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Early Diagnosis of Alzheimer's Disease: Is MCI Too Late?

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Abstract

The field of aging and dementia research is advancing rapidly toward the stage of earlier identification of clinical symptoms. Ultimately, clinicians would like to be able to identify individuals who are asymptomatic but at risk for developing the disease. In the interim, the construct of mild cognitive impairment (MCI) has come to represent an intermediate clinical state between the cognitive changes of aging and the very earliest features of Alzheimer's disease. A great deal of research has been generated in the past several years on MCI, and epidemiologic studies are characterizing its frequency in the general population. There are predictors of a more rapid progression from MCI to Alzheimer's disease, and these studies are suggesting techniques for altering future clinical trials. The neuropathology of MCI is intermediate between the neuropathologic changes of aging and fully developed Alzheimer's disease. The breadth of research in MCI is expanding and will be reviewed.

Keywords

Mild cognitive impairment; Alzheimer's disease; aging

Research in Alzheimer's disease (AD) is moving forward at a very rapid pace. Clinical investigators are attempting to move the diagnostic threshold for dementia and AD back to earlier stages of progression while basic scientists are correspondingly attempting to define biomarkers and genetic susceptibilities that will add specificity to the clinical diagnoses. The urgency of this issue is increasing with the baby boomers beginning to age into the period of risk for AD.

While a cure for AD is a lofty goal, strategies designed to modify its onset or progression would also have significant impact[1]. Sloane and colleagues modeled the impact of either delaying the onset of the disease by five years or slowing its progression on the projected rates of the disorder over the next several decades[2]. The strategy to delay on the onset of the disease would have a significant impact on the total number of cases projected, reducing them by 50% or more by 2050. Alternatively, delaying the disease progression may not reduce the absolute number of cases but would have the effect of reducing the severity of the disease such that more cases would remain in the mild stage rather than progressing on to moderate or severe disease. Finally, the combination of these strategies would have the dual benefit of reducing the absolute number of cases and minimizing the severity of the clinical disability in those who do develop the disorder. These strategies are quite reasonable and are being pursued by many investigators in the field[3].

It is also widely believed that the onset of the underlying pathology for AD likely begins years if not decades prior to the appearance of clinical symptoms. It is quite likely that the

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neurofibrillary damage and amyloid misprocessing that occurs in AD begins in a very gradual sense many years prior to the time of the clinical diagnosis of AD. Consequently, a great deal of research is focusing on the development of imaging and biomarkers to detect the very earliest signs of the disease in people who might be at risk[4].

From the clinical perspective, research is underway at characterizing the earliest clinical presentation of symptoms that might eventually evolve into the clinical diagnosis of AD. Mild cognitive impairment (MCI) has come to be recognized as an intermediate state of clinical impairment whereby individuals have cognitive symptoms of a mild nature but generally continue to function virtually normally in the community[5–7]. These subjects do not meet the clinical criteria for dementia or AD, yet their degree of cognitive impairment, usually a memory impairment, is beyond what we would expect for age and education[8]. As such, research in MCI will likely push back the threshold of recognition to an earlier state in the disease process to allow intervention at an earlier point than is currently done in typical AD clinical trials.

Clinical Features

Initially, mild cognitive impairment was described as being a precursor to only AD. The original criteria published in 1999 outlined the condition as follows: 1) A memory complaint from the subject or an informant, 2) memory impairment for age and education, 3) normal general cognition outside of memory, 4) largely preserved activities of daily living, and 5) not demented[6]. These criteria have been extensively evaluated over the years and modifications have been suggested[8]. The features of individuals with this degree of memory impairment have been described and followed in several large cohort studies[9–14]. At the Mayo Clinic in Rochester, Minnesota, some of these subjects have been followed for over ten years, and a typical cognitive profile of them is shown in Figure 1. When these subjects were followed longitudinally, they tended to progress to clinically probable AD at a rate of about 12% per year[6]. Other studies around the world have shown somewhat variable rates, but generally, they have coalesced around the figure of 10–15% per year[11–13]. It appears that studies following cohorts of individuals from referral centers such as an Alzheimer's or a memory disorders' clinic yield higher rates approaching 15% per year[7]. Epidemiologically-based studies that survey individuals in a random fashion have yielded lower progression rates of, perhaps, 8–10% per year[9, 12]. These findings imply that the source of the subjects in any particular study is important in interpreting the outcome. When individuals voluntarily come to a memory disorders' clinic for help, they are likely to be experiencing cognitive changes indicative of early features of dementia and, consequently, tend to be further along in the clinical spectrum of severity. However, when individuals are proactively recruited from a community setting, the symptoms are likely to be milder and the corresponding progression rates lower. Nevertheless, the same phenomenon can be described in both sets of subjects.

Subsequent work has indicated that not all forms of intermediate cognitive impairment involve memory, and the construct of MCI might be considerably broader. At a consensus conference on MCI held in Stockholm in 2003, the criteria were revised to include any type of cognitive complaint, not just forgetfulness[8]. Figure 2 demonstrates the current diagnostic algorithm for MCI broadening the cognitive concern to include any aspect of cognition. As can be seen in Figure 2, once the cognitive concern is characterized, and this concern can be raised by the individual, someone who knows the individual well, or by an examiner, the next step involves evaluating the person to be certain that they are not clinically normal nor are they demented. It is important also to determine, usually by history, that the person has experienced a decline from a prior level of cognitive function. That is, many individuals experience some changes in cognition as they age, but the clinician must

be certain that the person is describing a change in cognition that is beyond what one would expect for normal aging. This information usually can be obtained from an informant. Finally, the clinician must also assess the person's daily activities to be certain that the individual is still functioning well in the community. This ensures that the person has not reached the level of dementia in their clinical progression.

Once these criteria have been fulfilled, the person is designated as having MCI, and the next step is to determine whether there is a component of a memory impairment or not. Since a memory impairment is important in the development of the clinical syndrome of AD, testing must be done to assess memory function. Depending upon the resources available to the clinician, this can be done in the office using memory instruments that assess the individual's recent memory, that is, task requirements that exceed the person's attention span, and, typically, are best assessed using a procedure that involves delayed recall of 15–30 minutes. Often, neuropsychological testing can be very helpful in characterizing the cognitive profile of the individual. If neuropsychological testing is done, the clinician can then determine if memory is impaired out of proportion to what one would expect for age and can also assess function in other cognitive domains such as language, attention/executive function and visuospatial skills.

If memory is impaired, then the person is designated as having *amnestic MCI* and the final decision is made to determine whether any other cognitive domain in addition to memory is slightly impaired or not. Alternatively, if memory is not impaired, then the individual is designated as having *non-amnestic MCI*, and again, the presence or absence of impairment in multiple other cognitive domains is made. For example, in the latter instance, a person may have an impairment in attention and concentration and, on closer examination, also might be impaired in visuospatial skills. If these two cognitive domains are impaired, the individual is designated as having non-amnestic MCI of the multiple-domain type.

Once the clinical syndrome has been characterized as is shown in Figure 2, then the clinician must try to determine the etiology or the cause of that clinical syndrome. Typically, this is done by taking a careful history from the subject and an informant. Additional testing such as an MRI scan or laboratory studies may also be helpful. For example, if the individual has amnestic-MCI as a syndrome and the history reveals that the memory deficit has come on very gradually and insidiously, the suspected etiology is likely degenerative. This type of determination would be done in much the same fashion as one would elicit a history of clinical AD. That is, the clinician typically will ask the subject and informant when the symptoms began, and if the person gives a history of a gradual onset and slow progression, then the clinician makes the diagnosis of dementia or AD. In a similar fashion, a degenerative etiology of the MCI symptoms can be obtained. However, if the clinician obtains a history of poorly controlled hypertension, longstanding diabetes, and perhaps vascular episodes such as cerebrovascular symptoms or transient ischemic attacks, then a vascular etiology might be more appropriate. As is shown in Figure 3, the clinician then combines the clinical syndrome with the suspected etiology and, in so doing, can then make a reasonable prediction as to what the outcome of this syndrome might be. Most of the research on this entity has pertained to amnestic MCI of a degenerative etiology. This diagnostic scheme has been adopted by the National Institute on Aging sponsored Alzheimer's Disease Centers Program and by the National Institute on Aging sponsored Alzheimer's Disease Neuroimaging Initiative[15].

Clinical Case

A typical history of an individual who might qualify for the diagnosis of amnestic MCI might be as follows. A 68-year-old retired businessman has been noting the

gradual onset of forgetfulness. He has always had some difficulties with names of acquaintances, but now he is starting to forget appointments with physicians and important meetings that he is scheduled to attend. This has been happening on a regular basis, and his family is now noticing that he is starting to forget events that he formerly remembered quite easily. There has been a very gradual onset of these symptoms, but the forgetfulness appears to be increasing in severity and frequency. However, he still is functioning well in the community, driving without difficulty, handling the household finances, personal investments and is quite involved in social activities. He is not depressed and is not taking any medications that would be suspected of causing a memory impairment. He is in good general health otherwise with the exception of benign prostatic hyperplasia and low back pain. When he was examined by his physician in the office, he scored a 28 out of 30 on the Mini-Mental State Exam, missing 2 points on recall of the three words. His wife corroborates the entire history and is not concerned about his daily activities. Neuropsychological testing was performed and revealed an impairment in delayed recall of a paragraph in Logical Memory II of the Wechsler Memory Scale-III. He recalls only 20% of the material he learned in the paragraph. On a list learning exercise such as Auditory Verbal Learning Test, he learned 12 of the 15 words by trial five but remembered only four of them after a 30-minute delay. Otherwise, tests in language, attention, concentration and visuospatial domains are all normal and in the expected range for his age and education. An MRI head scan was performed and showed only mild atrophy of medial temporal lobe structures. Screening laboratory tests for thyroid function, vitamin B-12 levels and other standard screening measures were unremarkable.

This individual has a memory complaint, is believed to have had a change in cognitive function in recent years, is not normal for his age but is not demented, according to standard criteria. The entire history was corroborated by his wife, and the examination by the clinician revealed an impairment in memory corroborating the person’s concern but preservation of other cognitive functions. As such, this individual would meet the criteria for amnestic MCI single domain.

Epidemiology of MCI

Over the last several years, there have been reports of several epidemiologic studies on MCI that have been conducted worldwide. Several of these cohorts have been established in the past decade or so, and consequently, we are now beginning to appreciate the longitudinal followup of individuals who were diagnosed with MCI prospectively[9, 11–13]. In addition, there have been numerous other studies using a retrofitting of MCI criteria to existing databases[10, 16, 17]. These studies have provided valuable information for the field regarding the clinical characterization and outcome of individuals with MCI, but are partially limited by the retrospective nature of the data analyses. As such, the prospectively designed studies are more informative since they incorporate the newly established MCI criteria and can impose them on the recruitment and diagnosis strategies moving forward[9, 11, 12].

A study from Leipzig has been particularly informative since it looked at almost 1,000 subjects age 75 and older and found an MCI prevalence rate of around 19.3 percent with a progression rate of 8.7% per year to dementia[9]. The Italian Longitudinal Study of Aging evaluated almost 3,000 subjects and also found a prevalence rate of about 16.1% with an annual progression rate of 13.6 %[12]. A study conducted in India evaluating close to 1,000 subjects found a 15% prevalence rate of MCI, and the Austrian study of almost 600 subjects found a prevalence rate of 24% with a progression rate from approximately 11 to 19% per year depending on specific definitions[13]. Most of these studies used a similar set of

criteria to define MCI but implemented the criteria in various fashions. That is, while the same set of diagnostic parameters were used, the specific assessment instruments, the composition of the individuals evaluating the subjects and ancillary procedures varied considerably among the studies. Despite these potential sources of variability, the prevalence rate all appeared to be in the 15–25% range, which is becoming increasingly consistent across many different study designs.

The Mayo Clinic Study of Aging was established in 2004 as a population-based registry of non-demented individuals[18]. This study recruited 2,000 non-demented individuals and assesses them with a three-part evaluation: a comprehensive history from the subject and a study partner, a detailed neuropsychological test battery and a physician's examination including history, mental status exam and neurologic assessment. A consensus conference was held then to adjudicate each case. The subjects are then evaluated annually, and prevalence rates as well as incidence rates for MCI, its subtypes and other conditions are being generated. The initial reports from this study indicate that the prevalence rate of MCI is approximately 16.3% with a 2:1 ratio of amnestic to non-amnestic subjects in this age range of 70–89 years[19]. These subjects will continue to be followed longitudinally to confirm these figures.

As mentioned previously, from an epidemiologic perspective, while there has been a fair amount of variability over the years in the literature with respect to the types of studies, the characterization of the subjects, the nature of the implementation of the criteria and other factors, data appear to be coalescing now to indicate that, in a referral clinic setting such as an Alzheimer's disease center or a memory disorders clinic, the rates of progression from MCI to dementia appear to be in the 10 to 12% range. However, when studies are done in an epidemiologic setting where the subjects are proactively recruited for the study, the rates are perhaps in the 8 to 10% per year. While this does imply some variability, it is likely that the nature of the studies constitutes the difference, and all of these studies imply that the rates are considerably higher than previously expected.

Predictors of Progression

While the epidemiologic studies characterize the rates at which subjects will progress from MCI to dementia, there are factors that will indicate a more rapid rate of progression in some subjects. For example, an extensive amount of neuroimaging has been done on MCI subjects, and these data imply that degrees of hippocampal atrophy as well as whole-brain volume and ventricular volumes predict the rate at which subjects will progress to dementia[20–23]. In general, those subjects with smaller hippocampal volumes, more brain atrophy as either indexed by boundary shift integral techniques or volumetric measurements of the ventricles imply that these factors can predict the progression[24]. In addition, biomarkers such as cerebrospinal fluid (CSF) markers may be useful, as well. A recent study from Sweden indicated that those subjects who met MCI criteria but had the CSF profile of AD, e.g., decreased CSF Aβ42 and elevated tau, either total tau or phosphorylated tau, will progress more rapidly[25]. These studies are being confirmed in other settings and are likely to lead to our increased ability to characterize subsets of subjects with MCI who are more likely to progress more rapidly. These findings would have implications for the design of clinical trials at the MCI stage.

Alzheimer's Disease Neuroimaging Initiative

A major study is underway sponsored by the National Institute on Aging and the Foundation for the National Institutes of Health which represents a consortium of industry partners to evaluate the role of imaging and biochemical biomarkers in the characterization of MCI[15]. This study includes 200 cognitively healthy subjects, 400 amnestic MCI subjects and 200

mild AD subjects. All of the individuals receive an MRI scan done at 1.5 T strength approximately every six months for three years with the exception that the AD subjects were followed for two years, 25% of the subjects receive a 3T MRI scan, 50% of the subjects will receive an FDG-PET scan, and approximately 50% of all the subjects have undergone a spinal tap. A substudy to look at approximately 100 subjects receiving amyloid imaging scans using the Pittsburgh Compound B (PiB) is also being evaluated. Thus far, the subjects have been assessed initially, and most have received a one-year followup. The preliminary data on the progression from one condition to another are as follows: Of the 229 subjects recruited as being normal, 222 have remained normal while 7 have progressed to aMCI. Of the 402 MCI subjects, 280 have remained stable through 12 months of followup while 106 have progressed on to AD. Another 16 MCI subjects have reverted back to the cognitively healthy diagnosis. Of the 188 mild AD subjects, 184 have retained that diagnosis while 4 have reverted to MCI over the course of the 12 months. These data indicate an annual rate of progression from cognitively healthy to the aMCI state of 3% per year. In addition, 26% of the aMCI subjects have progressed to AD over 12 months while another 4% of the aMCI subjects have reverted to cognitively healthy status. A preliminary analysis of the imaging and biomarker data have revealed interesting subsets of subjects in both the cognitively healthy and aMCI diagnostic groups that may suggest individuals who are at greater risk of progressing to the next state of cognitive impairment. These data are being analyzed currently and will be reported soon[26].

Breadth of MCI Research

Over the past decade, there has been a significant expansion in the types of studies conducted within MCI[27]. As outlined above, there have been numerous studies on the epidemiology, clinical characteristics, neuroimaging, biomarkers, mechanism of disease, neuropathology and clinical trials all on MCI. These data have contributed a great deal of understanding to the early evolutionary stages of a variety of dementing illnesses, and this trend will likely continue. As an example of productivity in this area, in 1999, fewer than 50 papers were published in the medical literature on the topic of MCI while, in 2007, this number had approached 900 peer-reviewed studies. This increase in awareness and scrutiny for the field has been extremely valuable.

Neuropathology

From a pathologic perspective, as pathology studies accumulate on subjects who have MCI or have gone through an MCI stage, it appears that the neuropathology is transitional between the neuropathological findings of typical aging and very early AD[28]. These studies need to be interpreted in the appropriate clinical context from which the subjects have been derived. For example, a study from the University of Kentucky found that most of their MCI subjects had the underlying pathology of AD[29]. However, the authors indicate that their subset of MCI subjects may have been more clinically advanced than other series and, as such, may, in fact, represent the transition between MCI and AD. Studies from Washington University characterized the very earliest stages of AD since they do not employ MCI diagnostic criteria[30]. As such, these studies indicate that most of the people with a CDR 0.5 stage of clinical impairment have the neuropathological features of AD. In fact, of all of their subjects who have been classified with a CDR of 0.5, 92% of these individuals have neuropathologic AD, implying that these subjects are seen at a more advanced stage in the cognitive progression than in other clinics who evaluate people at the MCI stage[31]. Two recent studies from the Mayo Clinic, one characterizing subjects who died while their clinical classification was MCI revealed that most of these subjects had a low probability of having the neuropathological features of MCI according, to the National Institute on Aging—Ronald and Nancy Reagan Institute Criteria for the neuropathology of

AD[28]. Another study on these subjects indicated that those individuals who had previously been diagnosed with MCI and progressed on to dementia revealed that most individuals had eventually progressed to the neuropathologic state of AD[32]. However, it is noteworthy that a significant proportion, perhaps 20 to 30%, progressed on to other forms of dementia or had other neuropathological explanations for their clinical state. As such, while clinical aMCI is very suggestive of AD, it does not constitute the pathological condition at that point in the clinical spectrum.

Summary

The construct of MCI has been expanded to include, conceptually, a prodromal form of virtually all dementias. While initially characterized as a memory disorder that was likely to lead to AD at an accelerated rate, the construct has been broadened to include other types of cognitive concerns and cognitive impairments. As such, while the aMCI subtype appears to be most prevalent, other forms can likely precede other dementing illness such as frontotemporal lobar degeneration, vascular cognitive impairment, and dementia with Lewy bodies. It remains to be determined if these subtypes of MCI are useful in predicting progression to these other types of dementia.

These data indicate that MCI is an active area of research. The epidemiology, clinical characterization and outcome studies imply that this is a common condition encountered in clinical practices, and as such, it is important for clinicians to identify these subjects. The criteria have been suggested and are being fine tuned by many investigators in the field. The challenges remain around the borders of the condition, i.e. between normal aging and early MCI and between MCI and clinical AD. However, with the advent of new neuroimaging techniques and biomarker studies, these transitional states may be clarified. As such, in the design of future clinical trials involving MCI, it might be quite reasonable to use aMCI clinical criteria of a suspected degenerative etiology and then augment this clinical judgment with, perhaps, genetic data such as Apolipoprotein ε4 carrier status, MRI structural measures, FDG-PET metabolism measures, CSF indices of Aβ42 and tau and, perhaps, amyloid imaging. All of these measures may enhance the specificity of the outcome of the clinical diagnosis of aMCI.

Ideally, of course, we do not want to just characterize people at the MCI stage. We would like to move our diagnostic criteria into the asymptomatic range to capture people who are clinically normal but at risk for developing AD in the future. As such, the proposed outline for enhancing the specificity of MCI could be applied to the asymptomatic stage of the aging continuum and enhance our ability to develop compounds to prevent the disorder before the destruction of neural tissue has occurred. These studies are now underway.

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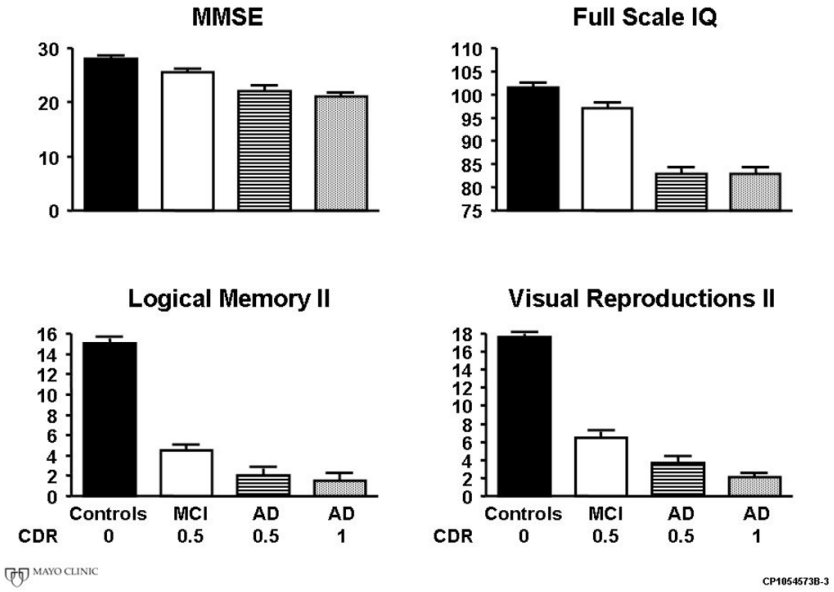

Figure 1.

Cognitive profile of typical subjects with MCI in comparison to normal aging and very mild AD. Reproduced with permission from the American Medical Association.

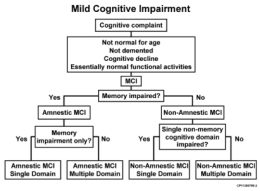

Figure 2.
Current algorithm used to classify the subtypes of MCI.

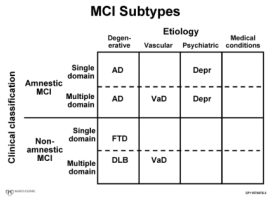

Figure 3.
The final diagnosis of MCI and its expected outcomes are characterized by a combination of the clinical syndromes and suspected etiology.