Mild Cognitive Impairment

by Howard Chertkow, MD, FRCPC

CASE STUDY:
Mr. C is a 63-year-old executive who presents to you complaining of memory loss. The problem began insidiously over the past year and he believes it has been getting worse. He previously had difficulty remembering the names of occasionally-seen employees, but now even the details of important current accounts and recent meetings escape him. He has started keeping copious notes and lists, and double-checking details with his secretary and wife (who confirms the memory decline). There has been no impact on his functional abilities at work and, according to him and his wife, he remains otherwise cognitively intact.

Mr. C denies experiencing depression. He admits to a high level of stress at work, poor sleep, occasional use of sedatives, but no alcohol consumption. He is in good health, with controlled hypertension. There is no history of transient ischemic attack (TIA) or cerebral infarction.

Physical examination is normal and his Folstein Mini-Mental State Examination (MMSE) score is 28 (he only recalled one of three words after a delay). His basic bloodwork results—including B12, folate, thyroid-stimulating hormone (TSH) and electrolytes—are normal, as is a computed tomography (CT) scan. He asks you for prognosis and treatment, and wonders whether he should retire.

The study of cognitive changes with aging has grown exponentially over the past few years. At one end of the spectrum is Alzheimer’s disease (AD), for which the best estimates of lifetime risk range from 14.5% to 26.2% of the population.1 The Canadian Study of Health and Aging (CSHA) has estimated the prevalence of dementia to be 8% in the population over the age of 65 years.2 At the other end of the spectrum are changes in cognitive performance that now are classified as normal. Over a two-year period, retesting elderly patients using memory tests revealed that approximately one third of them had subtle but measurable memory decline over time.3 On the WAIS-R IQ scale, an 85-year-old can achieve a score of 100 by correctly answering only half as many questions as a 21-year-old. Hence, before claiming that an elderly person shows “cognitive impairment,” it is best to compare that person to a group of individuals similar in age.

Definitions
Mild memory problems, falling between the two poles of “normal” and “dementia,” are a common phenomenon in older people. The CSHA documented a 16.8% prevalence of cognitive impairment without dementia in the elderly.4,5 Currently, the most widely used term to characterize this group is “mild cognitive impairment” (MCI), derived from the World Health Organization (WHO) and adapted by a number of centres.6-8 MCI is a clinical label which includes elderly subjects with short-term or long-term memory impairment and with no significant daily functional disability. The original diagnosis of MCI required a subjective report of cognitive decline from a former level, gradual in onset, and present for at least six months. This subjective complaint required supplementation with objective evidence of memory and learning decline, with other cognitive domains remaining “generally intact.”9 There was no clear delineation as to how the presence of memory loss was to be established. In all cases, the term MCI excluded individuals with significant depression, delirium, mental retardation, or other psychiatric disorders likely responsible for the impairment. If the memory loss was severe and accompanied by signifi-
The intent behind the concept of MCI was to capture and classify patients who seem to have a cognitive problem that one would hesitate to label as “normal,” but that is not severe enough to qualify as dementia.

MCI currently is the focus of natural history studies and biomarker studies, and is an important target group for future AD prevention studies. Since the majority of MCI individuals (who, after all, are complaining of memory troubles) are showing progressive memory decline due to the presence of AD pathology in its earliest stages, this may be the optimum stage at which to intervene with preventive therapies.

MCI will be used increasingly as a label by neurologists, geriatricians, and family physicians who treat elderly cognitively impaired individuals. It remains, however, a “fuzzy”, elusive and controversial concept, for reasons that will be discussed below.

Diagnostic Disagreements
Current interest is predicated largely on the fact that patients classified under MCI have a high rate of conversion to dementia, particularly AD. In most clinic-based studies of MCI, about 44% of individuals meeting the criteria for diagnosis of MCI progress to AD over three to five years, equating to a conversion rate of about 15% per year.\(^\text{10}\)

The controversial issue is whether all MCI individuals progress to AD with time. In an analysis by this author of 90 MCI subjects, it appears that about 25% will not progress to AD, even 10 years after onset of memory problems.\(^\text{11}\)

In population-based studies, the prognosis of mild cognitive deficits seems much less ominous. Ritchie et al\(^\text{12}\) found that only 22% of a group went on to a degenerative dementia, over an eight-year follow-up. In contrast, Morris et al\(^\text{13}\) have argued that, with sufficient time, most or all subjects in this category deteriorate to dementia, specifically AD.

Disagreement may centre on the different diagnostic criteria being used to assemble cohorts of subjects for study. There are at least seven different operational definitions of groups presented or discussed as having MCI. The CSHA study mentioned earlier utilized the general term “cognitive impairment, no dementia,” or CIND,\(^\text{2,5}\) which included numerous subjects that did not meet the MCI criteria (e.g., some had alcoholism, suffered strokes, or were mentally handicapped).

It is estimated that 50% to 66% of CIND subjects meet criteria for MCI. On Reisberg’s Global Deterioration Scale, most MCI individuals score as Stage 3—“Earliest subtle deficits”—but it is not clear whether the two concepts (CIND and MCI) are interchangeable.\(^\text{14}\)

Some studies have utilized the Clinical Dementia Rating (CDR) scale,\(^\text{15}\) a semi-structured interview with patient and caregiver, which assigns a rating of 0.5 (defined as “questionable dementia”) to subjects who are roughly equivalent to those with MCI. It has been pointed out, however, that a patient can be CDR 0.5 and also meet diagnostic criteria for AD and dementia, thus making this grouping significantly different from MCI. It is notable that Morris et al (who have the most pessimistic view of MCI prognosis) have based their conclusions on groups assembled using a CDR 0.5 rating as the inclusion criteria.

Another issue of disagreement surrounds the criteria for determining objective memory loss—the

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<th>Table 1: General Criteria for Mild Cognitive Impairment</th>
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<tr>
<td>• Subjective complaint of memory loss</td>
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<td>• Objective impairment of memory</td>
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<td>• Other cognitive abilities generally preserved</td>
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<tr>
<td>• Preserved basic, day-to-day functioning</td>
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<tr>
<td>• No other obvious medical, neurologic or psychiatric explanation for the memory problems</td>
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<tr>
<td>• Criteria for dementia not met</td>
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<td>Adapted from references 8 and 45.</td>
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key feature of MCI. In the clinic, one might accept impaired three-word recall as sufficient evidence of memory impairment in a complaining individual, as in the case presented above. A number of MCI studies have insisted, however, that there must be abnormal performance at least one standard deviation (SD)—or even 1.5 SD—below the norm for age-appropriate populations on standardized verbal memory tests. This attempt to establish neuropsychological criteria for MCI, while well-motivated, is fraught with difficulty and would restrict the diagnosis to centres having easy access to neuropsychological evaluation. Petersen has suggested that non-memory domains be “generally intact” in MCI, and in terms of bedside mental status testing, this is a reasonable criterion to apply.

It is possible, however, to impose more stringent criteria for MCI than the “fuzzy” clinical evaluations above. Ritchie and Touchon suggested that for patients to be considered as having MCI, all other domains besides verbal delayed memory should be within 1.5 SD of the age-adjusted norm. Unfortunately, when such constraints are firmly applied, few MCI subjects continue to qualify as such. In fact, detailed cognitive and neuropsychological testing shows that a range of subtle “low-normal” test results is the most common finding in groups of MCI individuals. These laboratory-test abnormalities, however, are not so evident with the much cruder bedside testing carried out by medical clinicians. Since one major goal of using the terms “MCI” and “dementia” is to allow general physicians to better assess, diagnose and treat patients, the diagnostic criteria are more meaningful when viewed with respect to clinical mental status assessment and “fuzzy” bedside testing, rather than when viewed as being dependent on more accurate (and often unavailable) neuropsychological criteria.

There are other problems with over-reliance on neuropsychological criteria for diagnosing MCI. For example, many elderly individuals are rated as “cognitively intact” but are substantially impaired on tasks that tap into a range of cognitive systems. Statistically speaking, there are “normal” patients who, for their entire lives, fall at the bottom of any Gaussian curve of neuropsychological results. These individuals must not be falsely labelled as having MCI.

Cultural, educational, and attentional factors (i.e., impaired attention due to stress, anxiety or depression) also can impact on neuropsychological testing. Thus, clinical judgement from a physician or psychologist is essential in assessing whether an MCI label is warranted. Neuropsychological tests can be used, however, to support such clinical decision-making.

For the above reasons, it is typical to encounter subtle but significant heterogeneity in MCI patients. Perhaps MCI would be best viewed as a general syndrome, akin to the status of the term “dementia.” Petersen describes most MCI patients as showing only memory impairment. These “amnesic” MCI patients are more likely to go on to develop AD. Rarely, MCI subjects show a non-memory domain affected, while memory remains normal. Presumably, these subjects are more likely to go on to another diagnostic entity, such as Primary Progressive Aphasia.

This author, and others, have found that most MCI patients show subtle deficits in other neuropsychological and reaction-time tests. Clinicians should not be surprised when an MCI individual performs slightly abnormally on, for example, placement of hands on clock drawing. Similarly, many MCI subjects (as in the case study above) demonstrate subtle functional changes; having to maintain written lists of things might be considered a functional alteration. Such changes should affect only “higher functions,” and should not represent “significant impairment,” although this is crudely defined.

Another important question is whether patients with mild depression should be excluded from consideration. Studies have found depression in up to 60% of MCI patients that go on to develop AD, and the presence of depression may, in fact, be a useful prognostic sign in MCI individuals.

As can be seen, there are many diagnostic issues that arise in characterizing MCI.
When is MCI Just an Earlier Stage of AD?

Numerous attempts have been made to delineate prognostic markers in MCI, most involving rather small samples of subjects followed for limited periods of time. Some of these markers are discussed below.

**CDR scale.** Daly et al. studied 123 subjects, recruited through the Boston media, who all met the criteria of rating 0.5 on the CDR scale. After a three-year follow-up, only 19% progressed to dementia (AD), 2% progressed due to strokes, and 5% became “normal.” It was found that most of the group suffered milder cognitive deficits compared to those in other studies, and that this explained the lower rate of progression/conversion to AD.

**ApoE status.** There have been suggestions that an individual’s apolipoprotein (apoE) status might be useful in determining risk for progression to AD. Petersen et al. found a major effect of apoE-4 load on progression to AD. However, in this author’s study group of 90 MCI subjects, followed over three to five years, apoE-4 failed to emerge as a useful predictor.

**Homocysteine.** One recent study targets high homocysteine levels as another biological risk factor for progression to AD, but this remains to be confirmed.

**Imaging markers.** Imaging markers may be useful in the prognosis of MCI, but they have been utilized mainly in academic research settings. Using magnetic resonance image (MRI) scans, the formal measurement of hippocampal volumes and the rate of change in global or hippocampal volumes are more powerful predictors of progression to AD. While visual inspection of standard single photon emission computed tomography (SPECT) brain images is not useful in prognostics, the sophisticated quantification of SPECT images may allow fairly accurate prognosis. Promising reports have emerged using positron emission tomography (PET) scanning and magnetic resonance spectroscopy in predicting onset of AD in patients with MCI.

Imaging remains a very active field of diagnostic investigation which should provide helpful indicators in the coming years.

**Neuropsychological and cognitive measures** have also been assessed for their predictive capacity. This author and colleagues found that MCI subjects with any disorientation to time, or even subtle problems with clock drawing, are more likely to progress to AD. In fact, the presence of any quantifiable abnormalities, beyond memory, constitute a risk for progression from MCI to dementia.

Batteries of different formal neuropsychological tests have been used together with the objective of stratifying risk of progression to AD. Tests of delayed verbal recall and executive function appear to have the best discriminating power for prediction. While promising, these tests are not sufficiently robust to prognosticate in all MCI cases.

**Other biomarkers.** Currently, a long series of other biomarkers are under investigation. These include smell testing, blood heme oxygenase 1, and cerebrospinal fluid (CSF) levels of tau and beta-amyloid protein ending at amino acid 42 (Abeta42), to note only a few.

Ideally, simple office tests are needed that can accurately stratify most MCI individuals, thereby preserving the more sophisticated testing for uncertain cases. This author and colleagues have devel-
oped a combination of low-tech and high-tech markers with moderate predictive power for MCI patients, based on retrospective analysis of our 90 MCI subjects. This approach is being validated in a new set of MCI subjects to determine whether it is sufficiently robust for use in prognosticating MCI cases.

**Current Treatments for MCI**

The three available cholinesterase inhibitors in Canada are approved for treatment of mild to moderate AD—not MCI; in provinces that reimburse such therapy, a diagnosis of MCI will lead to rejection of the application.

Symptomatic treatment of the memory complaints in MCI is, in fact, generally disappointing. This author’s anecdotal experience with MCI patients, using cholinesterase inhibitors, Ginkgo biloba, or stimulants such as methylphenidate (Ritalin®), is that none of these agents make a real impact on patients’ mild memory loss. Since there are no proven preventive therapies for AD at the present time, it follows that such therapies cannot honestly be prescribed for MCI patients. Having said this, it should be noted that cholinesterase inhibitors, various anti-inflammatories, estrogen, statins, drugs to block amyloid production, various antioxidants, and vitamin E could all, theoretically, delay or prevent progression to AD. Studies testing all of these agents are underway. These studies generally are several years in duration, and results will begin to reach the literature in the next 36 months (Table 2).

**The Options**

Given the lack of proven pharmacologic therapies to prevent cognitive decline, what therapeutic interventions should clinicians take when confronted with a patient such as the one in the case study above?

Stress, lack of sleep, and use of sedatives certainly need to be considered as contributing factors to the memory problems of the patient in the case study. Counselling regarding these issues should be given. Given our recent knowledge of vascular factors interacting with AD-symptom onset,39-41 it makes sense to aggressively treat vascular risk factors in MCI individuals. There is increasing evidence that physical, leisure, and mentally stimulating activities all have effects in decreasing cognitive decline and reducing AD risk.42,43 These activities should be recommended to patients with MCI.

Given the lack of clear prognostic markers, an uncertain natural history and, as discussed above, the lack of proven therapies to prevent cognitive decline, there is little consensus on the management of MCI patients.7 Such patients should be told that they meet criteria for MCI, which has a real statistical risk (but by no means any certainty) of progressing to dementia. This is vastly preferable to giving no diagnosis or to giving false assurances that “it’s just normal aging.” Physicians also should acknowledge their current lack of certainty regarding prognosis, as well as the lack of useful tests or proven biomarkers that should be administered or considered.

One important intervention for MCI patients is close follow-up. Baseline mental status (preferably with formal tools, such as the MMSE) should be carried out. Reversible causes of memory loss should be sought using laboratory tests or even brain imaging; these also could be applied to AD assessment. The patient should be seen at six-month intervals, over a long term. In previous work, this

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<thead>
<tr>
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<tr>
<td>• Cholinesterase inhibitors</td>
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<tr>
<td>• Anti-inflammatories</td>
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<tr>
<td>• Estrogen</td>
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<tr>
<td>• Statins</td>
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<tr>
<td>• Cholesterol-lowering drugs</td>
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<tr>
<td>• Anti-amyloid drugs (beta-secretase inhibitors, gamma-secretase inhibitors, glycosaminoglycan [GAG] mimetics, amyloid immunotherapy)</td>
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<tr>
<td>• Various antioxidants, including vitamin E</td>
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<tr>
<td>• Ampakines</td>
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<td>• Nootropics and psychic stimulants (e.g., piracetam)</td>
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Tests of delayed verbal recall and executive function appear to have the best discriminating power for prediction. While promising, these tests are not sufficiently robust to prognosticate in all MCI cases.
author and colleagues found that, for reversible dementias, the chances of reversal were higher if the causes were detected early.\textsuperscript{44} It probably is not appropriate to advise patients with MCI to stop work immediately, or to insist that they stop driving. The studies of Daly and Ritchie both noted that a subset of MCI individuals improved to normal over follow-up, and that MCI alone usually will not affect functioning at most workplaces.\textsuperscript{17,22}

Physicians also should acknowledge to patients that there currently is no sufficiently substantiated, government-approved treatment for MCI. Treating MCI individuals (or the healthy elderly) to prevent subsequent AD, using cholinesterase inhibitors, anti-inflammatory drugs, estrogen, statins, various antioxidants or even vitamin E, represent prescription beyond proven therapies.

In this author's opinion, it is advisable to refer eager MCI patients to a research clinic where randomized, controlled, clinical trials of the above agents and other preventive medications are underway. Only when the results of MCI drug studies begin to reach the literature will we be in a position to make informed scientific recommendations for such therapies (alone or in combinations) for the benefit of our patients.

References:
1. Drachman, D. If we live long enough, will we all be demented? Neurology 1994; 44:1563-5.