Issues to Consider When Using the New Diagnosis of Mild Cognitive Impairment

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Much attention has been focused in recent years on the concept of Mild Cognitive Impairment. The term MCI is generally used to refer to a transitional phase between normal cognitive functioning and dementia, most often clinically probable Alzheimer's disease [1]. A recent report of the International Working Group on Mild Cognitive Impairment suggests that the various terms used to describe this phase are essentially common. They all refer to non-demented persons with cognitive deficits that can be measured in some form or another, and represent a clinical syndrome that can be utilized to classify persons who do not fulfill a diagnosis of dementia but who have a high risk of progressing to a dementia disorder [2].

As the diagnosis of MCI is becoming more and more accepted in clinical use, several important practical and ethical considerations should be addressed. The first question that arises is whether such a diagnostic entity actually exists. This issue has been hotly debated for the past several decades with the recent acceptance of the MCI concept put forth by the Mayo Clinic [3]. Nevertheless, clinicians should be aware of the difficulties involved in attempting to make a precise diagnosis or choosing the necessary auxiliary diagnostic tests [4]. Secondly, clinicians must also consider issues related to certainty of prognosis. If we cannot predict prognosis, what is the merit of diagnosis? Is it right to provide one? Thirdly, if prognosis is unclear, what treatment should be offered? That is, if not every individual with MCI will eventually develop dementia, let alone Alzheimer's disease, and yet no approved treatment for MCI is currently available, is it right to offer the accepted medication for Alzheimer's disease (as suggested by some clinicians)? Finally there is the issue of legal competence. Although a diagnosis of MCI cannot by itself determine whether a person is legally incompetent, once it appears in a person's file it may be used against that person. Each of these four main issues is discussed below.

Diagnosis

For a diagnosis to be useful it must be valid. A brief history of the concept of MCI sheds light on some of the issues that deserve attention when appraising this concept. Kral [5] introduced the notion of Benign Senescent Forgetfulness, referring to elderly individuals who were unable to recall information such as a name or a date but were able to recall that they forgot that information. It was believed that this memory disturbance progressed slowly or not at all and did not have a major effect on daily functioning and personality, and therefore it was considered a variant of normal aging. In 1986, the term Age-Associated Memory Impairment (AAMI) was proposed, referring to memory changes in older individuals measured against memory of young adults [6]. The notion of Aging-Associated Cognitive Decline (AACD) was introduced next [7] to include cognitive domains other than memory. Both Age-Associated Memory Impairment and Aging-Associated Cognitive Decline did not draw the line between normal aging and incipient dementia. Further attempts to characterize cognitive function of insufficient severity to constitute dementia were presented by the term Cognitive Impairment-No Dementia (CIND), developed by the Canadian Study of Health and Aging [8]. Although differentiating normal aging from preclinical dementia is far from simple, failing to identify pathologic processes prevents their treatment, leaving these concepts somewhat moot.

The recent introduction of the Mayo criteria for MCI [3] clarified some of the controversy by declaring that the relevant comparison group for establishing a deficit must be of the same age as the individual. MCI thus describes a pathologic rather than a normal process. Originally, the Mayo 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 [3]. There is disagreement in the literature as to whether MCI represents a homogenous clinical syndrome in terms of its neuropsychological profile [9] and more than one clinical subtype of MCI has been identified (i.e., amnestic, single non-memory domain, multiple-domain with or without amnesia) [1,2]. Note that the nosologic status of MCI is not yet reflected in current psychiatric classifications, which use terms primarily intended to refer to other conditions, such as Mild Cognitive Disorder [10] and Mild Neurocognitive Disorder [11], or terms that offer no operational criteria, such as Age-Related Cognitive Decline [11].

Controversy exists regarding how to best assess MCI, partly because there is insufficient evidence to recommend specific

MCI = mild cognitive impairment

tests and/or cutoff scores [2]. Even though cutoff scores have been suggested to differentiate MCI from normal aging (e.g., 1.5 standard deviations below the mean of memory performance within the appropriate age group) [2], much is left to the judgment of the clinician since the applicability of this cutoff to the individual patient is problematic [12]. Moreover, deficits must not be so prevalent as to warrant a diagnosis of dementia, but the fine line between MCI and early-stage dementia is debatable and some authors believe that individuals with MCI are already at the early stages of Alzheimer's disease [13,14]. In fact, Alzheimer's disease may be viewed as a progressive and malignant chronic disease in which latent, preclinical phases precede many years prior to manifestation of the accepted clinical symptoms [15].

The screening process for MCI raises some important questions as well. A comprehensive neuropsychological assessment is recommended, yet it is time consuming and not necessarily appropriate for every individual because it requires full cooperation and a good mastery of the language of testing. It has been suggested that neuroimaging techniques, such as magnetic resonance imaging, SPECT, and PET, should become an essential part of the general evaluation of MCI [2]. In addition, cerebrospinal fluid markers (e.g., total tau, phospho tau and the 42 amino acid form of beta-amyloid) may differentiate early and incipient Alzheimer's disease from normal aging and certain other dementia types [16,17]. Several prognostic genes (e.g., the APOE epsilon 4 allele) are associated with a greater likelihood of progressing from MCI to Alzheimer's disease [18,19], although this is not unanimously agreed upon [20,21]. The combination of neuropsychological evaluation, neuroimaging, genetic tests, and a CSF marker investigation might offer the most comprehensive understanding of a specific individual with MCI [2]. Nevertheless, the question arises as to whether every person who is being evaluated for MCI must be subjected to any or all of those expensive, potentially risky, or experimental procedures.

Although difficult to apply at times, a clinically useful concept can facilitate early detection, offering the opportunity to further investigate treatment options. It may thus be valuable to diagnose individuals with MCI if only for research purposes.

Prognosis

While MCI may be common, it constitutes a challenge to epidemiologic studies [22], and data are limited with regard to its incidence. A recent study found that of 806 cognitively healthy elderly persons, 66 individuals (8.8%) converted to MCI during a 3 year follow-up, and the global incidence rate of MCI in the 60–76 age group was 25.94/1,000 person-years [23]. Reported prevalence ranges widely and depends to a large degree on the criteria being used and whether test scores are adjusted for age. Kumar et al. [24] report that prevalence rate varies up to sixfold according to the applied diagnostic criteria, with limited overlap between diagnoses, ranging from 3 to 36% [25]. Approximately 80% of individuals who meet the Mayo criteria for MCI will convert to dementia within 6 years [26]. In clinical populations the yearly conversion rate to dementia is 10–15% [27], while community-based studies tend to show lower rates of about 5–10% [28,29]. In view of the fact that prognosis cannot be predicted with sufficient precision, is it right to make a diagnosis?

To further complicate the matter, no adequate distinction between syndrome and etiology has been defined in MCI [30] so that MCI can be caused by various etiologies, such as degenerative, vascular, metabolic, or trauma [31]. Moreover, the currently available criteria for MCI do not sufficiently address emotional aspects, although psychiatric disturbances and MCI are not necessarily mutually exclusive [32]. The heterogeneity of clinical symptoms and etiology makes it difficult to predict prognosis for the individual person. Though many individuals with MCI will eventually develop dementia, not all of them will, some may be stable or may even recover, and those who develop dementia may differ in dementia type [33,34]. The lack of prognostic prediction undermines the usefulness of diagnosis and makes it difficult to use preventive measures or offer the most appropriate treatment.

Once a person is diagnosed with MCI, legal competence is at stake

Treatment

The main rationale for early detection of deficit is to offer early treatment. No medication has yet been approved for MCI. If MCI were indeed early-stage Alzheimer's disease, then the medications approved for Alzheimer's disease (e.g., cholinesterase inhibitors, memantine) would be appropriate – if not for recovery then for inhibiting disease progress. However, there is no evidence for long-term efficacy of pharmacologic treatments in MCI [35–37] and only modest evidence for symptomatic treatment efficacy in Alzheimer's [2]. Cost considerations impose limitations upon the prescription of these medications (e.g., a well-established diagnosis of Alzheimer's disease, specified degrees of severity, exclusion of concomitant physical or psychiatric disorders). In fact, the cost-effectiveness of donepezil (a cholinesterase inhibitor) is being seriously challenged in reference to Alzheimer's disease [38]. As for MCI, a recent report of the first 24 week trial of donepezil versus placebo in 270 individuals with amnestic MCI found no significant difference in the primary efficacy measures (e.g., a test of paragraph delayed recall, and the clinician's global impression of change), though some of the secondary cognitive measures (e.g., attention and psychomotor speed), as well as the subjective patient global assessment, showed a favorable effect for donepezil [35]. The lack of clear-cut results in that study might have been due to the

SPECT = single photon electron computed tomography
PET = positron emission tomography
CSF = cerebrospinal fluid

inclusion of patients with various etiologies, or to the fact that in those early stages the cholinergic systems presumably affected by donepezil are nearly intact [36]. Petersen and colleagues [37] have just reported a 3 year longitudinal double-blind study in which persons with the amnestic type of MCI were given 2,000 IU of vitamin E daily, 10 mg of donepezil daily, or placebo. Vitamin E had no beneficial effect on MCI, while donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first year of treatment. However, after 3 years, rates of progression to Alzheimer's were equal in the donepezil and placebo groups.

In addition, virtually all medications have potential side effects. Even though the side effects of cholinesterase inhibitors are considered minor (e.g., diarrhea, nausea, vomiting), many participants in the study by Salloway and co-workers [35] developed adverse effects that led to their withdrawal from the study (i.e., 22% of 133 in the donepezil group and 7.3% of 137 in the placebo group). It is important to note that patients with poorly controlled diabetes or other medical conditions were not included in that study and participants were generally healthy. In the study by Petersen et al. [37], diarrhea, muscle cramps, insomnia, nausea, abnormal dreams, loose stools, vomiting, and arthritis were significantly more common in the donepezil group compared to the placebo group, and those side effects led to a greater rate of treatment discontinuation. In light of these findings, should these medications be given to the usually non-selected clinical population who present with a plethora of medical problems?

In some cases, patients or their relatives might be "pushing" toward a diagnosis for which there is some official remedy (namely, Alzheimer) over a label of MCI for which no officially prescribed medication exists. How firm should the diagnosis of MCI be held in such instances? Professionals and families share the understandable human desire "to do something." As long as some treatment options are commercially available, and despite their low efficacy, if any, can these treatments be withheld from those who demand them? It is our belief that in elderly people who show no cognitive impairment, the "cosmetic" use of the above-mentioned drugs as mentation enhancers [39] is to be avoided. Such people should be followed and treated for other possible disturbances (e.g., emotional) and offered to enroll in new drug studies when appropriate.

At present, most individuals with MCI who are referred to specialist clinics receive various combinations of antioxidants, statins, anti-aggregants, vitamins, antidepressants, and/or treatments for hypertension, diabetes, or elevated blood lipids already prior to referral. Beyond diagnosis, the reasons for referral to a specialist clinic usually involve a request for "anti-Alzheimer" medication or a search for the most innovative treatments in the field. At this stage, major medical care should focus on exclusion of treatable causes of cognitive impairment and modifiable risk factors (e.g., vascular), as well as on treatment of behavioral and/or psychiatric symptoms. Longitudinal assessment and reevaluation of cognitive state must also be conducted in order to detect the very beginning of Alzheimer's disease and then offer the appropriate medication.

Competence

Once the term MCI is used, other concerns arise that involve the ability to make informed decisions regarding medical care, participation in research, financial decisions, or driving. Such decisions require legal capacity, which might be in question if a diagnosis of MCI is being made. In the case of dementia patients, a family member is often asked to co-sign an informed consent to participate in research along with the patient, a guardian may be nominated, and a driving competency evaluation may be scheduled. What should happen with persons suffering from MCI in whom activities of daily living are by definition not impaired or only minimally affected?

As in other cases, the clinician who sees a person with MCI might face the uncomfortable position of maintaining confidentiality in the delivery of medical care, while being called on by society to report suspected incompetence in a certain field (e.g., driving). Very little research has been dedicated to the question of competence in MCI. However, when financial capacity was assessed directly, individuals with amnestic MCI demonstrated impairments across a range of financial abilities (e.g., financial conceptual knowledge, bank statement management, bill payment skills) [40]. Currently, these domains are not directly evaluated in most standard assessments of instrumental activities of daily living, although it is highly likely that the results of such assessments will change our conception of everyday functioning in MCI.

At the same time, cognitive and functional decline documented by standard tests does not by itself make a person legally incompetent, and task-specific questions must be addressed according to local administrative and legislative ruling. For some competence issues the legal standard is quite low. For example, a testator/testatrix does not have to demonstrate intact cognitive abilities in all domains but has to merely be able to grasp the nature of a will, to know the extent of his/her assets, to recognize his/her legal heirs, and to appreciate the effect that his/her decisions may have on these heirs. Such requirements mean that even individuals with dementia might be considered competent to compose a will. Nevertheless, once the diagnosis of MCI has been placed in a person's file, those who wish to contest the validity of the will may use it to challenge the person's competence. Thus, the supposedly purely medical diagnostic decision might have far-reaching legal implications.

Final comments

People seek professional advice because they are bothered by something and wish to know what is wrong. On the one hand, if we cannot tell them what to expect or offer appropriate treatment, is it practical or ethical to provide a diagnosis? On the other hand, once some information is available concerning a person's condition, it cannot be withheld from him/her. Furthermore, finding that a person is not demented yet, even if the condition may evolve into dementia at an unexpected rate, can provide some comfort for the person and the family, and may offer them enough time to make the necessary arrangements for

further deterioration (e.g., a living-will, Power of Attorney, etc.). While we believe that there are no clear answers to all the questions raised above, their explicit discussion with patients, relatives, and colleagues, as well as clinicians' awareness of this discussion, is important in itself.

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