SPECIAL ARTICLE

Mild cognitive impairment: searching for the prodrome of Alzheimer's disease

PAUL B. ROSENBERG, CONSTANTINE G. LYKETSOS

Division of Geriatric Psychiatry and Neuropsychiatry, Johns Hopkins University School of Medicine,
5300 Alpha Commons Drive, Baltimore, MD 21205, USA

The concept of mild cognitive impairment (MCI) identifies persons who are neither cognitively normal nor demented. There is increasing evidence that MCI defines a group of persons who are at near-term risk of developing dementia and particularly Alzheimer's disease (AD). MCI thus constitutes an attractive target population for preventive treatments of AD. MCI is associated with aging and is more prevalent than dementia. There are several clinical and biological markers that are predictive of MCI prognosis, including depressive symptoms, cognitive deficits, brain imaging and neurochemical findings. The clinician needs to be especially alert to depressive and other mood symptoms which are common in MCI and potentially treatable. Trials of current medications for prevention of MCI progression to dementia have been largely negative. There are observational data suggesting that lifestyle modifications including exercise, leisure activities, cognitive stimulation, and social activities may be effective for prevention of MCI progression. There are many novel therapies currently in trials for early AD, and if effective they may prove to be helpful in prevention of MCI progression as well.

Key words: Mild cognitive impairment, Alzheimer's disease, aging, depressive symptoms, exercise, prevention

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Alzheimer's disease (AD) is the most common neurodegenerative disease. It is projected to affect 81 million persons worldwide by 2040 (1). It represents a major cause of disability for patients and caregivers, and is associated with huge financial burden to all societies. Clinically, the disease has an insidious onset and slow progression of characteristic cognitive and functional deficits (2,3) and near-universal incidence of neuropsychiatric symptoms (4). Neuropathologically, AD is associated with the deposition of insoluble amyloid-beta in extracellular plaques and phosphorylated tau in intraneuronal neurofibrillary tangles, microglial activation, and neuronal loss (5).

The disease probably affects the brain many years, possibly many decades (6), before its full clinical expression. By the time Alzheimer's *dementia* becomes clinically apparent, considerable brain damage has occurred, which is likely irreversible. Effective management of AD in the long term will rest on the ability to detect and manage its earliest manifestations in the brain and also clinically. This paper is focused on the latter, namely the earliest clinical manifestations of AD.

Clinicians have long noted that persons who develop AD have cognitive symptoms prior to the onset of dementia. As far back as the 1960s, investigators recognized a group of older persons who were neither cognitively normal nor demented but fit somewhere in between (7). While many of these persons developed dementia, a substantial number did not. This has given rise to the concepts of "cognitive impairment no dementia" (CIND) (8) and "mild cognitive impairment" (MCI) (3,9).

It must be emphasized that MCI represents a *risk group* and not a widely accepted clinical diagnosis. Even with the use of biomarker profiles and sophisticated clinical evaluations to refine the definition, a substantial number of persons with MCI will *not* develop dementia.

In this paper we seek to present the current state of knowledge of the MCI concept, as it applies to clinical evaluation and treatment, with particular emphasis on risk and prognostic factors, lifestyle interventions, and the future of treatment in this area.

MCI AND ITS SUBTYPES

Persons with MCI are by definition neither cognitively normal nor demented. The first part of the definition means that they have subjective cognitive complaints and/or objective evidence of abnormal cognitive testing. In addition to the above evidence of a *decline in cognitive functioning*, the "Petersen criteria" require that to meet criteria for MCI a person must also perform ≥1.5 standard deviations below age-education norms on at least one cognitive test (3). These criteria for MCI are most widely accepted, due to their relatively high specificity.

The second part of the MCI definition – that the person not be demented – means that the person has no functional deficits related to cognitive impairment, often defined as no impairment in instrumental activities of daily living (IADLs). In practice this criterion is harder to operationalize, largely because the cognitive demands of functional activities vary greatly by stage of life cycle and by life situation. For example, older persons still in the workforce often have greater day-to-day cognitive demands than persons who are retired, and thus are more likely to be diagnosed with dementia given the same degree of cognitive impairment. The presence of a living spouse often masks minor functional deficits; living in a retirement community likely decreases the cognitive demands of home maintenance, shopping, cooking etc.; while the need to adhere to a complex medical regimen likely heightens cognitive demands in daily life. Perneczky et al (10) found that persons with rigorously defined MCI in fact

had mild IADL impairments, particularly in tasks requiring memory or executive function. Thus, while persons with MCI have subtle deficits in IADLs consistent with their cognitive performance, they generally function independently. Only when their functioning declines in several areas, they are said to "cross the border" into dementia (Figure 1).

MCI has been further subtyped on the basis of cognitive deficits into amnestic vs. non-amnestic and single-domain vs. multiple-domain.

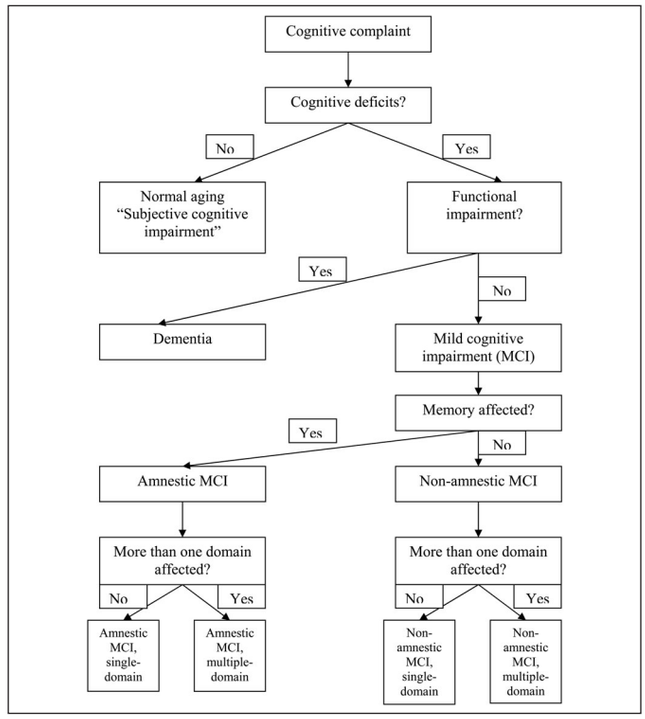

Figure 1 Mild cognitive impairment (MCI) and related syndromes (adapted from Rosenberg et al, 65)

EPIDEMIOLOGY AND PROGNOSIS

The prevalence of MCI in late life varies according to the sample and the definition. Amnestic MCI has a prevalence of 3-6% in population-based samples of older persons, while all MCI subtypes have a prevalence of as high as 16% (11,12). The prevalence of MCI increases with age, ranging in the Cardiovascular Health Study from 15% under age 75 years to 30% over age 85 years (12).

MCI was previously thought to entail an inevitable and relatively rapid progression to dementia. This grim prognosis has been revised recently. In an early study, the rate of progression to dementia was estimated to be 10-15% annually, with >80% of MCI patients developing dementia over 6 years (3,14). Similar rates were reported in the Cache County Study (13). Some investigators concluded that amnestic MCI is simply prodromal AD (15). However, population-based studies or studies with longer follow-up have revised these estimates downward: Devanand et al reported an annual progression rate of 5% (16), Solfrizzi et al of 7.4% (17), and Ganguli et al of 2.7% (18). Clearly the risk of dementia in MCI patients is highly variable, and appears lowest in general population samples.

A substantial number of patients with MCI "revert" to normal (i.e., no longer have subjective or objective cognitive dysfunction). The rate of "reversion" has been reported to range from 17% to 32% (19-21). The rate of progression to AD is highest, while the rate of reversion is lowest, in patients with rigorously defined amnestic MCI (19), particularly if it affects multiple cognitive domains (22), but is still significant in patients with non-amnestic MCI (23). The specificity of MCI subtypes risk for specific dementia subtypes is still unclear. Early reports that amnestic MCI was specific for AD and non-amnestic MCI for other dementias (particularly vascular dementia) have not been replicated (22,23) and are conceptually too simplistic.

Who with MCI is more likely to progress to dementia? In one study, MCI patients who progressed to dementia had worse verbal memory at baseline (24). In MCI patients with a very mild impairment, worse verbal memory and executive function was associated with greater risk of progression (25). Similar findings have been reported from the placebo arm of MCI medication trials (26). Additionally, subtle changes in IADL function predict a worse prognosis (25).

Brain imaging findings clearly can reflect prognosis of MCI. The rate of whole brain or regional volume loss in the hippocampus and entorhinal cortex (27,28), and possibly the rate of increase in ventricular size (29), appear to be good predictors of MCI progression. Decreased glucose uptake in the posterior cingulate and temporo-parietal cortices imaged with fluorodeoxyglucose positron emission tomography (FDG-PET) also predicts MCI conversion to dementia (30,31). Using Pittsburgh Agent B (PIB) (a new PET tracer for imaging amyloid plaques *in vivo),* binding is higher in MCI patients who progress to dementia than in those who remain functionally stable (32), suggesting that the density of amyloid plaques is higher in MCI patients who develop dementia. Functional magnetic resonance imaging (MRI) may also predict prognosis: for example, Miller et al (33) found that greater hippocampal activation during a visual scene-encoding task was a predictor of future cognitive decline.

Plasma and cerebrospinal fluid (CSF) amyloid and tau levels also hold promise as prognostic markers in MCI. Hansson et al (34) reported that a combination of decreased parietal blood flow and abnormal CSF amyloid-beta and tau levels was a strong predictor of MCI progression. Two studies reported that a decreased Aβ42/Aβ40 ratio is a risk factor for AD in MCI patients (35,36).

The strongest genetic association reported for AD is with the ApoE4 allele (14). This allele may also be a risk factor for progression of MCI to AD (26).

The association of depression and anxiety with MCI prognosis is of particular importance to psychiatrists. Depression, lack of motivation, and anxiety are more prevalent in MCI patients than in cognitively intact elderly (37). Both

major depression (38) and anxiety (37) markedly increase risk of MCI progression to dementia; further, depression and apathy were more common in MCI patients who later progressed to AD (21,39). The majority of older adults with major depression also met criteria for MCI, and their cognitive deficits persisted after remission of depression (40). Other studies of late-life depression have noted a particular association with executive dysfunction (41).

DIAGNOSIS

History

To make a diagnosis of MCI, the clinician must determine that the patient has subjective and/or objective cognitive symptoms, but not dementia. The border between MCI and dementia can be subtle, and the initial definition of MCI requiring no deficits in IADLs has been amended to allow for subtle deficits. The clinician needs to determine if the patient is no longer functioning at his/her baseline at work, home, hobbies, social activities, etc.

Patients with MCI are typically aware of their deficits and can provide a valid history, but confirmation with a knowledgeable informant (typically a family member) is important. Patients most commonly complain of deficits in short-term recall, with common examples being: a) cannot remember if they took medications; b) repeat questions; c) difficulty with driving directions in unfamiliar locations; d) difficulty recalling the time sequence of events; and, e) difficulty organizing complex projects, such as doing taxes or writing reports at work. MCI patients may additionally complain of deficits in executive functioning, such as using information to make judgments and decisions, appreciating the consequences of decisions, etc.; these tend to be more evident in the workplace and are harder to assess in retirees.

The importance of mood symptoms

It is clear that depressive and cognitive complaints often co-occur in older persons, and that depression is frequently prodromal to MCI and dementia. Therefore, the clinician must be alert to depressive symptoms in patients with cognitive complaints and must endeavor to distinguish primary mood changes from cognitive changes. Patients with MCI are among the most worried patients seen in a geriatric psychiatry practice; they often are convinced that they are demented and are prone to catastrophizing rather than adapting to their disability. For this reason, it is important that the clinician presents MCI as what it is – a syndrome and a risk group rather than a clearly defined illness.

There are certain mood features that are more common in MCI than in major depression. For example, patients may complain more of lack of motivation rather than sad or depressed feelings (42). Hopelessness is common, but suicidal ideation is not (43). The clinician should be highly attuned to the possibility that cognitive complaints are actually a presentation of an "atypical" depressive disorder and to make treatment decisions accordingly.

Cognitive assessment

Clinical assessment is rarely definitive in MCI, but useful for validating the patient's cognitive complaints. The Mini-Mental State Examination (MMSE) is neither sensitive nor specific enough to confirm or reject an MCI diagnosis, with one study showing 70% sensitivity and specificity using a cutoff of 26 or less for cognitive impairment (44). Instruments such as the Modified Mini-Mental State Examination (3MS or mMMSE) (45,46) or Montreal Cognitive Assessment (MoCA) (47) are more difficult, have less of a "ceiling effect", and as such are more useful in clinical practice for assessment of MCI. There are normative data for the 3MS derived from population-based samples (46); for example, the mean 3MS for a 75-79 year old person with a high school education is 90, while scores below 80 are below the 5th percentile. Neuropsychological testing adds further depth to the MCI evaluation, and there is growing evidence that sensitive tests of immediate and delayed recall particularly improve the predictive power of the evaluation (48).

Laboratory and physical assessment

While laboratory tests are not always necessary in the workup of MCI, it is important to rule out cognitive effects of medical illnesses other than neurodegenerative disease. For this reason, a thorough physical exam and laboratory assessment should be considered part of the assessment of MCI. Common conditions that either mimic or cause cognitive symptoms, even dementia, include hypothyroidism, vitamin B12 deficiency, neurosyphilis, and hypernatremia. A subacute onset of a delirium can mimic MCI, including in the context of urinary tract infection, pneumonia, congestive heart failure, and the effects of sedating medications (especially anticholinergics, benzodiazepines, and opioid analgesics). A thorough neurologic exam is important to assess for long-tract neurologic signs that might suggest an occult stroke, peripheral neuropathy, a myopathic process, or early Parkinson's disease, which can present with cognitive and motor slowing as a first sign and might mimic MCI.

Brain imaging

In current clinical practice, structural brain imaging is performed largely to rule out uncommon and occult causes of cognitive impairment, such as an occult stroke, subdural hematoma, or brain tumor. As such, it is not of the highest importance in the current diagnosis and manage-

ment of MCI. But, as reviewed above, new findings from structural MRI, FDG-PET and PIB-PET may greatly improve the clinical utility of these technologies in diagnosing and treating MCI.

MANAGEMENT

The most important aspect of the current management of MCI is making as clear a diagnosis as possible, and supporting patients and their families in the knowledge that they have a risk of dementia but no certainty of outcome. Specific aspects of management include: a) encouraging preventive strategies derived from observational data, and b) treating depression.

Strategies for preventing progression to dementia do not have proven efficacy to date, but there is suggestive evidence for the influence of lifestyle factors. We refer the reader to recent and comprehensive discussions of the biopsychosocial approach to treatment of depression in older persons (49,50) and restrict our comments to lifestyle strategies and medications.

Lifestyle strategies

Patients and families often ask the clinician whether exercise and cognitive activity will improve their memory or prevent dementia. The ideas are attractive and the mechanism of "use it or lose it" is intuitively appealing and widely cited as critical to dementia prevention. Supportive evidence comes from observational studies of community-based samples of older adults. A selection of recent studies is provided in Table 1.

Curiously enough, there is more evidence and stronger results for the protective effect of exercise than for cognitive activity, and moderate exercise (for example, twice weekly in a variety of exercise activities) is sufficient to demonstrate this association (51). The effect of cognitive activity has been less consistently observed and is confounded with education; in other words, education is observed to have a protective effect against dementia and to be associated with cognitive activities in older persons. There may be a similar salutary effect of social activities (52), although recent evidence suggests that reduction of social involvement is more likely to be the result, as opposed to the cause, of impend-

Table 1 Recent studies of lifestyle factors and incident dementia

Author	Lifestyle factor	Sample (mean follow-up)	Results	Comment
Podewils et al (51)	Number of exercise activities	N=3375 (5.4 years)	>3 activities associated with decreased dementia incidence (HR=0.58)	Effect seen in ApoE4 negative
Larson et al (66)	Frequency of exercise	N=1740 (6.2 years)	>3 times weekly exercise associated with decreased dementia incidence (HR=0.62)	Greater effect seen in persons with lower exercise performance levels at baseline
Wilson et al (67)	Number and frequency of cognitively stimulating activities	N=842 (4.1 years)	More cognitive stimulation associated with decreased dementia incidence (OR=0.36 for one-point increase in composite measure)	No effect seen for physical activity
Verghese et al (54)	Number of leisure activities	N=469 (5.1 years)	Greater number of leisure activities was associated with decreased dementia incidence	Activities associated with decreased dementia incidence included reading, playing board games, playing musical instruments, and dancing
Wang et al (68)	Performance-based physical function	N=2288 (5.9 years)	Higher levels of baseline physical performance were associated with decreased dementia incidence	Similar association with cognitive decline
Scarmeas et al (69)	Number of leisure activities dichotomized at the median	N=1772 (2.9 years)	Greater number of leisure activities was associated with decreased dementia incidence	
Rovio et al (70)	Midlife exercise frequency	N=1449 (26 years)	Exercise at least twice weekly in midlife was associated with decreased dementia incidence in late life (OR=0.48)	Note that the association applies to *midlife* (not late life) exercise frequency
Laurin et al (71)	Cognitive activity (composite measure)	N=801 (4.5 years)	Cognitively stimulating activities were associated with decreased dementia incidence	Similar association with global cognition, working memory, and perceptual speed

HR – hazard ratio; OR – odds ratio

The samples are selected to lack dementia or significant functional impairment at baseline, but are not chosen in a manner to include or exclude subjects with mild cognitive impairment

ing cognitive decline and dementia (53). In addition, cognitive activities fall into such a variety of categories that it has been difficult to determine the underlying mechanism subsuming different activities such as (for example) crossword puzzles and dancing (54).

The mechanisms of the protective effects of lifestyle factors are not well understood, but exercise and cognitive activity may lead to a greater "cognitive reserve" (55), conceivably through enhanced vascular supply to the brain or more efficient use of cognitive networks (56). "LIFE" is a randomized, controlled trial of an exercise program in physically frail elderly that will examine cognition and dementia risk as secondary outcomes (57).

We recommend that, with an eye toward prevention of cognitive deterioration, persons with MCI: a) pursue a regular but moderate, *variable* exercise program consisting of at least 30 minutes three times weekly of walking alternating with aerobically challenging exercise, and group sports; b) pursue cognitively stimulating activities according to personal interests, abilities and education; c) keep as socially engaged as practically possible.

Medications

Current FDA-approved medications for AD have been systematically studied for their effects on the symptoms and prognosis of MCI. In preclinical studies, all three acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and the NMDA antagonist memantine improved cognition in transgenic mouse models of AD (58). Galantamine improved memory symptomatically in MCI patients (59). However, the results of controlled trials of cholinesterase inhibitors on the prognosis of MCI have been largely negative (Table 2). The only positive finding, with donepezil, comes from a secondary analysis in a subgroup of patients, and had limited clinical relevance. There are no reported trials with memantine. Given the current state of knowledge, the clinician should not prescribe these drugs to MCI patients with the hope of preventing progression to AD. However, high-risk patients with amnestic MCI and declining cognitive function may symptomatically benefit from these treatments, since they likely have early AD.

CONCLUSIONS

What we know at the present

When patients present with memory deficits, clinicians can evaluate their near-term risk of developing dementia with the clinical tools and diagnostic assessments reviewed here. The most important concept for patients and families is that identifying a patient as having MCI assigns him or her to a *risk group* and is not a definitive diagnosis of disease, since a substantial proportion of persons with MCI will not develop dementia and will continue to function normally. Mood and anxiety symptoms are very prevalent in MCI and the clinician should pay particular attention to their diagnosis and treatment. Current medications for AD do not appear effective in preventing the progression of MCI to AD, but there is encouraging evidence for the beneficial role of exercise, cognitive stimulation, leisure activities, and socialization.

What the future holds

The rapid pace of innovation in preclinical and translational research in AD has led to an increasing pace of novel AD treatments entering clinical trials, including immunotherapies (60,61), secretase inhibitors (62), inhibition of the receptor for advanced glycation end-products (RAGE) (63), and anti-inflammatory agents (64). Since

Table 2 Randomized controlled trials of prevention of MCI progressing to dementia or AD

Author	Treatment	N (duration)	Outcomes	Results	Comments
Feldman et al (73)	Rivastigmine	1018 (48 months)	1. Progression to AD 2. Change on composite cognitive score	No difference between drug and placebo	No difference in MRI measure (ventricular volume)
Salloway et al (74)	Donepezil	270 (6 months)	1. Global impression of change 2. Change in delayed logical recall	No difference between drug and placebo	
Petersen et al (75)	Donepezil ± Vitamin E	769 (36 months)	Incident AD	1. Donepezil was not protective on primary outcome, but had a limited effect at 12 months in a secondary analysis. 2. No effect of Vitamin E	1. Donepezil effect observed at 36 months in ApoE4 carriers 2. No effect on rate of brain atrophy (76)

MCI – mild cognitive impairment; AD - Alzheimer's disease; MRI – magnetic resonance imaging
Two trials of galantamine in MCI have been reported as negative in a recent systematic review (72)

amnestic MCI includes a large group of patients with prodromal AD, if a new treatment is effective in early AD it may also prevent progression of amnestic MCI to AD. There is much investigation of biomarkers of preclinical AD which will help identify MCI patients at greatest risk of AD, and may allow for identification of patients before they develop MCI, so that treatment becomes possible in a preclinical state. Additionally, the near-future will likely produce an explosion of results on the effectiveness of lifestyle interventions in MCI. The clinician should keep alert for findings in all of these areas, which offer great hope of improving our management of MCI and possibly preventing incident AD and reducing its enormous public health burden.

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