slows disease progression. In a randomized trial that used the Cognitive Subscale of the Alzheimer's Disease Assessment Scale to compare the effect of a physical exercise program (brisk walking for 150 minutes per week) with that of usual care and education in persons with subjective memory loss, the exercise group had better cognitive function at 6 months (the primary study outcome), with some residual benefit noted at 18 months.[43]

AREAS OF UNCERTAINTY

More data are needed regarding the usefulness of various potential predictors of progression to dementia and their role in clinical practice. Further data on these concerns are awaited from the Alzheimer's Disease Neuroimaging Initiative, under way in the United States and Canada,[27,44] and from similar ongoing studies in Japan, Europe, and Australia. Some of the goals of these studies are to better understand the role of MRI findings (e.g., hippocampal atrophy),[22,45] findings on [18]FDG-PET (patterns of hypometabolism in the brain), cerebrospinal fluid markers (levels of Aβ42 and tau), and findings on molecular imaging (amyloid plaques in the brain) in identifying the subgroup of persons with amnestic mild cognitive impairment who are likely to undergo progression to clinical Alzheimer's disease.[27,46,47] Major challenges are to determine optimal cutoff points for these tests and to compare their relative reliability (alone and in combination). Randomized trials are needed to assess the potential benefits of pharmacologic and lifestyle interventions in persons with mild cognitive impairment who are predicted to be at high risk for rapid progression to Alzheimer's

disease according to the results of imaging and of tests for biomarkers. The costs of such predictive testing (not only in financial terms but also in terms of potential adverse psychological effects or compromised ability to obtain long-term care insurance) must be balanced against the potential benefits, especially given the absence of therapies with proven effectiveness for mild cognitive impairment.

GUIDELINES FROM PROFESSIONAL SOCIETIES

In an evidence-based review published in 2001, the American Academy of Neurology recommended that clinicians monitor and follow patients with mild cognitive impairment, since they are at increased risk for dementia, particularly Alzheimer's disease.[48] These guidelines are currently being updated in view of the considerable literature published since that time. Mild cognitive impairment is not included in the current edition of the *Diagnostic and Statistical Manual of Mental Disorders,* but the manual is being revised, and an entry for a condition similar to mild cognitive impairment, which precedes dementia, will be included.[49]

The National Institute on Aging and the Alzheimer's Association recently published new diagnostic guidelines for assessing the likelihood that mild cognitive impairment is caused by the under-

lying pathophysiology of Alzheimer's disease. The degrees of certainty are established according to the results of imaging and other tests for biomarkers[50] (Table 1). As stated above, research is needed to determine the criteria for abnormal results. Consequently, these new guidelines are largely intended to inform research rather than clinical assessment, but the expectation is that they may ultimately guide clinical care.

SUMMARY AND RECOMMENDATIONS

The description of the 70-year-old woman in the vignette, who is forgetful but otherwise appears to be functioning normally, suggests there is reason to suspect amnestic mild cognitive impairment. A neurologic examination, including an assessment of mental status, is indicated to objectively document her cognitive function. Depression should be ruled out. Referral for neuropsychological testing may be appropriate, particularly if the concern is the degree of impairment relative to the cognitive changes of aging. Documentation of memory impairment that is not in proportion to that expected, given her age and education, with minimal involvement of other cognitive domains, such as attention, executive function, language skills, and visuospatial skills, and preservation of functional independence would confirm the diagnosis of amnestic mild cognitive impairment. An MRI scan is suggested to rule out other conditions that might explain her memory loss (e.g., vascular disease, tumor, or hydrocephalus); the results might also show changes (e.g., hippocampal atrophy) suggesting that she is at increased risk for rapid progression to Alzheimer's disease, although more data would be needed to justify the use of MRI for this purpose.

I would recommend a clinical reevaluation in 6 months to determine whether the forgetfulness is worsening. At this time, I would not routinely recommend tests to predict the risk of progression (e.g., [18]FDG-PET or measurement of biomarkers in cerebrospinal fluid) but would encourage the patient to consider participation in research evaluating these tools. I would explain that at present there are no FDA-approved medications for this condition; I would also review the negative results of medication trials thus far and explain the costs and potential side effects of pharmacotherapy. I would recommend engagement in aerobic exercise, involvement in intellectually stimulating activities

Table 1. Suggested Criteria for the Likelihood That Mild Cognitive Impairment Is Due to Alzheimer's Disease.*

Likelihood of Alzheimer's Disease	Evidence of Aβ42	Evidence of Neuronal Injury
Unknown	Not tested	Not tested
Low	Negative	Negative
Intermediate	Positive	Not tested
	Not tested	Positive
High	Positive	Positive

* The presence of Aβ42 (β-amyloid peptide 42) can be detected with positron-emission tomography of the brain and analysis of cerebrospinal fluid. The presence of neuronal injury can be detected with MRI (e.g., hippocampal atrophy), with ^{18}F-fluorodeoxyglucose–PET in patterns of hypometabolism (e.g., in the parietotemporal or precuneus regions) or with analysis of cerebrospinal fluid. Low levels of Aβ42 and elevated levels of tau in the cerebrospinal fluid are associated with progression to Alzheimer's disease, as is a low ratio of Aβ42 to tau in the cerebrospinal fluid. At present there is no consensus on the cutoff points that should be used to determine the values of low, intermediate, and high; the criteria are now being used only for research purposes. Adapted from Albert et al.[50]

and participation in social activities, given that these might be beneficial and pose little risk, although more data are needed to inform their efficacy in reducing the risk of progression to the dementia stage of Alzheimer's disease.

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