Mild cognitive impairment as a diagnostic entity

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The concept of cognitive impairment intervening between normal ageing and very early dementia has been in the literature for many years. Recently, the construct of mild cognitive impairment (MCI) has been proposed to designate an early, but abnormal, state of cognitive impairment. MCI has generated a great deal of research from both clinical and research perspectives. Numerous epidemiological studies have documented the accelerated rate of progression to dementia and Alzheimer’s disease (AD) in MCI subjects and certain predictor variables appear valid. However, there has been controversy regarding the precise definition of the concept and its implementation in various clinical settings. Clinical subtypes of MCI have been proposed to broaden the concept and include prodromal forms of a variety of dementias. It is suggested that the diagnosis of MCI can be made in a fashion similar to the clinical diagnoses of dementia and AD. An algorithm is presented to assist the clinician in identifying subjects and subclassifying them into the various types of MCI. By refining the criteria for MCI, clinical trials can be designed with appropriate inclusion and exclusion restrictions to allow for the investigation of therapeutics tailored for specific targets and populations.

Keywords: mild cognitive impairment, Alzheimer’s disease, aging.

Background

Increasing attention is being paid in recent years to the mild end of the cognitive spectrum spanning normal ageing to Alzheimer’s disease (AD). There likely is a transitional period between normal ageing and the diagnosis of clinically probable very early AD, and this transitional zone has been described using a variety of terms such as mild cognitive impairment (MCI), dementia prodrome, incipient dementia, isolated memory impairment, amongst others [1]. We will use the term, ‘mild cognitive impairment or MCI’, in the present discussion. In particular, we will discuss this construct as a diagnostic entity.

Cognitive continuum

The diagnosis of definite AD can only be made by neuropathological confirmation of persons who had been studied in life and met criteria for dementia [2]. However, the accuracy of the clinical–pathological correlation has been quite good when standard published criteria for the clinical diagnosis of AD are employed [3]. In Fig. 1, this conceptual scheme presumes that individuals are functioning normally as they age. In a subset of persons, in particular those who are destined to develop AD, there is a decline in cognitive function, which can be very subtle at first. Currently, the criteria for clinically probable AD identify people after a substantial
degree of cognitive decline has taken place. The construct of MCI proposes to identify these individuals at an earlier point in the cognitive decline such that if therapeutic interventions become available, clinicians can intervene at this juncture.

Another manner in which to view this continuum is shown in Fig. 2. This figure demonstrates MCI as interposed between the cognitive changes of normal ageing and what might constitute very early dementia. Note that there is overlap on both ends of the MCI bar indicating that the distinction between normal ageing and MCI can be quite subtle and, in addition, the specific transition between MCI and very early dementia can also be challenging. We will use this theoretical construct as a background against which to discuss the concept of MCI as a diagnostic entity.

The continuum outlined in Fig. 2 can apply to a variety of underlying dimensions. Most commonly, we refer to clinical criteria to distinguish between normal ageing and MCI and between MCI and dementia. One could also put measures of cognitive function such as neuropsychological testing, biomarkers or neuroimaging measures on this continuum as well. Presumably there are features of each of these measures that will help distinguish between normal ageing and MCI and MCI and dementia. It may ultimately be the case that a combination of measures, clinical features, neuropsychological testing, biomarkers and neuroimaging may be necessary to improve our diagnostic accuracy.

Terminology

Over the years, several terms have been used to describe an intermediate stage of cognitive impairment. Benign senescence forgetfulness was one of the initial descriptors of this concept, and this term was believed to be a variant of normal ageing [4]. In recent years, there has been a further study of this concept, and whilst it was originally felt to reflect a stage of normal ageing, more recent data have cast some doubt on that [5]. In 1986, an National Institute of Mental Health (NIMH) work group proposed the term, age-associated memory impairment (AAMI) and this concept was meant to characterize memory changes in ageing which were felt to be a manifestation of normal cognition [6]. These criteria referenced memory function in older individuals to the performance of younger adults and this proved to be problematical for a wider application of the term [7]. More recently, the term, ‘age-associated cognitive decline’ (AACD) has been proposed by individuals of the International Psychogeriatric Association to refer to multiple cognitive domains presumed to decline in normal ageing [8].

The Canadian Study of Health and Aging has used the term, ‘cognitive impairment no dementia’ (CIND), to characterize intermediate cognitive function of insufficient severity to constitute dementia [9]. This concept has been rather heterogeneous with regard to its inclusion of a variety of types of cognitive dysfunction, but more recently has been refined to correspond more closely to MCI [10].

Consequently, there have been a variety of terms used to discuss transitional stages between normal ageing and early dementia in the literature. MCI has come to be recognized as a pathological condition, i.e. not a manifestation of normal ageing, and has received a great deal of attention as a clinically useful entity.
Clinical characterization

There is no agreement in the field on a single set of criteria for MCI. A great deal of research is moving forward to characterize certain features of the construct and likely additional work will continue. In general, the concept of MCI refers to a group of individuals who have some cognitive impairment but of insufficient severity to constitute dementia. Usually these individuals have very slight degrees of functional impairment and most clinicians would have difficulty distinguishing these functional problems from those encountered by normal individuals as they age. The most important aspect of the criteria concerns the judgement on the part of the clinician that the person does not meet criteria for dementia. This represents a challenge in the field as there are no strict criteria as to the degree of functional impairment necessary to constitute a dementia.

Whilst there is not a consensus on set of criteria for MCI, when the studies are combined in aggregate, there does appear to be an increased risk of developing dementia relative to an age-matched normal population [11]. The most typical MCI patient is one who has a memory impairment beyond what is felt to be normal for age but is relatively intact in other cognitive domains. Most of the literature to date, however, pertains to those individuals with a memory impairment and, as such, it is useful to review these studies to determine the outcome of these individuals.

Outcome

As indicated above, with the increasing attention being paid to MCI, several studies have been conducted in recent years in a variety of research settings. At the Mayo Alzheimer’s Disease Research Center/Alzheimer’s Disease Patient Registry, a group of approximately 220 individuals of a mean age of 79 years has been followed for 3–6 years using the Mayo criteria [12]. The original Mayo criteria focused on a memory impairment with relative preservation of other cognitive domains. Specifically, these criteria were as follows: (i) memory complaint, preferably corroborated by an informant, (ii) objective memory impairment for age, (iii) relatively preserved general cognition for age, (iv) essentially intact activities of daily living, and (v) not demented. As will be discussed below, these criteria have since been expanded and refined but in their initial form serve as the set of data against which many other studies in the literature have been compared. Using these criteria, the subjects in the Mayo studies have progressed to dementia at a rate of approximately 12% per year [11]. This is in distinction to incidence rates from the same community which document a progression from normal to dementia at a rate of 1–2% per year. When these subjects are followed for up to 6 years, approximately 80% of them will have converted to dementia and consequently, this group represents a population at risk.

When individual measures are evaluated in the MCI group, the subjects tend to fall midway between individuals ageing normally in the community and those with very mild AD as is shown in Fig. 3. Similarly, the progression rates are intermediate between normal control subjects and those with very mild AD.

Mayo investigators have also evaluated a variety of measures which are thought to predict a more rapid progression to dementia. Amongst these apolipoprotein E4 allele carrier status has been one of the most prominent variables [13]. In addition, there is a trend towards abnormal performance on a cued memory task that predicts a more rapid progression and several neuroimaging measures such as volumetric measurements of the hippocampus have also been useful as predictors [14–16].

Tierney and colleagues in Toronto have followed a similar group of individuals who had been recruited from family doctor [17]. As these subjects were followed for 2 years, 29 individuals developed AD and 94 remained stable. They found that memory tests for delayed recall and an index of mental control were better predictors of progression and that apolipoprotein E4 carrier status was a reliable indicator only when combined with memory tests.

Investigators from the Alzheimer’s Disease Patient Registry in Seattle followed subjects for 5 years and found that slightly <50% of the subjects developed dementia over this period [18]. No individual memory test was felt to be better than any other.

The New York University research team using the Global Deterioration Scale followed subjects with a Global Deterioration Scale Rating of 3 which they felt represented a mild impairment [19]. Over a time span of 2 years, 32 of the subjects with a Global
Deterioration Scale of 3 were followed and 23 of them progressed to dementia.

In a study from Harvard, Daly and colleagues recruited a cohort of individuals through media advertisements and followed them longitudinally. These investigators used a modification of the Clinical Dementia Rating (CDR) to detect individuals who had subtle memory impairments [20]. This group demonstrated a progression rate of 6% per year which is somewhat lower than other studies. This lower rate may represent a combination of factors including the recruitment strategy using media advertising and the use of the CDR as the sole instrument for evaluation.

A study from France employed MCI criteria and criteria for AACD to evaluate a cohort of 833 subjects who had been followed longitudinally [21]. In this epidemiological study, the investigators retrospectively applied neuropsychologically based criteria to diagnose MCI and compared the outcome of those subjects with that of a group who met criteria for AACD. These investigators felt that MCI was an unstable construct and that the AACD subjects showed a higher conversion rate. However, the literal retrospective application of MCI criteria using neuropsychological cutoff scores likely contributed to the instability of these rates.

The PAQUID study from France also followed a population-based cohort 1265 subjects longitudinally [22]. These investigators found that overall MCI was a good predictor of progression to AD but also indicated that MCI may be unstable over time. These investigators used one neuropsychological test of nonverbal memory to characterize the memory impairment. As such, they found that 40% of their sample had reverted to normal and therefore concluded that MCI could be unstable. However, their use of a single nonverbal memory test may have also contributed to the instability and therefore, further refinement of the implementation of the memory criteria are needed.

The Religious Order Study is a research project concerning nuns and priests who constitute a volunteer cohort and are being followed longitudinally [23]. Investigators from Rush Alzheimer’s Disease Center followed 211 of these individuals and diagnosed them with MCI which included multiple domains of impairment in addition to memory. These subjects were followed for a mean of 4.5 years and the authors concluded that MCI subjects developed AD at a rate 3.1 times those subjects who did not meet criteria for MCI.

Investigators from the Cardiovascular Health Study applied criteria for the amnestic type of MCI (a-MCI) and multiple domain-MCI (md-MCI) to their sample and calculated prevalence figures [24]. They found that the overall MCI prevalence in the Pittsburgh site was 22% with a-MCI accounting for 6% and md-MCI representing 16%. These are the first population-based prevalence data on MCI subtypes.

The Canadian Study of Health and Aging evaluated separate features of the criteria for a-MCI from their CIND subjects to determine the relative contribution of each of the factors [10]. They concluded the subjective complaint and an impairment in instrumental activities of daily living may be
unnecessary for the definition of MCI; however, regardless of the definition, most people with MCI progress to dementia, mostly AD.

Investigators from Stockholm used the Kungsholmen Project to evaluate the outcome of subjects with their definition of CIND [based on Mini-Mental State Exam (MMSE) scores] [25]. They found an increased risk of developing dementia based on the level of severity of CIND and noted that those subjects who improved from CIND did not have an increased risk of subsequently progressing to dementia.

A decade ago, Dawe and colleagues reviewed the concept of MCI at that time and concluded that there was a wide discrepancy in rates of progression varying from 1 to 25% [26]. These investigators speculated that there were several factors contributing to this variability including the source of the subjects, specific criteria used, methods for implementing the criteria and length of follow-up. All of these issues remain relevant today.

A more recent review of MCI with recommendations for future research was recently reported by Lui and colleagues at Mt Sinai Medical Center in Miami [27]. They advocated for additional research to develop appropriate and sensitive neuropsychological and functional measures, reliable methods to assess progression, and epidemiologically oriented instruments that are sensitive to multiple cultures.

As is apparent from the literature, there is variability with regard to the characterization of subjects with MCI. Some of this variability relates to the source of the subjects, i.e. clinic based versus epidemiologically derived and also to the specific criteria employed as well as the implementation strategies. When one defines a memory impairment, there are numerous procedures that can be used to characterize these subjects and this likely contributes to differences amongst studies. Nevertheless, in spite of this apparent lack of agreement, there also is a relatively consistent pattern that indicates that subjects with MCI, however defined, are at an increased risk of developing dementia and consequently merit further study [28]. We will now turn to the issue of applying MCI criteria diagnostically.

Diagnosis of dementia and Alzheimer’s disease

To put MCI in perspective, we need to consider how we make other comparable clinical diagnoses, e.g. dementia and AD. If we consider the diagnosis of dementia or AD in the clinic, we can evaluate a typical set of criteria such as those in Diagnostic and Statistical Manual of Mental Disorders (DSM) IV [29]. The essential features of these criteria include: (i) memory impairment, (ii) aphasia and/or apraxia, agnosia or an impairment in executive function. In addition, these deficits must include a significant impairment in social or occupational functioning and constitute a change from a previous level of performance. They also need to exclude other psychiatric disorders or neurological explanations for the decline in function. Practically, the requirements for apraxia, agnosia, and executive dysfunction have been substituted with impairments in relevant cognitive domains such as language, attention/executive function, and visuospatial skills. These domains can be assessed by commonly used cognitive measures. At times other domains are also used such as problem-solving, constructional praxis or behavioural features, but, in general, any commonly accepted domain beyond memory is regarded as being sufficient for the diagnosis of AD. It is important to note that in addition to these cognitive impairments, there needs to be a concomitant impairment in functioning either socially or occupationally. These features constitute the hallmarks of AD.

Most clinicians are well familiar with these criteria and make this diagnosis on a regular basis. A recent evidence-based medicine review of the literature on the validity of the criteria for dementia and AD demonstrated that these criteria and other variations of them are quite accurate in identifying AD clinically when the diagnosis is confirmed with postmortem analysis [30]. As such, the criteria are valid. Although, as will be discussed later, it is likely that these criteria are more precise when applied in the clinic setting than in epidemiological field work.

The most relevant issue concerning these criteria for the present purposes relates to the manner in which they are operationalized. Certainly, the DSM-IV criteria are quite open with respect to the manner in which the criteria are to be met. Specifically, cognitive functions are mentioned but not specified, e.g. agnosia, and certainly instruments or cutoff scores are not designated. The National Institute of Neurologic and Communicative Disorders and Stroke (NINCDS) and Alzheimer’s Disease and Related Disorders Association (ADRDA) criteria are somewhat more specific insofar as they indicate
that the diagnosis of AD can be established by mental status testing and confirmed by neuropsychological tests [31]. This is a bit more precise but also stops short of specifying particular instruments and cutoff scores.

This approach to the diagnosis of AD is quite reasonable. It would be virtually impossible for the clinical/scientific community to agree upon domains, instruments and cutoff scores for cognition and equally problematic for social or occupational function impairments. Therefore, the assumption is that clinicians will use their experience and instruments of their choosing to make these judgements. As indicated above, these decisions have been quite accurate.

In addition, in the setting of presumed AD, the aetiology of the clinical disorder is assumed to be degeneration. This is accounted for in the criteria by statements concerning the gradual onset and progression of symptoms. In the more general situation the diagnosis of dementia using criteria such as those found in DSM-III-R or in DSM-IV, criteria are presented for the cognitive impairment in multiple domains in addition to a functional impairment component. These criteria do not include any statements about the nature of the onset or the course of the progression. Rather, in these instances once the diagnosis of a general dementia has been made, one searches for potential aetiologies by evaluating the nature of the onset, time course, variability in cognitive presentation, etc. Occasionally, ancillary tests such as laboratory studies and imaging procedures can contribute to the differential diagnosis of the dementia. These data then in combination lead to the conclusion that the dementia is based on a degenerative process, e.g. AD, frontotemporal dementia, dementia with Lewy bodies or a vascular basis such as in vascular dementia. The diagnosis is essentially made in a two-step procedure with the clinical determination of dementia emerging first, followed by the aetiology of the dementia. This would be a typical approach to the diagnosis of a dementing condition made by most clinicians. Again, this approach has been shown to be quite accurate.

As research on MCI has advanced, it has become apparent that several clinical subtypes of MCI exist [1, 32]. Most research has focused on the a-MCI but other types have been recognized as well. A second type of MCI called md-MCI involves various degrees of impairment in multiple cognitive domains such as language, executive function and visuospatial skills with or without a memory impairment. Those with a memory impairment (amnesia) are labelled md-MCI + a and those without are labelled md-MCI – a. This distinction becomes relevant when one discusses the outcomes of subjects with MCI. The third, and least common type of MCI, is single nonmemory domain MCI in which a person has an impairment in a single nonmemory cognitive domain such as language, executive function or visuospatial skills. These subjects likely have a different outcome from those with a memory impairment. It is also imperative that all of these clinical subtypes of MCI have minimal impairments in functional activities, i.e. do not represent a significant change in function from a prior level, and do not meet criteria for dementia.

In addition to the clinical subtypes, there can also be multiple aetiologies or causes for each subtype as depicted in Fig. 4. Therefore, if one selected the a-MCI subtype of a presumed degenerative aetiology, this would likely represent a prodromal form of AD. However, one could also add the subtype of md-MCI + a since this subtype has a high likelihood of progressing to AD also [33]. However, the other subtypes such as those emphasizing impairments in nonmemory domains such as executive function and visuospatial skills, may have a higher likelihood of progressing to a non-AD dementia such as dementia with Lewy bodies [34]. Therefore, the combination of clinical subtypes and putative aetiologies can be useful in predicting the ultimate type of dementia to which these persons will evolve.

Fig. 4 Classification of clinical subtypes of mild cognitive impairment with presumed aetiology (with permission from Ref. [1].
Application of amnestic MCI criteria

If we now consider the proposed approach for making the diagnosis of a-MCI, we can consider a parallel set of procedures to those used for making the diagnosis of AD. The criteria for a-MCI are shown in Table 1. In a fashion similar to that used for the DSM-IV or the NINCDS/ADRDA criteria for AD, the MCI criteria can be implemented. The first criterion refers to the subjective memory complaint. This is meant to capture the notion of a change in performance. Ideally this should be corroborated by an informant, but occasionally this can be difficult. This criterion is ‘soft’ and may be a challenge to implement, but without prior cognitive function testing, it is critical for the purpose of excluding individuals with lifelong static cognitive deficits [9].

The second criterion refers to an objective memory impairment for age. This has been a major source of contention in the literature. This criterion can be fulfilled with the assistance of neuropsychological testing, but once again, no particular test or cutoff score is specified. Rather, this was left to the judgement of the clinician in the appropriate clinical context. In the literature, the cutoff score of 1.5 SD below age norms has been suggested by some investigators. In the original description of the MCI cohort followed at the Mayo Clinic, the MCI group’s mean performance was 1.5 SD below their age-mates. However, this was not a cutoff score, and of course, nearly half of the group had memory performance score falling somewhat <1.5 SD below the mean. This criterion should be interpreted in conjunction with the first criterion. The memory complaint is meant to represent a change in function for the person. The second criterion corroborates the complaint by attesting to an actual impairment in performance. The clinician may be challenged by persons who are of either high intellect whose performance is now in the statistically ‘normal’ range, but this level of performance represents a change for that person, and by the person with a low education whose lower cognitive performance may not represent a change. However, the preferable approach to this challenge is to allow the clinician to use judgement in combining all of these criteria. A precise history from the patient and an informant coupled with neuropsychological testing can be invaluable.

The third criterion regarding general intellectual function can be interpreted in a comparable fashion. General intellectual function refers to the other nonmemory cognitive domains, e.g. language, executive function, visuospatial skills, in a fashion similar to the constructs of apraxia and agnosia were used in the diagnosis of AD. Here again, performance in these domains should be judged relative to age-appropriate standards, but no specific instruments or cutoff scores are predetermined. Neuropsychological testing can be very useful in this context in making these determinations, but ultimately, the judgement of the clinician is required.

The essentially normal activities of daily living criterion can be fulfilled largely through a history from the subject and preferably from an informant as well. Several activities of daily living scales are available to assist in this determination, but just as is done with the dementia history, the degree of impairment is a clinical judgement [35]. Often there are minor inconveniences in daily function because of the memory deficit, but these are generally believed to be of insufficient severity to constitute a major disability. This also, however, can be a difficult judgement especially with older subjects. The criterion requires that the functional impairment be due to the cognitive reasons, and this can be difficult to determine in older subjects who may have several medical comorbidities and physical limitations. This underscores the necessity of a clinical assimilation of all of the data available.

Finally, the last criterion, ‘not demented’, is also made on the basis of the clinician’s best judgement. This results from a combination of the assessment of criteria 1–4 and hinges on the degree of functional impairment. Many of these subjects will have a slight degree of general cognitive impairment, but it will not be of sufficient magnitude to be clinically significant. Similarly, there may be some functional impairment, but in the setting of medical comorbidities, this impairment is best judged to be not due to cognitive dysfunction and is sufficiently minor. In general, these subjects appear more normal than not. The difficult

Table 1 Criteria for amnestic mild cognitive impairment (a-MCI)

| Memory complaint usually corroborated by an informant |
| Objective memory impairment for age |
| Essentially preserved general cognitive function |
| Largely intact functional activities |
| Not demented |

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distinction is between normal ageing and MCI rather than between MCI and AD.

As one can see, the application of the MCI criteria is very similar to that employed for the diagnosis of dementia or AD. The fundamental change involves a shift in threshold of cognitive impairment that the clinician is willing to recognize. This presents a challenge for all of us insofar as the standards for normal ageing, as will be discussed below, can be difficult to determine. In the older subjects, a degree of memory impairment is frequently seen and felt to be associated with ageing and consequently, the demarcation between normal ageing and early MCI can be a clinical challenge. Nevertheless, the concept is reasonable and several multicentre studies have now documented that these criteria can be implemented on a reliable basis across institutions [35].

Proposed diagnostic scheme

To consider a procedure for generating a diagnosis of MCI in a new patient, Fig. 5 may help to guide the diagnostic process. Ultimately this scheme will lead to the classification outlined in Fig. 4. Presuming a person or another individual with knowledge about the person expresses some concern about the person’s cognitive function, the doctor must make a judgement. Based on the history and a mental status exam, the doctor makes a judgement as to normal cognition or suspected dementia. For example, if the person has a clear impairment in functional activities and scores 20 of 30 on the MMSE, this person will likely be demented. Although, if the person scores 29 of 30 on the MMSE and shows no impairments in complex activities of daily living, despite the subjective complaint, the person may be normal. Of course, other explanations for this cognitive complaint, such as depression, must also be entertained. There are many instances, however, in which a clinician is uncertain as to the precise cognitive status of the person and may entertain the diagnosis of MCI. In this instance, the diagram in Fig. 5 may help the diagnostic process [36].

Once the clinician has determined that the person is neither normal nor demented, the next decision involves assessing a decline in function. This is done through a careful history from the patient and preferably a collateral source. If there is evidence for a decline in cognition, the clinician must then determine if this change in cognition constitutes a significant impairment in functional activities such that the person might be considered for having a very mild dementia. However, if the functional impairment is not significant, the clinician may entertain the diagnosis of MCI and the next task is to identify the clinical subtype. The clinician should next assess memory more carefully, perhaps with a word list learning procedure or paragraph recall. There are no generally accepted instruments for this determination, and neuropsychological testing may be useful.

If the clinician determines that a significant memory impairment is present, the person is described as having a-MCI with a memory impairment. However, if no memory impairment is present then the person has non amnestic MCI (na MCI). The next step in the process is to determine if the person has an isolated cognitive domain impairment or not. Therefore, if the person has a-MCI, the clinician needs to assess other cognitive domains such as language, attention/executive function or visuospatial skills, to determine if the impairment is just memory or involves other domains as well and hence is a-MCI-multiple domain. If memory is the only domain impaired in a relative sense, then the classification is a-MCI-single domain. If other domains are impaired in addition to memory, the classification is a-MCI-multiple domain. Similarly, if memory is not impaired, na-MCI is the classification, and again the determination is then made of either a single nonmemory domain or multiple nonmemory domains being impaired yielding na-MCI-single domain or na-MCI-multiple domain, respectively. This classification scheme will serve of heuristic value to

Fig. 5 Flow chart of decision process for making diagnosis of subtypes of mild cognitive impairment (with permission from Ref. [36].

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determine the ultimate outcome of these four subtypes of MCI.

Variability in the literature

As research on MCI progresses, several areas of controversy have arisen. Some studies have used alternate criteria for MCI leading to variable results. In particular, the operationalization of the criteria have led to mixed results. Longitudinal studies have differed on their outcomes and follow-up characteristics.

Rating scales

Whilst the criteria outlined in Table 1 represent commonly accepted guidelines for a-MCI, these recommendations are by no means universally accepted. It is not uncommon for research groups to substitute various stages on rating scales as equivalent to the clinical diagnosis of MCI. This can lead to difficulties. A commonly used instrument in research on ageing dementia is the CDR [37, 38]. The CDR is a rating scale ranging from normal (CDR 0) to questionable dementia (CDR 0.5) and ultimately to varying stages of dementia, mild (CDR 1), moderate (CDR 2) and severe (CDR 3). Some research studies have equated a CDR 0.5 to MCI; however, it should be noted that the CDR is a severity rating scale and not a diagnostic instrument. Therefore, subjects with a CDR of 0.5 may meet the criteria stated above for MCI or they may represent very mild AD. This can have implications for the interpretation of progression of subjects. For example, in clinical trials, some studies have enrolled subjects with MCI and used progression to AD as a primary outcome [39]. Other studies have proposed progression along the CDR from 0.5 to 1. This is fundamentally different, however, as the clinical classification of AD may reside in the CDR of 0.5 or 1. Therefore, if one uses the clinical progression from MCI to AD as the outcome measure, the subject may still remain in a CDR 0.5 category.

Similarly, the Global Deterioration Scale (GDS) is another commonly used severity rating scale for dementia [40]. On the GDS, a score of 1 or 2 represents variations of normal function with and without a subjective complaint, respectively. Higher stages of GDS from 3 to 7 represent varying stages of increasing degree of cognitive impairment. In this scale, a GDS of 3 can represent either MCI or AD in much the similar fashion as a CDR of 0.5. Consequently, if the research group characterizes their subjects as having a GDS 3, one is not certain if they are referring to subjects of similar MCI category or mild AD [19, 41, 42].

Therefore, whilst rating scales can be useful in certain settings, they also have inherent limitations and should not be confused for the operational equivalent of clinical criteria. This can cause confusion in the literature.

Normal reference standards

A great deal of clinical judgement is involved in making a decision concerning normal versus MCI. Inherent in this decision is a discussion of what is ‘normal’ as a reference point. Normal performance can be viewed from a variety of perspectives including, amongst others, optimally normal, typically or statistically normal. Some groups have studied individuals who are ageing optimally [43]. These subjects have been selected from those elderly individuals who are relatively devoid of comorbid illnesses. This is a reasonable approach to studying optimal health and characterizing potential performance of individuals. This approach can lead to the inference that any decline in performance is due to some disease, yet studies often demonstrate that even in the absence of significant disease, some cognitive decline is inevitable.

Another approach is to study typical or statistically normal subjects [44]. In this instance, criteria for normal function are identified similar to those used in the Mayo research studies: (i) no active neurological or psychiatric disease, (ii) no psychotropic medications, and (iii) the subjects may have medical disorders but neither they nor their treatment compromise cognitive function. This group of reference subjects constitutes a typical ageing cohort but it must be recognized that these subjects may also be experiencing slight cognitive impairments. A question arises as to whether these cognitive impairments are associated with disease or the ageing process itself.

The NIMH work group in the mid-1980s suggested using young normals’ performance as a reference point [6]. This position assumed that any change in performance relative to young normals represented a change because of ageing. However, subsequent research has documented that depending...
upon which instrument and measures were chosen, one could classify up to 90% of all older individuals as having AAMI [7, 45].

Finally, some investigators have argued that a change in performance is an index of abnormal function [46]. This position assumes that normal subjects will remain stable or improved over time but any decline likely represents incipient disease. The difficulty with this position is that the course of change in normal subjects is variable and may be instrument-dependent. Some research has indicated that repeated testing of normal subjects results in improved performance, at least initially [47].

None of these approaches to defining normal performance in ageing is absolutely right or wrong. Each reflects a different position for characterizing performance. Many research groups use a variation of age-adjusted normative neuropsychology data to gauge impairment. Some argue that this approach results in an underassessment of impaired performance as most normal subject groups include incipient cases of dementia who are going to develop the full manifestation of the disease process in ensuing years [48]. Counter arguments claim that this effect is minimal [45]. At present, there is no definite solution to this problem, but readers of the literature need to be aware of the set of assumptions being employed in any research study.

Source of subjects

A third component of the variability with regard to studies in the literature pertains to the sources of subjects for a particular study. A great deal of literature on MCI has been generated from clinical settings such as dementia or memory disorders clinics [12, 17–20]. This rather constrained environment has several implications for the outcomes of these studies. The referral nature of these clinics predisposes to a certain type of patient population. Depending upon the recruitment mechanism of the clinic, certain preselction criteria may be in place, which may lead to recruiting subjects who may have a degenerative aetiology of their symptoms. Cases, which are ‘messy’, such as those involving trauma or substance abuse, may be excluded. As such, the resultant cohort might be ‘cleaner’ than a community-based sample. In addition, these subjects may have a cognitive complaint or their problems may have been brought to the attention of family members who are concerned about the subject’s cognitive function. There may be a higher representation of cases with a positive family history for dementia as well.

On the contrary, cases recruited in these settings may get more thorough evaluations including extensive histories from the subject and an informant as well as detailed neuropsychological testing and a variety of neuroimaging studies. This evaluation may lead to more precise diagnoses and a possible careful classification of MCI subtypes. Presumably, this may also lead to a more pure culture of cases with greater stability in their outcome.

Alternatively, if the MCI cases are derived from an epidemiological study, other considerations apply [21, 22, 49]. For example, by definition there is no restriction on the nature of the sample. If it is a truly random sample of certain age groups, there will likely be multiple types, degrees and causes of cognitive impairment encountered. As such, this type of study must be capable of addressing clinical heterogeneity and determining which types of cognitive impairment may lead to various forms of dementing illnesses. Therefore, in certain respects, the challenge is greater for the epidemiological studies, yet the tools of evaluation may be somewhat limited. Since the study of large populations requires relatively brief assessments with screening batteries, questionnaires and assessment techniques, the breadth of the data may be somewhat compromised. This is not a criticism of the investigators performing the studies; rather, it is a result of the research environment. Out of necessity, less thorough examinations need to be done because of the large number of evaluations that must be carried out. These are generally carried out by very skilled research staffs who are trained at performing screening evaluations on large cohorts of subjects as opposed to making fine clinical discriminations as may be required in the setting of MCI.

Consequently, whilst the sources of subjects can be very important for the outcome of the study, this factor is likely confounded with the nature of the evaluation procedures. In the clinic setting, the subjects may be subtly preselected to yield a certain type of presentation, and the subjects likely undergo very thorough evaluations by expert clinicians. In the field study, there is likely to be more heterogeneity in the subject population and out of necessity, the evaluations must be somewhat more cursory.
Therefore, since the studies from the two settings are being performed for different purposes, the outcomes are likely to be different.

One example of this may manifest itself in the longitudinal outcome rates of the various studies. Clinic-based longitudinal studies of MCI cohorts report instability rates in the range of 10%; whereas population-based studies show instability rates of 25–40% in various studies [21, 22, 49]. It should be noted, however, that just because the population-based study shows instability on the short-term basis, this does not mean that the construct under investigation or the criteria used are necessarily inaccurate. It may well be the case that the population-based studies with their less precise clinical diagnostic tools may show more year-to-year variation, but these subjects will eventually decline in longitudinal follow-up. Therefore, one should be cautious in concluding prematurely that the construct based on these findings is unstable. Greater longitudinal follow-up will be necessary to document the eventual fate of these subjects.

Conclusion

In summary, MCI represents a useful clinical entity. Most practitioners recognize persons in their clinical practices who meet criteria for MCI. The challenge is to help the clinicians revise their thresholds for detecting subtle cognitive impairments to enable them to identify persons with suspected MCI. It is most important to realize that MCI is a clinical diagnosis which is the same as are the diagnoses of dementia or AD. Whilst cognitive tests and functional measures are very useful, ultimately, the final determination relies on the clinician’s judgement. The procedures outlined here were designed to assist in that process.

As the field matures, we will learn more about the various subtypes of MCI and their ability to predict various forms of cognitive impairment. Hopefully, as therapeutic interventions become available, we will be able to tailor treatments for specific prodromal forms of cognitive impairment and dementia.

Conflict of interest statement

No conflict of interest was declared. Dr Petersen is a consultant to Elan Pharmaceutical Co. and GE Global Research.

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