UPDATE ON MILD COGNITIVE IMPAIRMENT

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Introduction

Mild cognitive impairment (MCI) represents an intermediate state of cognitive function between the changes seen in aging and those fulfilling criteria for dementia or Alzheimer's disease (AD).[1] This syllabus reviews the key points regarding MCI. For a more in depth review, please see the recent Continuum review on MCI.[1b] As they age, most individuals follow a course of a gradual cognitive decline, typically in memory, over the life span, but the degree of decline is minor and, while it may be a nuisance, it does not compromise a person's ability to function. A relatively few people go through life with virtually no cognitive decline, and these individuals are regarded as aging successfully. However, more recently, a subset of persons who are experiencing a change in cognitive function beyond typical aging that is apparent to themselves and those around them, has been identified and characterized. These individuals are now identified as having MCI and are receiving a great deal of attention in clinical practice and research settings.[2]

Persons with MCI have some, but not all, of the findings of dementia, and if the underlying cause is believed to be AD, these people are designated as having pre-dementia AD. **Generally, there are two subtypes of MCI: amnestic MCI (aMCI) and non-amnestic MCI (naMCI).**[3] Amnestic MCI refers to patients with a cognitive profile that includes significant memory impairment representing a change over time. Typically, patients are aware of their increasing forgetfulness, and family members perceive a change. However, other cognitive capacities such as executive function, language and visuospatial skills are relatively preserved, and importantly, **functional activities are intact except perhaps for some mild inefficiencies. These patients do not meet criteria for dementia.** Non-amnestic MCI is similar except that other, non-memory cognitive domains, are impaired with the relative preservation of memory and functional activities. aMCI and naMCI are sometimes sub typed further by the involvement of more than one domain of cognition (Figure 1) naMCI is probably less common than aMCI and may be the forerunner of non-AD dementias such as frontotemporal lobar dementia or dementia with Lewy bodies.[4]

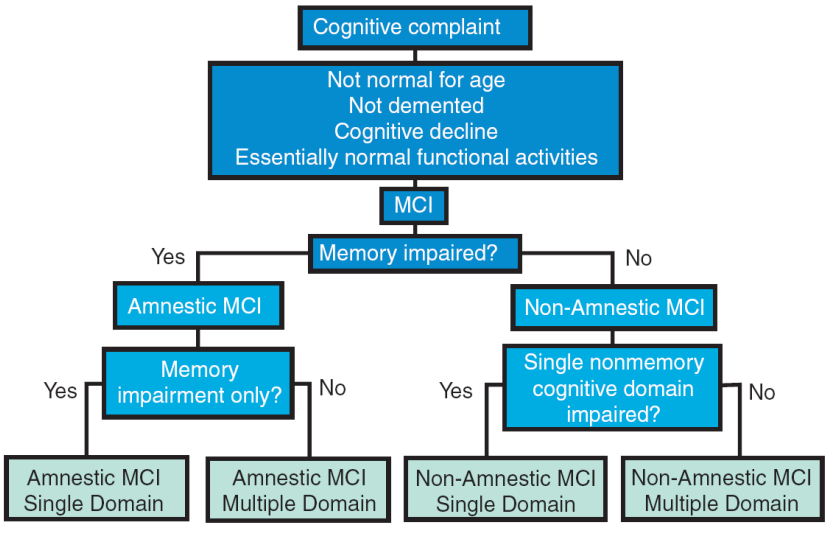

Figure 1. Algorithm for clinical diagnosis of MCI. From Petersen, RC. J Intern Med. 2004.

When the clinical syndrome of MCI is characterized as outlined above, the next step is to determine the putative etiology. That is, through the history, examination and laboratory testing, e.g., MRI scans, neuropsychological testing, one can determine the suspected underlying cause, such as degenerative, vascular, medical comorbidities, trauma or psychiatric factors just as one would do in any medical setting, i.e., determine the clinical syndrome first and then unravel the suspected etiology.

The literature on MCI is expanding rapidly, and while not all data are consistent, the majority, including several longitudinal international studies, suggest that **the clinical entity of MCI may be useful at predicting outcomes**.[5-10] A recent prospective epidemiological study on the incidence and prevalence of MCI documented its frequency.[11] The Mayo Clinic Study of Aging is a prospective, population-based epidemiologic study of non-demented individuals in Olmsted County, Minnesota. These individuals were ages 70-89 years at enrollment, and using the international classification criteria for MCI,[3 12] the investigators found a prevalence rate of 16.0% for all MCI and 11.1% for aMCI and 4.9% for naMCI.[11] A similar prospectively designed MCI study from Pittsburgh found a prevalence rate of 17.7% using their implementation of the international MCI criteria based on an algorithmic formula of neuropsychological tests.[12]

In recent years, there have been several other epidemiologic studies on MCI documenting its prevalence in the community and in clinical practices.[5, 6, 8] For example, **studies from Germany, Italy and the U.S. have shown the prevalence to be in the 10-20% range**.[7, 8, 10] As such the clinical scope of the condition is not trivial, and with the aging of most societies around the world, the healthcare impact is evident.

Once patients have been characterized with MCI, their rate of progression to dementia is variable but elevated over the dementia incidence rates in the general population of 1 to 2% per year. **If, however, patients are identified in an epidemiologic setting, the annual rate is in the 5-10% range.[13, 14] In subjects who have been identified in a clinical practice setting, the rate of progression to dementia is in the 10-15% per year range, largely due to the higher rate of prevalent disease by the time the individual chooses to seek attention** (8, 10-12).

Clinical Evaluation

A challenge for the clinician resides in making the distinction between MCI and normal aging. Subtle forgetfulness, such as misplacing objects and word finding difficulties, can plague individuals as they age and likely represent normal aging, but the memory loss in aMCI is more prominent. Typically, these persons will start to forget important information, items that they previously would have remembered easily, and the forgetfulness will become apparent to those around them. Examples of forgetfulness include missed appointments, forgotten telephone conversations or an inability to recall recent events such as outcomes of sporting events if the person were a sports fan. However, virtually all of their other aspects of function are preserved, and to the casual observer, the person appears quite normal.

The history can raise the suspicion of a real change in cognition, usually memory, but it may take neuropsychological testing to confirm this. At times, the "worried well" can give a convincing history, but neuropsychological testing reveals normal performance. More often, however, the history is suggestive of progressing forgetfulness, and the neuropsychological testing will reveal a relative impairment in memory function, particularly delayed recall of a word list or story, in the setting of preserved attention, executive function, language and visuospatial skills. This pattern combined with the appropriate history would be quite suggestive of aMCI.

On the other end of the MCI spectrum, **the differentiation from dementia is generally not difficult**. Typically, at this stage of impairment, the cognitive deficits are having an impact on daily function which represents the transition to dementia. Since most individuals with MCI progress to dementia, the precise time at which this transition occurs is often arbitrary and less important, and usually this information is provided by the patient or a family member. Neuropsychological testing can be useful here to document the progression in the memory domain and involvement of other cognitive domains, **but it is the history concerning a functional impairment that is critical, and this can be supported by instruments such as the Functional Activities Questionnaire which characterizes impairment in function in the dementia range**.[15] Imaging and biomarkers are less useful in documenting this transition.

Ancillary Testing

When a patient is diagnosed with MCI, a common question arises as to the rate at which a person will progress from MCI to dementia. The rate of transition can be predicted, and recent information in the literature supports this. **While the general rate of progression from MCI to dementia may be in the 5-15% per year range, certain factors predict a more rapid progression.**

Several studies have indicated that those **individuals who are carriers of the Apolipoprotein E ε4 allele will progress more rapidly**.[16, 17] This finding has been replicated in numerous settings, and since Apolipoprotein E ε4 carrier status is a risk for AD, this may be of clinical utility. Next, a great deal of research has been conducted on evaluating various MRI measures at predicting progression.[18-20] Most of the data on the volume of hippocampal formations indicate that **atrophic hippocampi are strong indicators of a subsequent progression**.[21-23] In addition, other MR markers such as dilated ventricles, reduced total brain volume, white matter hyperintensities have been useful predictors.[24-29] Newer measures such as magnetic resonance spectroscopy, diffusion tensor imaging and arterial spin labeling have also suggested that other markers may be prognostic, but are still under study.[30, 31]

Functional imaging measures such as fluorodeoxyglucose F18 positron emission tomography (FDG PET) have contributed to the field. It appears that **the FDG PET pattern of hypometabolism in the temporal and parietal regions that is suggestive of AD may also be useful in predicting which MCI subjects might progress more rapidly**.[32-34] Presumably, FDG PET is providing an index of synaptic integrity, and as this capacity is lost, patients are more likely to progress to higher degrees of cognitive impairment.

One of the more active areas of research in MCI at present pertains to the role of cerebrospinal fluid (CSF) markers in predicting progression.[35] A recent Swedish study indicated that those individuals with MCI who had a low Aβ42 and an elevated tau or phospho-tau level or a ratio of these measures in the CSF are likely to progress much more rapidly to AD than those MCI individuals without that profile.[36] An international multi-center study of 750 MCI subjects also corroborated these findings and a study of CSF markers blinded to clinical status demonstrated added utility of CSF as a predictor.[37, 38] However, there remains a technical challenge in this field since **the reliability of measurements of these CSF markers is quite variable across laboratories, and consequently, there is an international standardization exercise currently underway to address this problem**.

In a research setting, molecular imaging, particularly of amyloid plaques, has gained great popularity.[39-42] Recent studies documenting the presence of amyloid using the ^{11}C Pittsburgh Compound B (PiB) also suggest that research subjects who have positive amyloid imaging scans are more likely to progress more rapidly.[43] The presumption is that the presence of amyloid accompanied by clinical symptoms implies that the presence of amyloid may be the determining factor for the person's clinical symptoms, and this may herald the earliest stages of AD. The clinically available PET ligand to amyloid, florbetapir, is now being studied for the same purpose.

One of the first biomarker studies on MCI evaluating the new NIA-AA criteria for MCI due to AD documents that while most subjects with MCI have the AD biomarker profile of amyloid present on PET and some sign of neurodegeneration including either MRI atrophy, FDG PET hypometabolism, or both, many do not.[43a] In particular, a group of subjects labeled as MCI-SNAP (MCI with suspected non-AD pathology) were found and they progressed to dementia at an accelerated rate.

Finally, **those subjects who are more severely impaired on the clinical spectrum may also be more likely to progress more rapidly**.[44, 45] This may simply imply that these individuals have progressed further on the clinical spectrum and are nearing the threshold for dementia. Ultimately, a combination of these factors may be most useful at predicting progression. As will be discussed below, several large international efforts are currently underway evaluating the roles of multiple clinical, neuroimaging and biomarker measures in predicting progression. Figure 2 demonstrates the current theories behind the timing and pathologic role of AD biomarkers.

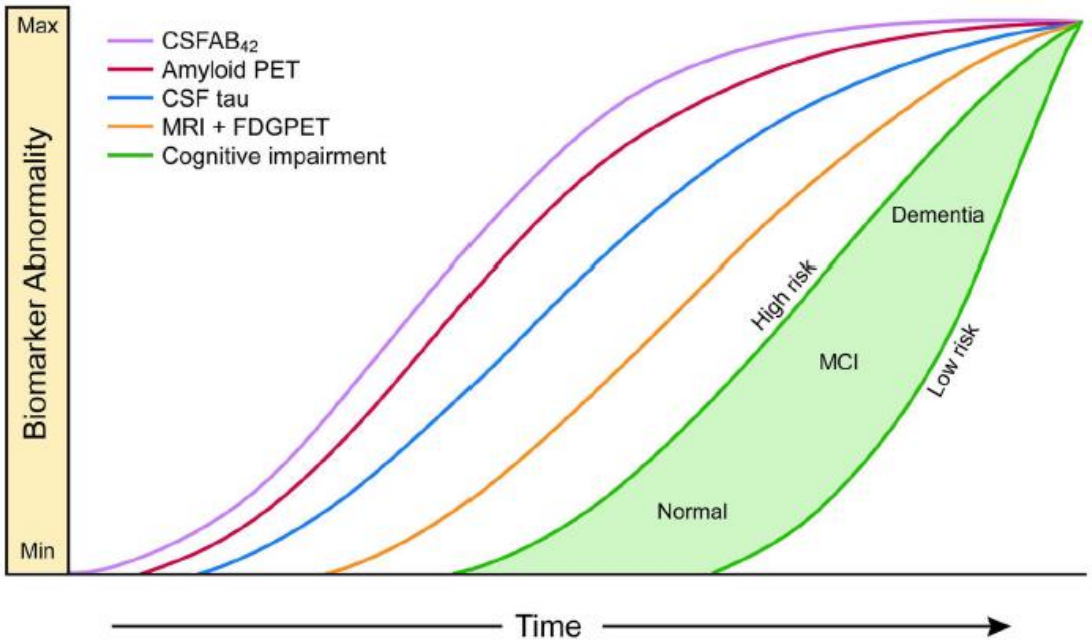

Figure 2. Hypothetical biomarker cascade in AD. From Jack CR, et. al. Lancet Neurology, 2013.

Therapeutic Options

At present, there are **no FDA approved pharmacologic treatments for persons with MCI. Several recent clinical trials have been conducted on MCI subjects evaluating the standard therapies for AD, and all have been unsuccessful**.[46-50] One trial sponsored the National Institute on Aging through the Alzheimer's Disease Cooperative Study and partially supported by Pfizer, Inc. evaluated the role of high-dose vitamin E and donepezil in lowering the rate of progression from MCI to AD.[46] This study demonstrated that donepezil was effective at reducing the risk of developing AD for the first 12 months of the study and up to 24 months in subjects who were Apolipoprotein ε4 carriers. However, over the 36-month course of the entire study, there was no significant effect. A subsequent 18-month trial of donepezil alone failed to replicate the Alzheimer's Disease Cooperative Study trial, and several other clinical trials in MCI have been negative.[47-50] Nevertheless, since this clinical state is attractive for treatment interventions, several clinical trials of potential disease-modifying therapies are under investigation at present, using subjects at the MCI stage.[51]

At this point, while there are no approved pharmacologic treatments, many clinicians will entertain a discussion with individual patients to determine if they would like to consider treatment at the MCI stage.[46] The discussion indicates that this would be off-label and that an acetylcholinesterase inhibitor might be worth considering if the physician and patient believe that this is the earliest manifestation of an AD-like process.

There is also a growing literature that non-pharmacologic cognitive rehabilitation approaches may be effective and are worth considering for patients.[52] Several recent systematic reviews of the literature on cognitive intervention programs for MCI demonstrated a statistically significant improvement at the end of training.[53,53a] There is limited evidence that physical activity regimens may lead to an improvement on cognitive function in patients with MCI.[53b] There is also evidence that combining multiple non-pharmacologic interventions may provide additive benefits. A recent two-year study showed that a multi-domain intervention for patients at risk for dementia, including patients with MCI, improved performance on a neuropsychological test battery. The intervention included diet counseling, an exercise program, cognitive training and group discussions aimed at effecting lifestyle changes.[53c]

Challenges with the Construct of MCI

A factor affecting the negative outcomes in clinical trials for MCI may relate to the heterogeneity of subjects diagnosed with MCI. As the diagnostic threshold moves earlier in the clinical spectrum, greater sensitivity with respect to the diagnosis is achieved but at the expense of a loss of specificity. As mentioned above, clinical severity is an important predictor of the rate of progression.[45] As such, while many subjects progress from aMCI

to AD, some do not. **From a clinical perspective, it is not acceptable to label patients at the MCI stage with "early AD, prodromal AD or MCI of the AD type," since not all of these subjects will progress to AD**, and clinicians cannot mislabel patients with this type of a diagnosis. If clinicians label a person with "prodromal AD," the patient and family will likely only hear the AD aspect of the diagnosis and not appreciate the uncertainty surrounding this preliminary diagnosis. Therefore, it is incumbent upon the clinicians to be objective with the patients with respect to the imprecise nature of the characterization at this point in the clinical spectrum.[54]

Many clinicians prefer to use the term "MCI" to characterize patients at this intermediate stage and relay the probabilistic outcomes of the diagnosis rather stating that this is early AD. A recent survey on attitudes toward the clinical utility of MCI was conducted by the American Academy of Neurology.[55] This random sample of 448 neurologists indicated that most of these clinicians see patients with mild memory problems in their practices, frequently use the term "MCI" and prefer it over early AD or other prodromal dementia labels. Interestingly, many clinicians treat MCI patients at this stage with acetylcholinesterase inhibitors and believe that the clinical label of MCI is useful in characterizing this type of patient.

A major effort to evaluate these factors with respect to the utility of predicting which MCI subjects might progress to AD is supported by the National Institute on Aging and the Foundation for the National Institutes of Health. This study known as the Alzheimer's Disease Neuroimaging Initiative (ADNI) is currently underway in the U.S. and Canada.[56, 57] There are parallel efforts progressing in Japan, Europe and Australia. The ADNI is a multi-center study designed to simulate clinical trials using subjects with aMCI and assessing the relative utility of neuroimaging measures such as structural MRI, FDG PET, CSF markers and amyloid imaging PET scanning to determine the merit of these ancillary tests. Preliminary data from these studies indicate that hippocampal atrophy seen on MRI,[58-60] hypometabolism on FDG PET and low CSF abeta and elevated tau may be useful in defining a subset of subjects with aMCI who are likely to progress to clinical AD.[56 27, 61] Thus far in ADNI, the participants who have been characterized with aMCI of a degenerative etiology have progressed to AD at a rate of greater than 20% per year.[57] In addition, neuroimaging and biomarkers have suggested subsets of subjects who are likely to progress even more rapidly, and these studies are being corroborated.[38] Since the subjects currently enrolled in ADNI with aMCI are of moderate severity, new studies are being proposed to look at aMCI subjects with a milder degree of memory impairment. The goal of this work would be to move the threshold for detection of AD to an earlier point in the clinical spectrum while not sacrificing specificity by using additional imaging and biomarkers to clarify which subjects would progress more rapidly. **The ultimate goal of this research is to allow intervention with presumable disease-modifying therapies at an early point in the disease spectrum.**

Recent studies have shed some light on the construct of stability of the MCI diagnosis.[61a, 61b] **While it is true that at times subjects who have been diagnosed with MCI at one point in time will be diagnosed as "cognitively normal" on a subsequent visit. These studies revealed that if subjects are followed sufficiently long, that ultimately most of those who revert to normal will ultimately be reclassified as MCI and later dementia at high rate** implying that temporary instability is simply a feature of mild symptoms, like labile hypertension. However, eventually most of these subjects are impaired and develop dementia.

Future Directions and New Criteria

In 2001, the American Academy of Neurology in an evidence-based medicine review of the literature recommended that clinicians should monitor and follow patients with MCI since these persons are at increased risk of developing dementia, particularly AD.[62] Since 2001, thousands of studies have been conducted on MCI, and consequently, the American Academy of Neurology is repeating this evidence-based medicine exercise at the present time. Mild cognitive impairment is not included in any of the diagnostic manuals at this point, but the most recent revision of the Diagnostic and Statistical Manual for Mental Disorders-5 includes a diagnosis of Mild Neurocognitive Disorder which is analogous to the concept of mild cognitive impairment.[63] Proposals for revising AD criteria to include a pre-dementia state of clinical impairment are also being entertained.[64] Currently, there is an ICD-9 code for MCI (331.83) and ICD-11 is being developed. As the field evolves, it is likely that more revisions of MCI will appear in diagnostic schemes.

Recent modifications of the MCI clinical criteria are underway to augment the current clinical criteria with imaging and fluid biomarkers. Three panels have been organized by the National Institute on Aging and the Alzheimer's Association to better characterize criteria for three putative stages of the Alzheimer's disease pathophysiological

processes. Inherent in this process is the assumption that the deposition of amyloid is the initiating pathologic process followed by neuronal injury and ultimately clinical symptoms. The three panels were designated as 1) Pre-clinical AD, 2) MCI due to AD and 3) Dementia due to AD. With respect to the MCI stage, the criteria start with those described above and then augment the likelihood that the clinical syndrome of MCI is due to AD using imaging and chemical biomarkers to enhance the certainty. The first level involves the clinical syndrome itself and this represents the lowest degree of certainty, although, as noted above the clinical syndrome of amnestic MCI is reasonably predictive of a subsequent dementia. The next level involves the clinical syndrome augmented with a single imaging/biomarker measure for AD being positive, e.g., amyloid (PET imaging or CSF AB42) or neuronal injury (structural MRI, FDG PET or CSF tau) and the other class of marker is not available or uninformative. The highest level of certainty results from a combination of the clinical syndrome with both types of biomarkers, one for amyloid deposition and one for neuronal injury. Finally, the least level of certainty that AD is accounting for the clinical syndrome results from the clinical syndrome in the setting of negative biomarkers, e.g., negative amyloid imaging or CSF AB or negative MRI atrophy pattern, FDG PET or CSF tau. The levels of MCI certainty are summarized in Figure 3. **At this point, only the MCI diagnosis made on clinical grounds has been studied extensively to yield reasonable prediction to dementia; the other entities need to be investigated in multiple clinical settings and are not ready for clinical application**. It is anticipated that these criteria will be validated in coming years.

MCI criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
MCI–core clinical criteria	Uninformative	Conflicting/indeterminant/untested	Conflicting/indeterminant/untested
MCI due to AD—intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD—high likelihood	Highest	Positive	Positive
MCI—unlikely due to AD	Lowest	Negative	Negative

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.

Figure 3. Current MCI diagnostic criteria including use of biomarkers. From Albert MS, et. al. Alzheimers and Dementia. 2011

For the dementia stage, the previous standard criteria for dementia are invoked with a few slight modifications and augmentation of certainty with biomarkers. While a prominent, early memory impairment is still the most common clinical presentation of the dementia of AD, it is not an absolute requirement. The less common clinical presentations of the dementia of AD are acknowledged such as the visual variant or the posterior cortical atrophy presentation of AD. These patients typically present with prominent visuospatial difficulties such as reading, driving and trouble perceiving objects in the environment. However, the amnestic presentation is still the most common form of incipient dementia of AD. The clinical diagnosis of dementia is augmented by the biomarkers of amyloid deposition and neuronal injury as in MCI. In addition, if there is contradictory information from the biomarkers, this reduces the likelihood that the dementia syndrome is due to AD.

The most recent addition to the progression of AD process, and probably the most controversial, pertains to the pre-clinical stage of AD. In this stage, by definition persons are asymptomatic. Nevertheless, some of these individuals are destined to develop the MCI and dementia stages of AD and the designation of "pre-clinical AD" is intended to capture these individuals. Three stages have been outlined for this condition. Stage 1 characterizes persons with only a positive amyloid biomarker, in the absence of a measure of neuronal injury or any clinical signals. Stage 2 refers to the presence of an amyloid marker and an index of neuronal injury. Finally, Stage 3 combines a positive measure of amyloid deposition, neuronal injury and a very subtle suggestion of a clinical change despite performance being in the normal range by most estimates of performance. As one can imagine, this is the aspect of the new criteria that is most speculative, but it is hoped that these formulations will move the field forward to allow the earliest intervention with disease modifying therapeutics when developed.

Summary

In summary, the construct of MCI is assuming a central role with respect to the clinical characterization of individuals who are in the prodromal state of AD. While not all of these individuals will progress to AD, a significant proportion will advance. Efforts are underway to enhance the specificity of the outcome at this early clinical state. The current state identifies AD at the dementia stage. It is likely that this threshold will move to the

left into the MCI range with the enhancement of specificity provided by ancillary tests such as neuroimaging measures and biomarkers.[65, 66 67] Ultimately, since the goal is preventing or minimizing damage to the central nervous system, as the imaging and chemical biomarkers are validated, we hopefully will be able to characterize persons at risk who are asymptomatic as is shown on the left side of the figure. As such, MCI occupies a pivotal role in AD research.

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