MILD COGNITIVE IMPAIRMENT (MCI) – CURRENT RELEVANCE OF THE CONCEPT

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ABSTRACT

The term ‘mild cognitive impairment’ has been introduced to represent the border between frank dementia and changes related to aging. How do the memory difficulties in MCI differ from those of normal aging? This is a very difficult question which has no permanent answer yet. This review discusses the definition of terms in the field of cognitive impairment and the relevance for current clinical settings and clinical trials.
Key words: aging, cognitive impairment, dementia

DEFINITION OF MILD COGNITIVE IMPAIRMENT

Mild cognitive impairment (MCI) is a stage of transition between the cognitive decline of normal aging and more important problems which are caused by Alzheimer’s disease. The disorder presents a variety of symptoms. Memory loss is the predominant one, but many areas of thought and action can also be affected, for example: judgement, reasoning, language, attention, reading and writing. MCI was intended to capture the patients with the risk of developing dementia.

Studies suggest that MCI affects 10-17% of the elderly population. Although not all MCI people will progress to more advanced stages of cognitive impairment, a part of them eventually develop Alzheimer’s disease. Some of them remain stable and others can even return to a normal state.

MCI can be classified in:

A) MCI: represents a heterogeneous condition including early dementia of multiple types; vascular MCI; reversible causes of multiple types of depression; the “worried well” and long lasting cognitive problems. This form presents:

1. evidence of cognitive impairment
2. preserved general cognitive abilities
3. not demented

B) Amnestic MCI: was nominated as the earliest stage of Alzheimer’s disease and it is characterized by:

1. memory complaint
2. objective memory impairment
3. normal general cognition
4. not demented

C) Operationalized amnestic MCI: represents people with risk of developing early Alzheimer’s disease:

1. memory complaint, verified by an informant
2. memory impairment, 1.5 standard deviations below normal (adjusted for age and education)
3. normal general cognition (mini-mental state score of 24 or above)
4. dementia not present as defined by preserved activities of daily living
5. clinical dementia rating of 0.5.

EPIDEMIOLOGICAL STUDIES OF MCI

Prevalence estimates for MCI show significant variability ranging from 2.8% to 23.4%. For example applying MCI criteria to a population which consists of individuals 60 years old and older led to MCI prevalence estimates of 3%.

Another study defining MCI as impairment in visual memory with normal general cognitive function (MMSE score not <1SD below the mean) demonstrates the prevalence of MCI to be 2.8%. Another study showed that nearly 25% of individuals had some form of cognitive impairment. The exact criteria used to define MCI and the sample to which it is applied influence how broadly MCI

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is characterized and contribute to various results across studies. Estimates of the risk of "conversion" from MCI to Alzheimer's disease are also different, ranging from 3.7% per year to 25% per year in the selected samples.

Vascular lesions and Parkinson's disease usually coexist with Alzheimer's disease, both of them occurring in about 25% of Alzheimer's disease cases.

Currently, there is no standard neuropsychological test of memory forin order to establish objective evidence of memory impairment.

ETIOLOGY OF MCI

Changes may include:

- Plaques, which are abnormal clumps of beta-amyloid protein
- Tangles, which are abnormal clumps of tau protein
- Shrinkage of the hippocampus
- Strokes
- Lewy bodies

Risk factors:

- A specific change in the apolipoprotein E gene (APOE), which is linked to Alzheimer's disease
- Diabetes
- Low levels of physical, social and mental activity
- Fewer years of education
- High blood pressure
- Stress
- Depression
- Family history of dementia

Commonly used features for the diagnosis of MCI include:

1. evidence of cognitive impairment
2. preservation of general cognition and functional abilities
3. absence of diagnosed dementia.

NEUROPATHOLOGY OF AGING

The neuropathological limit between aging and dementia is still controversial. Quantitative post-mortem studies demonstrate that slow neurofibrillary tangle accumulation occurs in non-demented adults, piling up with age in a predictable pattern. The distribution of NFT's is usually limited to the medial temporal cortex. This indicates that in a normal lifespan, the age-related accumulation of tangles may not revolve in dementia, although it may possibly underlie cognitive complaints of "normal aging". When neocortical plaque pathology is present, there seems to be an acceleration of the normal age related NFT deposition and increased neocortical involvement.

The amyloid pathology in the case of non-demented subjects appears to be separable in two groups: little to no plaque pathology and large numbers of diffuse senile plaques. In the first group plaques can be entirely absent in individuals up to 90 years old. In the second group neuritic and diffuse plaques are distributed in the neocortex and limbic areas and the patients are cognitively stable. The possible explanations why these individuals are not suffering from dementia could be that they could indeed not have AD, they may be under the influence of various protective factors that reduce the AD manifestations, and the lesions have yet to culminate in a great deal of neuronal destruction. In the latter case, these patients have a form "preclinical AD", defined as a stage when the disease is neuropathologically present but has not produced clinically detectable cognitive modifications yet. Individuals who are not demented, with and without preclinical AD do not seem to have significant neuronal loss in the entorhinal cortex. The comparison of the brain of non-demented individuals with and without AD pathology fails to indicate differences in the amount of neurons in the entorhinal cortex. In contrast, individuals in the earliest stages of AD have 32% reduction neurons in the entorhinal cortex. Age-related deposition of neurofibrillary tangles is accelerated by the amyloid plaques. Clinically recognizable cognitive decline becomes obvious with the substantial loss in the ERC and hippocampus cognitive changes of early AD.

NEUROPATHOLOGY OF MCI

The studies have shown that AD and MCI have similar neuropathological discoveries. Decreases in neuron numbers in layer 2 of the entorhinal cortex have been observed in subjects with MCI and AD. In another studies individuals with MCI had increased plaques, neuritic and neurofibrillary tangles compared with normal control. The neuritic plaques were not different in MCI compared to AD, although there appeared to be increasing neurofibrillary tangle pathology from normal, MCI, and AD subjects. These studies suggest the fact that the neuropathology of MCI is that of AD. The neuropathological study of MCI individuals is essential in order to establish a causal link between

the clincal symptoms and a neuropathological etiology.

The clinical studies of MCI subjects demonstrate that cognitive deficits and clinical features are similar with the ones in AD, only less severe. The genetic risk factors are similar in AD and MCI patients. Individuals with MCI and AD share similar neuropsychiatric profiles.

NEUROIMAGING

Medial temporal lobe volume loss has been confirmed in AD subjects as well as in MCI. Functional imaging studies using SPECT and PET demonstrate a similar distribution of metabolic defects in AD and MCI patients. AD-associated hypometabolism in the posterior cortical region has been reported and is proposed as an early diagnosis marker of AD. MCI subjects have posterior cortical hypoperfusion in comparison with normal controls and patients presenting AD.

MCI SYMPTOMS: deficient memory, preferably confirmed by another person, normal judgement, perception and reasoning skills, normal activities.

In the daily living, reduced performance on cognitive tests compared with tests taken by other people of the same age and educational background, may also indicate iritability, anxiety and agression.

Common symptoms of MCI and early AD are the following: memory loss, executive dysfunction in simple activities.

Memory loss:
- forgetfulness of recents events details
- repetition of questions
- misplacement of items

Executive dysfunction:
- difficulties in managing a checkbook/ household finances
- decline in cooking skills
- decline in home repaire skills
- trouble in operating household appliances: microwave, remote control, telephone

Daily activities:
- impaired performance in:
  - hobbies
  - playing cards
  - reading
- difficulty in:
  - driving
  - getting lost
  - indecisiveness
  - minor or major accidents
  - shopping

Individuals with MCI and AD share similar neuropsychiatric profiles with symptoms such as: agitation, depression, apathy, delusions, hallucinations and sleep disorders.

DIAGNOSIS

The cardinal information needed to diagnose dementia and make a differential diagnosis comes firstly from clinical information. Diagnosing AD is based on determining whether cognitive decline is present to such an extent that it interferes with function in usual activities. The principles of this criteria include cognitive decline and interference with functioning, as the ultimate validation of the presence of dementia.

Clinical hallmarks of dementia:

- Gradual onset
- Progressive decline
- Memory loss
- Other cognitive domains impaired
- Interferes with function

The patient with MCI complains of difficulty with memory. These complaints include trouble remembering the flow of a conversation, trouble remembering the names of people they met recently, and an increased tendency to misplace things. In many cases, the subject is aware of these difficulties and will compensate with increased reliance on notes and calendars.

Most importantly, the diagnosis of MCI relies on the fact that the individual is able to perform all their usual activities, without needing assistance from others.

Common symptoms of MCI and early AD are:
– Memory loss
  - Forgetfulness of the details of recent events
  - Repeating questions
  - Misplacement of items
– Executive dysfunction
  - Difficulties managing checkbook/household finances
  - Decline in cooking skills
  - Decline in home repair/maintenance skills
  - Trouble operating household appliances – microwave, remote control, telephone
– Daily activities
  - Impairment performances in hobbies
    - Playing cards
    - Reading

- Difficulty driving
  - Getting lost
  - Indecisiveness
  - Minor or major accidents
- Shopping
  - Frequent trips for forgotten items
  - Doubling up on items

INFORMANT BASED HYSTORY

The patient will first undergo a complete physical exam, along with a detailed history of symptoms and medical history, including medication therapies. The patient and people familiar with them will be questioned about the patient's emotional state and day-to-day routines. The family members or close friends can provide important information about changes in the patient's behavior and personality.

The memory loss of MCI is generally well compensated and family members may be inclined to disregard the cognitive changes. When the informant is not observant or is unavailable, true decline can be difficult to identify. Another difficulty is in separating the impact of co-morbid conditions on an individual's daily functioning from the effect of cognitive decline. As a result, there are numerous tests and questions for each patient.

The evaluation of this patients is similar to that given to individuals with more severe memory problems, and is directed towards better defining of the problem and looking for medical conditions that might have an effect on the brain (infections, nutritional deficiencies, autoimmune disorders, medication side effects, etc).

NEUROLOGICAL EXAMINATION

The examination by neurology specialists will help identify signs of Parkinson's disease, strokes, tumors and other medical states that may impair memory and thinking, as well as the physical function. They will also be asked about possible alcohol or drug abuse, head traumas and other causes for memory loss. Depending on the results of this evaluation, further testing may be necessary, including blood tests and brain imaging.

The neurological exam may test:

- Reflexes
- Eye movements
- Balance
- Sense of touch

MENTAL STATUS AND NEUROPSYCHOLOGICAL ASSESSMENTS

To determine which thinking and memory functions may be affected and to what extent, the patient will be asked questions in order to measure cognitive functions for attention, learning, recall, language and visuospatial abilities. The tests are compared to the tests of others of similar age and education.

Psychometric / Mental status testing **instruments are:**

1. Cognitive screening tools:

- MMSE
  - assesses orientation, memory, language and visuospatial skills on a 30 point scale
  - a score greater than 24 used to define intact general cognitive functioning as part of the MCI criteria
- The seven minute screen
- Clock drawing test – useful in detecting mild dementia

2. Neuropsychological batteries

- Mattis dementia rating scale

3. Informant-based instruments

- CDR (Clinical dementia rating)
- GDS (Global deterioration scale)
- IQCODE (Informant Questionnaire on Cognitive Decline in the Eldery)

Psychiatric Assessments

In addition, the patient may have a psychiatric assessment to discover if depression or other mental illness is present.

Although normal results on neuropsychological tests do not 100% guarantee that the individual will not develop dementia, the current data indicates that normal results are quite reassuring, at least for the next few years.

BLOOD TESTS

The patient's blood sample will be checked for infections or disorders like vitamin deficiency, anemia, medication levels, disorders of the thyroid, kidneys or liver, and other factors that can cause memory loss. Simple blood tests can exclude physical problems that can affect the memory, such as vitamin B-12 deficiency or an underactive thyroid gland.

Although normal results on neuropsychological tests do not 100% guarantee that the individual will not develop dementia, the current data indicates that normal results are quite reassuring, at least for the next few years.

DIFERENTIAL DIAGNOSIS

1. AFFECTIVE DISORDERS

Not all individuals diagnosed with MCI will develop dementia, and some of them may even improve over time. Many healthy aging individuals are convinced that they suffer from dementia. This is why they have the tendency to exaggerate and overreact. Typical complaints of these patients include: lapses in memory retrieval, word-finding difficulties during a conversation, brief episodes of geographic confusion in familiar places, or forgetting a routine activity such as locking a door or taking their medicine. These are "worried-well" individuals and they represent a diagnostically challenging group of patients. In contrast, incipient dementia is often accompanied by a loss of self appreciation and many individuals never acknowledge their memory impairments but their manifestations are quite apparent to the family members or friends. Self reported memory loss that is not verified by a collateral source usually raises the suspicion of "worried-well". Low-grade cognitive impairment is not benign, and the affected patients often require follow-up evaluations.

An important part of the evaluation process is screening for depression, particularly in individuals with mild memory complaints which are frequent symptoms of depression. Depression can mimic dementia, in this case it is called pseudo-dementia and it is reversible with an adequate treatment plan. It is known that depression can coexist with AD and cognitively normal older individuals who develop depression have an increased risk of developing subsequent mild cognitive impairment. Depression is more often a predictor of dementia than it is an imitator and when it is associated with early AD, it induces an acceleration of cognitive decline.

2. NEURODEGENERATIVE DEMENTIA

MCI represents a prodromal state of AD and longitudinal studies demonstrate that individuals characterized as having amnestic MCI primarily progress to AD. Less common types of MCI may represent a prodromal state of non-AD clinical syndromes such as fronto-temporal dementia, dementia with Lewy bodies, or cortical basal degeneration. Dementia with lewy bodies, vascular dementia, and the fronto-temporal dementias are considered to be the most common forms of non-AD dementias.

- Dementia with Lewy bodies

The term DLB characterizes a Parkinsonian syndrome in which neuropsychiatric disturbances are proeminent. The clinical diagnosis of DLB requires: the presence of dementia and at least one of three cardinal features:

a) Visual hallucinations
b) Parkinsonism
c) Fluctuating cognitive status

Greater frequency of exatrapyramidal features an relatively better memory performance may be characteristic for DLB as opposed to AD.

- Vascular dementia

Pure cases of vascular dementia are rare. Cerebrovascular lesions have an important role in contributing to AD onset and severity level. Vascular dementia interacts additively or synergistically with AD to produce mixed dementia. In identifying the majority of dementia patients with at last some cerebrovascular pathology, the modified Hachinski Ischemic Score may be useful; a score of 7 or more is consistent with cerebro-vascular pathology.

- Fronto-temporal lobar dementias

The frontotemporal lobar degeneration syndromes are predominantly pre-senile (they occur frequently before 65 years of age), they are often familial and have been classified into three disorders based on clinical presentation:

a) Frontotemporal dementia (early behavioral dysfunction with desinhibition, impulsivity, impaired judgment, disturbed social comportment)
   - Pick's disease is the prototypical FTD
b) Semantic dementia (early impairment in semantics resulting in empty fluent speech and loss of speech comprehension)
c) Progressive non-fluent aphasia (early loss of fluent speech and prominent anomia)

OTHER CAUSES OF COGNITIVE DECLINE

- **Infectious disorder** (chronic meningitis, encephalitis, HIV, Lyme disease, progressive multifocal leukoencephalopathy, neurosyphilis, whipple's disease)
- **Toxic** (drugs, medications) **/ metabolic encephalopathies** (endocrine – thyroid, parathyroid;

nutritional – B 12 and thiamine deficiencies, hypoglicemia etc.)
- **Inflammatory** – vasculitis, sarcoidosis
- **Demyelinating** – multiple sclerosis
- **Neoplastic**
- **Neurogenetic disorders** (eg. mitochondrial)

TREATMENT

Pharmachological treatment

Currently there is no specific treatment for MCI. Studies are in progress to investigate the usefulness of treatments for Alzheimer's disease, such as **cholinesterase inhibitors G** and **vitamin E**, in preventing cognitive deterioration in patients with MCI, and the results of these studies should be available within the near future.
- Alzheimer's drugs
  - During the first year of a three-year study, the rate of progression from mild cognitive impairment to Alzheimer's was much lower in the people who took Donepezil (Aricept). However, that difference disappeared by the end of the study.
  - An Alzheimer's drug called Galantamine (Razadyne) increases the risk of sudden death from heart attacks and strokes when used in people who have mild cognitive impairment.
- High blood pressure drugs
  - People who have mild cognitive impairment are also more likely to have problems with the blood vessels inside their brains. High blood pressure can worsen these problems and cause memory difficulties. That's why it's important to keep your blood pressure at normal levels.
- Antidepressants
  - Depression is common in people who have mild cognitive impairment, and depression itself can cause memory problems. Treating depression may help improve the memory, while making it easier to cope with the changes in life.

In the future, new treatments for Alzheimer's disease will be tested on patients with MCI as well. If any unusual causes of memory impairment are uncovered in the process of an evaluation, such as vitamin deficiency or thyroid disease, specific treatments should be instituted.

Lifestyle and home remedies

Study results have been mixed about whether the following activities can prevent or reverse mild cognitive impairment. But they can be part of a healthy lifestyle for older people with or without mild cognitive impairment.
- **Exercise of the muscles**. Physical exercise may help reduce the risk of developing memory problems.
- **Exercise of the brain.** Engaging in intellectually challenging activities has been associated with better memory skills.
- **Avoid isolation.** People who have a limited social network may have a much greater risk of developing dementia.
- **Good sleep.** Memory problems have been associated with sleep disorders.

Alternative medicine

- **Vitamin E.** This antioxidant may help protect brain cells from the oxidative stress that appears to play a role in dementia, but it works no better than placebo in relieving the symptoms or delaying the progression of mild cognitive impairment.
- **Ginkgo.** This supplement appears to improve memory and concentration in older adults with no major memory problems, but it's still uncertain if ginkgo can help the memory problems associated with mild cognitive impairment.
- **Music therapy.** Older adults with Alzheimer's disease and other memory disorders have been successfully treated with music therapy to reduce their aggressiveness and to improve their mood and willingness to cooperate in daily activities.

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