

Early Treatment of Mild Cognitive Impairment for Reduction in Conversion rates to Alzheimer's Disease

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Summary

Alzheimer's disease (AD) is numerically the most important cause of dementia, particularly in the elderly. Studies suggest that cognitive, imaging and pathological changes predate, by many years, the fulfillment of standard clinical criteria for a diagnosis of Alzheimer's disease, and in particular that all patients diagnosed are likely to have progressed through a stage of relatively isolated (usually amnesic) cognitive deficits. As a result the concept of mild cognitive impairment (MCI) has become established to describe individuals who cognitively lie somewhere between normal ageing and dementia. This review focuses on the recent emerging treatment modalities for treatment of MCI and the importance of early detection and treatment of MCI for reduction in conversion rates to Alzheimer's disease.

Keywords: Mild Cognitive Impairment (MCI), Dementia, Alzheimer's Disease

Introduction

Dementia is one of the commonest and most disabling late-life mental disorders. The most recent estimates suggest that 24 million people worldwide have dementia with 4.6 million new cases diagnosed annually.¹ Alzheimer's disease (AD) is numerically the most important cause of dementia, particularly in the elderly.² A gathering number of studies suggest that cognitive, imaging and pathological changes predate, by many years, the fulfillment of standard clinical criteria for a diagnosis of Alzheimer's disease, and in particular that all patients diagnosed are likely to have progressed through a stage of relatively isolated (usually amnesic) cognitive deficits. As a result the concept of mild cognitive impairment (MCI) has become established to describe individuals who cognitively lie somewhere between normal ageing and dementia.³

MCI is defined as a slight impairment in cognitive function (typically memory) with otherwise normal function in the performance of activities of daily living. On the continuum of cognitive function, MCI lies between and overlaps normal aging and AD, and it is recognized as a risk factor for AD. MCI signifies the transitional stage between age-related memory decline and Alzheimer disease (AD). It is a broad term that encompasses several subtypes of cognitive dysfunction of varied etiologies.

Other terms used to describe the condition range from concepts such as “benign senescent forgetfulness,”⁵ “age-associated memory impairment,” (AAMI)⁶ “age-associated cognitive decline”(AACD),⁷ and “age-related cognitive decline”

MCI is broadly classified into the following types;⁸

Amnesic MCI (a-MCI) is characterized by a memory deficit on neuropsychological tests in comparison with the performance of persons of a similar age and education level.

Multiple-domain MCI (md-MCI) is characterized by impairment in several cognitive domains (eg, language, executive function, visuospatial skills). Patients with md-MCI may also have memory impairment.

MCI Single (Non-memory domain)

Third subtype of MCI involves patients with impairment in a single cognitive domain that does not involve memory.

Diagnosis of MCI

MCI with memory complaints and deficits (amnesic mild cognitive impairment) is consistently shown to have a high risk of progression to dementia, particularly of the Alzheimer type. Predominantly two clinical staging systems are used by clinicians to assess ageing and dementia. These are the clinical dementia rating (CDR)⁹ and the global deterioration scale for ageing and dementia (GDS)¹⁰. The term mild cognitive impairment was first used in association with stage 3 of the GDS.¹¹

The first step in the prevention of AD is the recognition of MCI transition phases between healthy ageing and dementia. The diagnosis of dementia or AD in the clinic, depends on typical set of well established criteria such as those in Diagnostic and Statistical Manual of Mental Disorders (DSM) IV.¹² A major problem in timely diagnosis of MCI is that the decline in cognitive function can be very subtle at first.¹³ The diagnosis of MCI can be made based on the following factors;

Cognitive and Functional Assessment

A wide range of cognitive functions like memory, attention, language, visuospatial skill, perceptual speed and executive functioning appear to decline during memory impairment. The Montreal Cognitive Assessment (MoCA)¹⁴ is a 30 point test administered in 10-minutes which assists the physicians in cognitive screening. It covers 10 cognitive domains using rapid, sensitive, and easy-to-administer cognitive tasks.

The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately 5 minutes. Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point). Multiple aspects of executive functions are assessed using an alternation task adapted from the Trail Making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points). Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each). Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points),

and the aforementioned fluency task. Finally, orientation to time and place is evaluated (6 points).

Many other factors, including age, education, occupational experience, socioeconomic status, personality style, premorbid abilities, and coexisting medical, neurologic, and psychiatric conditions, may contribute independently to the development of MCI.

Although cognitive symptoms and tests have been the core features of mild cognitive impairment up to now, there is increasing awareness of a behavioural component, which includes anxiety, depression, irritability, and apathy.^{15,16} The presence of behavioural and psychological signs, including depression, predicts a high likelihood of progression to dementia.¹⁷

With regard to the extent to which MCI may be a prodromal phase of dementia, several studies have suggested a significantly increased risk of Alzheimer's disease in MCI patients, with estimates of 10% to 15% of MCI patients developing dementia in 1 year,¹⁸ 40% over 2 years,¹⁹ 20% over 3 years,¹⁶ 30% over 3 years,¹⁸ 53% over 3 years,¹⁹ and 100% over 4-5 years.²⁰

Neuroimaging in MCI Patients

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.²¹

Biomarkers in MCI

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.²²

A Japanese study studied fifty consecutive individuals complaining of memory dysfunction by the Japanese version of the Wechsler Memory Scale--Revised (WMS-R).²³ Subjects were functioning fairly well in the community and were neither psychoactive drug users nor excessive alcohol drinkers. Depression also was excluded by using the Geriatric Depression Scale. Thyroid function tests and vitamin B12 and folic acid levels were all within normal range. Because delayed episodic memory was found to be most severely impaired in MCI,²⁴ scores of logical memory II, visual reproduction II, verbal paired associates II, and visual paired associates II in the WMS-R subscales were summed and expressed as "delayed recall score" after adjustment for age.

As a result, 28 individuals (mean age=71.1±5.5) fulfilled the criteria, and the other 22 subjects (mean age=68.5±8.5) were judged as having no cognitive impairment (NCI).

Cerebrospinal fluid (CSF) tau protein (CSF-tau) and CSF amyloid-β1-42 peptide (CSF-Aβ₁₋₄₂) were quantitated. Regional cerebral blood flow in the posterior cingulate cortex (rCBFpc) was measured on (¹²³I)iodoamphetamine--single positron emission computed tomography (IMPSPECT).

The CSF-tau levels were significantly higher in the amnesic MCI group than in the NCI group (524.7 ± 238.6 vs 201.5 ± 89.6 pg/mL, $P < .0001$). The rCBFpc was significantly lower in the amnesic MCI group than in the NCI group (0.91 ± 0.12 vs 1.00 ± 0.08 , $P = 0.005$), but there was no significant difference in CSFA β_{1-42} levels between the two comparison groups. For the distinction between amnesic MCI and NCI, the cutoff level of 341.0 pg/mL of the CSF-tau yielded a sensitivity of 83.3% and a specificity of 95.0%. Despite a moderately invasive technique, CSF-tau appears to be the most appropriate indicator to support a differential diagnosis between MCI and normal elderly people. This study also demonstrates that amnesic MCI is not merely an age-associated condition, but appears to be a more pathological state that is associated with abundant neuron death, as revealed by elevated CSF-tau levels.

Recent Evidence suggests that phosphotau 231 and isoprostane can increase the diagnostic accuracy of conventional cognitive and magnetic resonance assessments in people with mild cognitive impairment.²⁵

Genetics and MCI

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.

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. 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 e4 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.²⁶

MCI Approaches to Treatment

The concept of mild cognitive impairment (MCI) is crucial for clinical research because it describes a stage of severity for specific disorders that have not yet reached the dementia threshold and might be prodromal Alzheimer's disease (AD).²⁷ Given the high rate of progression from MCI to AD, these people might benefit from widely used drugs that are approved for symptomatic treatment of AD (eg, cholinesterase inhibitors [ChEIs]).²⁸ The results of treatment could be substantial because the symptomatic effect (improved memory function) or the possible pathophysiological effect (neuroprotection) of these drugs might prevent, or at least attenuate, the deleterious social and economic consequences of AD.²⁹

Currently available treatments

Acetylcholinesterase inhibitors:

The acetylcholinesterase (AChE) inhibitors are presently the established treatment strategy in Alzheimer's disease and are considered as first choice candidates for the treatment of MCI.³⁰ This intervention is based on the cholinergic hypothesis of AD³¹, which is built on the findings of cholinergic deafferentation of the cerebral cortex as a result of the selective loss of cholinergic neurons in the basal forebrain^{32,33} as well as on the positive effects of double-blind placebo-controlled trials of up to 26 weeks duration with five AChE inhibitors.³⁴

Antioxidants:

Oxidative stress has been proposed as a central pathogenetic mechanism in various neurodegenerative diseases, including AD.³⁵⁻³⁸ Large amounts of unsaturated lipids and catecholamines in the brain are particularly vulnerable to free radical damage. β -protein precursor, A β , presenilins and apolipoprotein E are linked to reactive oxygen species (ROS) production and apoptosis. In addition, oxidative stress is also recognized as a contributing mechanism in atherogenesis³⁹, which increases the risk of cognitive impairment through the process of atherosclerosis and thrombosis.

A longitudinal population-based study of older subjects showed that high plasma levels of lipoperoxidation markers were a significant risk factor for cognitive decline during the 4-year follow-up period.⁴⁰ Currently available therapies directed towards the reduction of oxidative stress include the elimination of free radicals through interaction with free radical scavengers, and prevention or decrease of their production by antioxidants.⁴¹

Two independent observational studies found an association between dietary intake of vitamins E and C and reduced risk of developing AD.^{42,43}

Nootropics:

These agents can mainly result in symptomatic effects as modes of action are nonspecific and include effects on energy metabolism, cholinergic mechanisms, excitatory amino acid receptor-mediated functions and steroid sensitivity.⁴⁴

Piracetam was used in a clinical multicentre, multiphasic, cross-over doubleblind trial with nondemented patients with memory impairment, and positive effects were reported on tests of attention and memory.⁴⁵ A combination of piracetam and memory training in patients with age-associated memory impairment (AAMI) was also effective in a double blind, randomized trial.⁴⁶

Antiinflammatory Drugs:

There is increasing evidence that inflammatory processes are involved in the pathogenesis of AD. Experimental studies suggest that there is an upregulation of inflammatory cytokines and acute phase proteins, activation of the complement regulatory proteins as well as an accumulation of activated microglia, which is also revealed at autopsy in brains of AD patients in association with amyloid plaques.⁴⁷

Dopamine receptor agonists:

Cerebral aging is accompanied by a progressive reduction in central dopamine receptors, correlated with a decrease in cognitive performances⁴⁸. Also, dopamine agonists have been shown to mostly have an antioxidant effect. The randomized controlled-study by Nagaraja and Jayashree (2001) reported a significant improvement in Mini Mental State

Examination (MMSE) scores in the group treated with the D2/D3 dopamine receptor agonist piribedil, versus the placebo arm, in 60 patients with suspected MCI.⁴⁹

Sex steroid hormones:

Possible beneficial effects of estrogen on cognition have been suggested in several studies and specific protective effects have been observed in the verbal memory domain.^{50,51} Cherrier et al.⁵² studied the effect of weekly injections of 100 mg of testosterone enanthate in 15 AD and 17 MCI patients versus placebo over 6 weeks. The supplementation with testosterone appeared to be beneficial in the two groups of patients, particularly in terms of spatial memory.

Newer Paradigms

The ultimate goal of early therapeutical interventions in individuals at risk of developing dementia is to prevent, delay or slow the progression of the disease⁵³. These disease-modifying effects could be expected only if more proximal and central events in the pathogenetic cascade and their substrates are ameliorated, such as amyloid production and aggregation, phosphorylation of tau, formation of neurofibrillary tangles NFT, and apoptosis.

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. Comparisons between the general population and clinical settings are of particular importance. Verifying and validating screening instruments and neuropsychological scales for assessing MCI is also needed.

Treating comorbidities and controlling risk factors is another important aspect of management of MCI. Identification of newer risk factors and expanded knowledge on their interactions may, in the future, explain the heterogeneity of the MCI population in terms of its clinical presentation and natural history. This will also initiate thinking about new therapeutical approaches and various neuroprotective strategies. For example, presence of vascular risk factors during midlife in a large longitudinal population-based study was related to late-life MCI⁵⁴. This study showed that individuals with raised systolic blood pressure or high serum cholesterol concentrations had significantly higher risk of developing AD in later life⁵⁵. Because vascular disease is an important contributor to dementia development, identification and control of treatable vascular risk factors in asymptomatic subjects as well as in those with MCI could delay clinical expression of dementia.

Three retrospective epidemiological studies have raised a lot of interest by showing that statins, i.e. cholesterol-lowering agents, decreased the risk of developing AD by 70%⁵⁶⁻⁵⁸

The Need for Early Intervention:

Difficulties remain in defining the boundaries between normal ageing and mild cognitive impairment, and between mild cognitive impairment and mild dementia⁵⁹. Clinical evidence has shown MCI to be a condition which places the patient diagnosed with it at increased risk for development of dementia i.e. AD. This warrants early diagnosis and aggressive management of MCI to delay the onset of AD in this patient population. Hence there is a need for validated diagnostic tools, understanding of causative and

conversion factors, early prognostic counseling, pharmacologic intervention, and health care. Recent insights into molecular pathogenesis, biomarkers and epidemiological studies on MCI, have increased our knowledge about the disease and disease modifying strategies to be adopted. There is a need to implement these disease modifying strategies in an aggressive manner and there has to be improved awareness about the need to diagnose and treat MCI in middle aged and elderly population.

Earlier recognition of MCI can lead to revision of the current diagnostic criteria of AD and can make MCI a clinical condition which needs to be identified and treated urgently.

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