

KEY SYMPOSIUM

Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment

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Abstract. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund L-O, Nordberg A, Bäckman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC (Karolinska Institutet, Stockholm, Sweden; Johns Hopkins University School of Medicine, Baltimore, MD, USA; Tohoku University Graduate School of Medicine Sendai, Miyagi, Japan; Uppsala University, Sweden; Gothenburg University, Sweden; New York University School of Medicine, New York, NY, USA; University of California at Davis, Sacramento, CA, USA; Helsinki University Hospital, Helsinki, Finland; University of Geneva Medical School, Switzerland; National Institute on Aging/National Institute of Health, Bethesda, MD, USA; Mayo Clinic, Rochester,

MN, USA; Australian National University, Canberra, Australia; French National Institute of Medical Research (INSERM), Montpellier, France; Erasmus Medical Center, Rotterdam, The Netherlands; University of Maastricht, The Netherlands). Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment (Key Symposium). *J Intern Med* 2004; 256: 240–246.

The First Key Symposium was held in Stockholm, Sweden, 2–5 September 2003. The aim of the symposium was to integrate clinical and epidemiological perspectives on the topic of Mild Cognitive Impairment (MCI). A multidisciplinary, international group of experts discussed the current status and future directions of MCI, with regard to clinical presenta-

tion, cognitive and functional assessment, and the role of neuroimaging, biomarkers and genetics. Agreement on new perspectives, as well as recommendations for management and future research were discussed by the international working group. The specific recommendations for the general MCI criteria include the following: (i) the person is neither normal nor demented; (ii) there is evidence of cognitive deterioration shown by either objectively

measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; and (iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired.

Keywords: MCI, consensus, mild cognitive impairment, definition, clinical criteria, pre-clinical dementia, Alzheimer's disease.

Mild cognitive impairment (MCI) was the topic of the First Key Symposium held in Stockholm, Sweden, 2–5 September 2003, and supported by The Royal Swedish Academy of Sciences and the *Journal of Internal Medicine*. The aim of the symposium was to integrate clinical and epidemiological perspectives in discussing current concepts in MCI and to identify pertinent questions for future research.

A multidisciplinary and a worldwide group of experts from Asia, Australia, Europe and North America participated in the meeting. During the first day and a half, five topics were debated by three experts: one main speaker, and a clinical and epidemiological discussant. The topics covered clinical presentation, cognitive profiles, genetics, neuroimaging and biomarkers. Following this, a day of discussion on the topics was conducted with the speakers, discussants, chairpersons and symposium's Scientific Committee. The current status of MCI and new perspective discussed at the meeting are summarized here, in addition to recommendations for management, treatment and future research.

Clinical presentation

Current status

The term MCI is generally used to refer to a transitional zone between normal cognitive function and clinically probable Alzheimer's disease (AD). Although many researchers have suggested and utilized a variety of criteria for defining cognitive impairment, they are essentially common with regard to their aim and theoretical framework in that they (i) refer to non demented persons with

cognitive deficits measurable in some form or another, and (ii) represent a clinical syndrome that can be utilized to classify persons who do not fulfil a diagnosis of dementia, but who have a high risk of progressing to a dementia disorder. As the literature on MCI has expanded, there has been some confusion concerning the specific boundaries of the condition.

Agreement of new perspectives

Mild cognitive impairment is useful both clinically and as a research entity, and is a concept encompassing much more than a preclinical state of AD. The heterogeneous aetiology of MCI is reflected in the literature. When persons with MCI are followed over time, some progress to AD and other dementia types, but some are stable or even recover. Moreover, epidemiological studies on elderly persons have shown that the risk of mortality is high amongst persons with MCI. MCI is also heterogeneous in its clinical presentation and should be considered in a

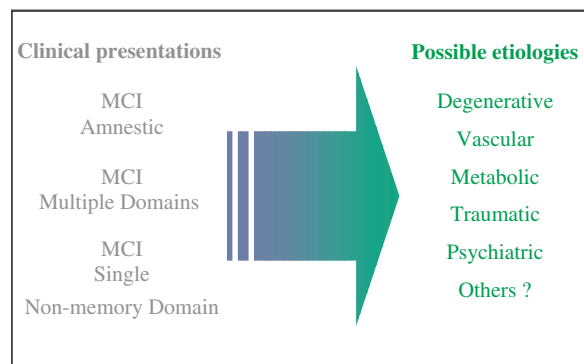


Fig. 1 Heterogeneity of the clinical presentation of mild cognitive impairment (MCI) and potential multiple aetiologies.

broad clinical context. The principal cognitive impairment can be amnesic, single nonmemory domain or involving multiple cognitive domains. Each of these clinical presentations could have multiple aetiologies (see Fig. 1). For example, although a neurodegenerative process could be the aetiology of a patient with amnesic MCI, memory impairment could also evolve as a result of other conditions such as ischaemia, trauma, metabolic disturbance, etc. Within this theoretical framework, numerous additional aetiologies may potentially be involved, such as psychiatric illness (burn out or depression) or other somatic conditions such as cardiovascular disease. For an alternative clinical interpretation of this figure, please refer to Petersen in the current issue (Fig. 4).

Cognitive and functional assessment

Current status

A wide range of cognitive functions appear to decline in persons who will be later diagnosed with AD compared with persons who remain dementia-free, including memory, attention, language, visuospatial skill, perceptual speed and executive functioning. However, controversy exists as to how MCI can be best assessed and defined, as there is insufficient evidence to recommend specific tests or cut-off scores. In a clinical setting, the degree of impairment can be assessed neuropsychologically, but fulfilment of MCI criteria is ultimately determined through clinical judgement using information from these tests within a framework including other tools.

Agreement of new perspectives

Both cognitive and functional abilities need to be considered in the evaluation of MCI. Individual slopes of decline in both functional and cognitive performance may be better measures than deficits assessed according to age-specific norms. However, consensus can only be achieved after longitudinal studies establish the age-specific levels of cognitive functioning, as well as normal rates of cognitive decline over specific time periods. The same issues apply to the assessment of complex instrumental activities of daily living. Specific domains of instrumental activities that might be impaired in MCI need to be determined.

Neuroimaging

Current status

The few MCI studies on neuroimaging have used magnetic resonance imaging (MRI) evaluations of atrophy of the hippocampus or entorhinal cortex, where relationships with transition of MCI to clinical AD and from normal ageing to MCI have been found. There is also evidence that deficits in regional cerebral blood flow as measured by SPECT and regional cerebral glucose metabolism as measured by FDG-PET could predict future development of AD in individuals with MCI.

Agreement of new perspectives

Neuroimaging techniques (such as MRI, CBF-SPECT and FDG-PET) are an essential part of the general evaluation of MCI subjects. Neuroimaging can be used from two essential perspectives. First, brain imaging has an important role in identifying specific and treatable causes of cognitive decline (e.g. subdural haematoma, brain tumour and normal pressure hydrocephalus), and thus, in establishing differential diagnoses. Secondly, neuroimaging can be used for predicting probability of developing dementia and measuring progression of neurodegenerative disease. Thus, brain imaging may provide supplementary diagnostic information on the pathological processes responsible for cognitive decline.

Biomarkers

Current status

There are limited studies investigating biomarkers in MCI. To date, most work has focused on tau and/or A β ₄₂ and the relationship to neuroimaging and clinical symptoms in persons at risk for AD. Some investigations have indicated that CSF markers [e.g. total tau (t-tau), phospho tau (p-tau) and 42 amino acid form of β -amyloid (A β ₄₂) etc.] may differentiate early and incipient AD from normal ageing and certain other dementia types. Focus on these biomarkers in the CSF raises a number of other issues, for example, access to CSF requires an invasive procedure (risks/benefits and patient acceptance of lumbar puncture), and there is lack

of normative data on changes of these CSF markers with age. Furthermore, the effect of medications on changes in CSF markers is not established.

Agreement of new perspectives

Currently, biomarkers, particularly CSF markers, can be used mainly as a research tool and optionally by specialists with the purpose of identifying persons at risk of progressing to AD in conjunction with other instruments. The findings from a small number of studies conducted in selected clinical samples cannot yet be generalized to the general population.

Genetics

Current status

Mild cognitive impairment is a genetically complex condition and currently there are no major genes known to be involved in MCI. Each of the disorders possibly underlying MCI (such as AD, vascular pathology and depression) may partly have a genetic origin, and thus, different genes could underlie the aetiologies of MCI. Furthermore, various factors (both genetic and environmental) may interact, which creates an even more complex picture.

Agreement of new perspectives

Identification of mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1) and 2 (PSEN2), tau, PRNP and α -synuclein may be useful in determining the aetiology of cognitive impairment in younger patients where there is a family history of AD or other neurodegenerative diseases. Prospective phenotypic studies of mutation carriers (APP, PSEN and α -synuclein) and apolipoprotein E (APOE) ϵ 4 carriers may be useful for understanding the early clinical features of AD.

There may be several prognostic genes that may help to identify persons with a higher risk for progression from MCI to dementia. A few studies have suggested that the APOE ϵ 4 allele is associated with a greater likelihood of progressing from MCI to AD. However, more studies are needed to determine the value of APOE and other genes in this context taking into account age, gender and gene-environment interactions.

Recommendations

General criteria for MCI

Not normal, not demented (Does not meet criteria (DSM IV, ICD 10) for a dementia syndrome)

Cognitive decline

- Self and/or informant report and impairment on objective cognitive tasks and / or
- Evidence of decline over time on objective cognitive tasks

Preserved basic activities of daily living / minimal impairment in complex instrumental functions

Fig. 2 Recommendations for the general criteria for mild cognitive impairment (MCI).

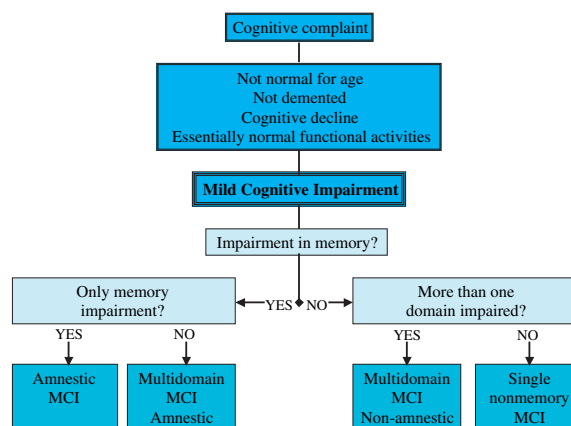


Fig. 3 MCI classification process (adapted with permission from Lippincott-Raven Publishers, Williams & Wilkins.)

Recommendations

General criteria for MCI

The recommendations for general MCI criteria are shown in Fig. 2. The classification of MCI can be carried out in a stepwise fashion, taking into account each criterion. First, persons should be judged as not normal besides not fulfilling diagnostic criteria for dementia. Secondly, functional activities of the person are mainly preserved, or at least that impairment is minimal. Furthermore, the person should have evidence of cognitive decline, measured either by self and/or informant report in

conjunction with deficits on objective cognitive tasks, and/or evidence of decline over time on objective neuropsychological tests.

Figure 3 provides a flow chart that could guide the classification process in a diagnostic setting. An alternative depiction is also shown in Fig. 5 of Petersen's manuscript in this issue. First, the patient or another individual with knowledge about the person expresses some concern about the person's cognitive functioning. Based on the history and a mental status examination, the doctor would judge whether the person has normal cognition or suspected dementia. For example, if the person has a clear impairment in functional activities and scores low on the Mini-Mental State Exam, it is likely that this person has dementia.

Once the clinician has determined that the person is neither normal nor demented, assessing decline in cognitive functioning would be the next step. This could be achieved via taking a structured history from the patient and, where possible, a close relative or friend. If there is evidence for decline in cognition, the clinician must then determine whether this change causes impairment in functional activities to an extent that the person would be considered as having very mild dementia. If the functional impairment is not significant, MCI would be the appropriate classification. The clinical presentations of MCI can then be classified according to three subtypes: amnesic, multiple domain and single nonmemory domain (e.g. language and visuospatial). In order to determine the specific subtype of MCI, comprehensive cognitive testing is necessary, using neuropsychological testing, although there are currently no generally accepted instruments recommended. Specific domains of episodic memory might be assessed with, for example, a word list learning procedure or paragraph recall. If the subject's memory is significantly lower than would be expected for their age, the clinician must determine whether other cognitive domains are also impaired, e.g. language, executive function or visuospatial skills. If the nonmemory domains are intact, the person would be classified as having amnesic MCI. If there are mild deficits in a number of different domains, the person would be considered as having multidomain MCI (with or without a memory component). Alternatively, if there appears to be a cognitive impairment in a single nonmemory domain, such as an isolated deficit in visuospatial skill, then single nonmemory domain

MCI would be the appropriate classification. Please see Petersen's Fig. 5 in this volume for another characterization of these concepts.

Once the clinical subclassification has been made, the proposed cause or aetiology of the clinical syndrome should be determined, similar to the evaluation that most clinicians do to determine subtypes of dementia. For example, if the clinician suspects that a person with amnesic MCI has a degenerative disorder, then this would likely be prodromal AD. Other explanations for cognitive complaint, such as depression, should also be considered.

Management

The recommendations for management follow two perspectives, clinical and epidemiological, with suggestions at three levels: general population, primary care and specialized secondary care.

At the population level, evidence-based information on established risk factors could be disseminated for broad public use (increase knowledge on modifiable risk factors for cognitive impairment, dementia, vascular problems, etc). Screening at the population level for either MCI or prodromal AD cannot currently be recommended. There is insufficient evidence for sensitive and specific tools (such as cognitive tests, imaging techniques, or biomarkers) that have both high positive and negative predictive values for use in the general population.

At the primary care level, general practitioners should pay attention to subjective cognitive complaints and verify cognitive deterioration by structured history taking. This, in addition to routine clinical examinations, can identify possible treatable causes of cognitive impairment such as somatic illness (e.g. hypothyroidism and anaemia), medication side-effects, modifiable cerebrovascular risk factors (e.g. diabetes, hypercholesterolaemia and high blood pressure), psychiatric illness (e.g. depression) and vitamin deficiency (e.g. B₁₂ and folate). As many of these conditions (such as depression) could also be risk factors for dementia development or possible precursors of AD and other dementias, periodical follow-ups are necessary with emphasis both on the primary disorder and cognitive deficits. In case of persistent or deteriorating cognitive impairment, patients should be referred to secondary care.

At the specialist level, patients with memory complaints should be clinically examined (including somatic and neurological status) to determine cognitive status, with detailed neuropsychological investigation to determine cognitive subtypes of MCI and laboratory investigations such as neuroimaging (MRI, SPECT and CT) and possible CSF biomarkers and PET. The physician can utilize these tools to make a clinical judgement and then follow the patient to assess progression.

Treatment: pharmacological and lifestyle interventions

There is no evidence for long-term efficacy of currently approved pharmacological treatments in MCI, and only modest evidence for symptomatic treatment efficacy in AD. Epidemiological studies have indicated a reduced risk of dementia in persons taking antihypertensive medications, cholesterol-lowering drugs, antioxidants, anti-inflammatories and oestrogen therapy; however, data from randomized clinical trials are needed to verify these associations. Currently, population-based intervention strategies relevant to MCI can only be limited to information on maintaining a healthy lifestyle. At the primary care level, intervention is restricted to primary prevention and management of known modifiable risk factors for cognitive impairment and dementia. Specialized medical care should focus on exclusion of treatable causes of cognitive impairment, treatment of behavioural/psychiatric symptoms and longitudinal assessment and re-evaluation of persistent or deteriorating cognitive impairment.

Pharmacological treatment for primary degenerative dementia and particularly AD currently show only moderate effects on cognition, behaviour and function. Acetylcholinesterase inhibitors (AChEI) approved for the symptomatic treatment of mild-to-moderate AD stabilize disease symptoms up to 1 year. Another antidementia drug, memantine, has been approved for treatment in severe AD. There are no randomized controlled clinical trials providing evidence that currently approved drugs for dementia could have efficacy in MCI and risk-benefit ratio is questionable. Answers may be provided in future by currently ongoing clinical trials in MCI with several AChEI, their combination with vitamin E and a piracetam trial. In the light of the current recommendations for MCI, clinical

trials could begin focusing on specific subtypes of MCI such as amnesic MCI with presumed degenerative aetiology.

Future research

An imperative element of reaching a consensus on the current and future directions of MCI is to establish clear research goals and provide evidence for the unanswered questions described above. Here we provide a summary of important areas for future research at the population level, as well as in primary and specialized medical settings.

Future research should focus on identifying the prevalence of the three clinical presentations of MCI as well as to establish the aetiology behind the impairment, both with clinical data and especially population-based studies. Specific questions should determine the prevalence and incidence of the MCI subtypes in different populations and age groups. Comparisons between the general population and clinical settings are of particular importance. For example, is amnesic MCI more common than multidomain MCI in memory clinics, but less frequent in the general population? Which aetiologies do the subtypes commonly relate to? Is the most common aetiology for amnesic MCI degenerative in nature? Can other aetiologies (such as psychiatric and somatic) be added to the current conceptual framework? What factors can help to determine the aetiology and future outcome?

Verifying and validating screening instruments and neuropsychological scales both for assessing MCI and detecting preclinical dementia is needed. Focus is required to establish normative rates of cognitive decline in specific domains in ageing. Of special interest will be comparisons between defining cognitive impairment based on age- and education-specific norms and the individual decline on cognitive tasks. Assessment of complex activities of daily living in MCI is potentially of great interest, as there is little information on this topic so far. Which activities are impaired in MCI and are there tasks of complex activities that can help predict outcome of persons with MCI? Establishing tools, norms and normative rates of decline on such tests are needed before conclusions can be made.

The possibility of neuropsychological testing laboratories at the primary care level has been discussed. This could involve general practitioners

referring patients to a setting in which cognitive functioning can be assessed using computerized tests. Much in the same way as other laboratory tests are analysed (e.g. blood test analysis, X-rays, etc.), a neuropsychological test profile could then enable the clinician to determine the cognitive status of the patient and thus assess the need for further examinations. The efficacy and cost of such a proposal will be of interest in future investigations.

Developments in brain imaging techniques include the potential for neurochemical imaging such as neurotransmitters, enzymes or receptors and possible imaging of specific pathological aggregates such as beta amyloid or neurofibrillary tangles. The use of standardized neuroimaging protocols would permit greater use of results from individual centres and pooling of such data could provide important insights into the value of neuroimaging in MCI. Relevance of white matter lesions to the diagnosis of MCI and prediction of progression to AD/dementia also needs to be further evaluated. Another future focus should be on developing guidelines for the use of neurophysiological methods (EEG and quantitative EEG in particular) as widely available, cheap and noninvasive diagnostic tools in the assessment of MCI and its subtypes. For example, there is evidence that EEG is normal in pseudodementia (depression) and that MCI subjects who progress to AD differ at baseline from those who remain stable. Consensus on recording and analysing standards as well as multicentre replication studies with population-based subjects are needed.

Biomarker investigations should aim at standardizing methodology and establish validation in larger cohorts and more heterogeneous populations. Furthermore, efforts should be made to assess changes over time and to investigate markers of other aspects of pathology, including inflammation, trophic factors and synaptic loss. It is also essential to investigate the relationship of current markers with genetic factors and quantify the added value of clinical markers to, for example, neuropsychological testing and neuroimaging. Another interesting question is whether biomarkers for identifying early stage disease (i.e. for AD) are the same as

those that should be used to monitor progression within MCI.

Genetic studies will hopefully identify more susceptibility genes not only for AD, but also for other dementia subtypes. Current evidence suggests that genes involved in lipid metabolism, hypertension, haemostasis and homocysteine might also be candidates for involvement in susceptibility for various dementia syndromes. Research may also find prognostic genes that could help to predict persons with a higher risk for transition from MCI to dementia. The value of APOE genotype in this context should be further evaluated taking into account age, gender and gene–environment interactions.

Additionally, there is potential for the future implementation of a multivariate approach that combines demographic and genetic variables, cognitive measures, brain-imaging data and laboratory test results into a common prediction model. Of specific interest will be whether the various markers contribute unique variance and thus increase overall prediction accuracy for dementia. For example, can neuroimaging identify persons who will develop AD who are not detected with neuropsychological measures?

Better definition and earlier recognition of MCI could lead to revision of the current diagnostic criteria of AD or possibly other dementia subtypes. Research efforts regarding treatment should focus on designing drug trials for MCI and incorporate knowledge on natural history (time needed to reach next clinical milestone—transition to dementia) and surrogate markers of progression suitable for primary and secondary outcome measures (cognitive, neuroimaging, and CSF biomarkers). These methodological aspects are crucial for future preventive trials with neuroprotective and disease-modifying drugs currently under development.

Conflict of interest statement

No conflict of interest was declared.

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