

Mild cognitive impairment and its management in older people

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Abstract: Mild cognitive impairment (MCI) is a common condition in the elderly. It is characterized by deterioration of memory, attention, and cognitive function that is beyond what is expected based on age and educational level. MCI does not interfere significantly with individuals' daily activities. It can act as a transitional level of evolving dementia with a range of conversion of 10%–15% per year. Thus, it is crucial to protect older people against MCI and developing dementia. The preventive interventions and appropriate treatments should improve cognitive performance, and retard or prevent progressive deficits. The avoidance of toxins, reduction of stress, prevention of somatic diseases, implementation of mental and physical exercises, as well as the use of dietary compounds like antioxidants and supplements can be protective against MCI. The modification of risk factors such as stopping smoking, as well as the treatment of deficiency in vitamins and hormones by correcting behaviors and lifestyle, can prevent cognitive decline in the elderly. The progressive increase in the growth rate of the elderly population can enhance the rate of MCI all over the world. There is no exact cure for MCI and dementia; therefore, further studies are needed in the future to determine causes of MCI and risk factors of progression from MCI to dementia. This will help to find better ways for prevention and treatment of cognitive impairment worldwide.

Keywords: AD, Alzheimer's disease, cognition, dementia, MCI

Background

The improvement of health care support has greatly extended the average life expectancy, which has resulted in a substantial increase in the number of individuals aged 65 years and above. Memory impairment is the usual consequence of the ageing process in the elderly¹ and can be a marker of Alzheimer's disease (AD)² and dementia. It presents with declines in both episodic and immediate memory. Episodic memory is the ability to recall recent experiences and events, and it decreases in the early stages of adulthood. Immediate memory also decreases with advancing age, and it is characterized by a lower ability of thinking and deciding.³

The rate of memory impairment varies among different populations, which can be explained by the possible effects of factors including average age of respondents, type of questions asked, sex differences, educational level, and depression.¹ With the substantial increase in the incidences of dementia, early detection of possible precursors, diagnosis, treatment, and control of modifiable risk factors are important to reduce the rate of disease.⁴

Cognition is a bodily function that is decreased by ageing when there is the impairment of memory, judgment, language, and attention.⁵ It can occur due to neurodegenerative, vascular, and dysthymia/dysphoria problems.⁶ Impaired cognition and reduced cognitive abilities can affect social, functional, and occupational activities.⁵

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The estimated prevalence of cognitive impairment, which varies widely in different research, can be attributed to the use of different definitions. Age-associated memory impairment and cognitive impairment–no dementia are more prevalent than mild cognitive impairment (MCI).¹

The prevalence of MCI is about four-times greater than dementia.¹ Petersen et al were the pioneers in introducing MCI.⁷ MCI characteristics are declining and disturbance of cognition, minimal impairment of complex activities, ability to perform regular daily functions, and absence of dementia.⁴ In typical MCI, memory impairment^{8–10} as well as cognitive decline are at a greater rate than expected for an individual's age^{9,10} and educational level⁹ without impairing daily activities.^{8,9} MCI is a transitional level between normal state of brain and dementia^{7,11–14} with different features including amnesic MCI (aMCI), single-domain non-amnesic MCI, and multiple domain MCI.⁶ The amnesic type is a prodromal stage of dementia^{7,9} and presents itself predominantly with memory impairment.⁶ While memory gets damaged in aMCI,^{7,15} general cognitive function and daily activities are normal.^{7,15,16} Non-amnesic MCI accompanies deficits in cognition⁷ and motor performances¹⁷ without affecting memory.⁷ Memory loss and cognitive decline occur in multiple-domain MCI.⁶ Amnesic and multiple-domain pose an equal risk for progression towards AD.⁶

Although MCI has a greater risk of progression to dementia,^{1,9,18} sometimes it reverts to normal status or has no progression to dementia.^{11,18} It has been reported that up to 44% of patients with MCI at their first visit are estimated to return to normal after a year.¹⁹ Various research indicate that the progression rate of MCI to dementia depends on factors such as the return to normal state,¹⁹ the definitions of MCI applied, sample size, geographic region, the nature of individuals, cultural background, length of follow-up, neuropsychiatric symptoms, assessment procedures, and cutoff points when considering age and education.^{18,20}

Cognitive impairment is a common problem in the elderly^{21,22} that is associated with age,^{8,21,23} with an occurrence rate of approximately 21.5–71.3 per 1,000 person-years in seniors.⁸ MCI rates range from 3% to as high as 42% in population studies,⁸ and from 6% to 85% in clinical settings.^{6,24} The MCI conversion rate to dementia is about 10% per year,^{1,6,16,21,25–27} which is increased to 80%–90% after approximately 6 years.²⁸ It is estimated that a new case of dementia is added each 7 seconds.²¹ The prevalence of dementia in the elderly population is between 1% to 2% per year.^{11,29} It is forecast that number of cases in the developing world will increase by 100% between 2001 and 2040.²¹ It seems that the

rate of dementia will increase from 9.4% in 2000 to 23.5% by 2050 in the population over 60 years of age.³⁰

It is projected that the number of elderly people in the world will increase by 21% in the next 50 years. The elderly population in the developing and developed countries will increase by 140% and 51% respectively. The growing rate of elderly people in the Asian and Pacific regions is faster than the past. Asia–Pacific is a region near the Western Pacific Ocean containing much of East Asia as well as Southeast Asia countries such as Australia, New Zealand, Pakistan, Indonesia, Malaysia, Philippines, Japan, India, Singapore, People's Republic of China, Thailand, Sri Lanka, South Korea, Hong Kong SAR, and Chinese Taipei.³⁰ Among Asian countries, the difference in prevalence of MCI is greater than five-fold.^{8,20} The prevalence of MCI is increasing among developed and developing countries. Rapid demographic ageing in low- and middle-income countries makes it a priority to identify the people at the risk of developing dementia at early stages for targeting preventive interventions. MCI is an intermediate phase between normal ageing-related cognitive decline and dementia; therefore, the identification of MCI can play an important role in early intervention, prevention,²⁰ and proper treatments.¹⁶

Until now, data are scarce for determining the type of cognitive decline, MCI, or dementia. It is necessary to investigate MCI in-depth and find new therapeutic methods and modifiable risk factors.⁴ Although there are many risk factors (Table 1), the greatest risk factor for cognitive decline is age, but the exact cause is still unknown.³¹

The identification of genetic risk factors increases the ability to identify individuals at a higher risk for developing cognitive impairment and/or its progression to dementia.²² The progression into dementia is faster when there are concurrent co-morbid medical conditions³² and gross pathological changes.⁶ MCI proceeds into dementia when amyloid plaques and neurofibrillary tangles deposit in the neocortex of the brain.¹⁴ Apolipoprotein E (ApoE) epsilon 4 carrier can also enhance the risk of conversion from MCI to AD in individuals with cognitive decline.⁶ Cognitive and genetic characteristics of people with aMCI¹ and amnesic multiple-domain MCI¹³ elevate the risk of progression to dementia.²² Due to environmental effects³³ as well as genetic complexity,⁶ finding a responsible single gene or allele to generate MCI seems difficult. Until now, only a small proportion of genetic-related late-life cognitive impairment has been identified.²²

The different fields of science such as psychiatry, neurology, neuropathology, neuroimaging, neuropsychology,

Table I Some of the possible mild cognitive impairment risk factors in the elderly

Somatic factors	
Metabolic conditions	Hyperhomocysteinemia Chronic renal failure Deficiency of vitamins (B12, B6, D, E) Folate deficiency
Endocrine problems	Testosterone deficiency Subclinical thyroid dysfunction Reduced level of estrogens
Cardiovascular problems	Hypertension Hyperlipidemia
Age	
Vision and hearing loss	
Lower physical activity	
Diet	
Educational level	
Socioeconomic status	
Sleep disorder	
Substance abuse	
Environment	
Chronic pain	
Ethnicity	
Living alone	
Sex	
Stress	
Depression	
Fatigue	
Neuroticism	
Smoking habit	
Alcohol consumption	
Down syndrome	
Excess exposure to aluminum	
Head injury	
Genetic factors	
	Apolipoprotein E Paraoxonase Catechol-O-methyltransferase Brain-derived neurotrophic factor Non-coding RNAs, such as miRNA

geriatrics, clinical trials, and ethics are working eagerly to summarize the current state of MCI.¹⁶ This present review intends to provide an up-to-date overview on MCI management.

Framework of MCI diagnosis

MCI is an intermediate stage of dementia, which increases the need for diagnostic tests and markers such as neuropsychological tests, neuroimaging, and biological markers.⁶ The lack of specific tests, gradual loss of memory, health issues changing memory;³⁴ the absence of exact pathological changes in the brain;¹² and the lack of similar signs and symptoms make it more difficult to diagnose MCI. Consideration of memory

loss as a normal event and a part of ageing is another limit in identifying MCI cases.³⁴ The individuals diagnosed with MCI have no dementia and no medical, neurologic, or psychiatric problem to cause memory loss. Diagnosis of MCI is based on subjective complaint of memory loss, memory impairment based on brief cognitive or neuropsychological testing, decline in normal function, and unchanged basic daily functioning.⁸ However, there are some ways to diagnose MCI. One of the methods relies on asking questions about memory (language skills, recall, attention span, and visual-spatial abilities), medications, health status, and comorbidities (depression and emotional health concerns). Interviews with family members and close friends can also increase the chance to ascertain information about the patients' memory, personality, and behavior changes. Diagnosis can be assured when this method is combined with additional tests and brain imaging techniques.³⁴

Biomarker assessment, clinical measurements, and imaging techniques are extra methods.³⁵ Biological markers such as tau protein increase the specificity and acuity of diagnosis to predict the risk of cognitive decline.³⁵ Acute phase proteins, cytokines, cholesterol, isoprostanes, homocysteine, and ApoE4 allele are more potential biomarkers for MCI and AD diagnosis.³⁶

The low plasma levels of amyloid beta (A β) including A β 1–40, A β 1–42, and A β 1–42/A β 1–40 ratio can indicate cognitive decline.³⁶ A β and tau levels such as A β 1–42 and tau phosphorylated at threonine 181 (P-tau181p) in cerebrospinal fluid (CSF) are also used to diagnose MCI and AD with at least 85% sensitivity and 80% specificity.³⁷ A β 42 factor is more important than P-tau181p in the diagnosis of MCI.³⁷ The levels of A β and tau in MCI are less than those in AD.^{38,39} In addition, these biomarkers can predict the risk of functional decline and MCI conversion to AD.³⁷ The lower level of A β in CSF and a high ratio of total-tau/A β can support the diagnosis of prodromal AD in cases with MCI.¹⁸ Furthermore, finding plasma biomarkers such as epigenetic regulators including microRNA are useful to better diagnose individuals at a higher risk of MCI and developing AD in future.⁴⁰ Neuroimaging techniques are also used to diagnose MCI by measuring structural and functional parts of the brain (Table 2).⁶ Imaging tests can show hippocampal volume loss and temporal lobe atrophy in MCI.³⁷ There are amyloid abnormalities in CSF and imaging tests in approximately 70%–74% of subjects with aMCI.¹⁸

The combination of MRI and CSF tau/A β 42 can provide a better prediction of MCI and its progression to AD³⁷ that is extremely helpful in developed countries compared to in

Table 2 List of some neuroimaging techniques to diagnose mild cognitive impairment

Neuroimaging technique
Computed tomography
Magnetic resonance imaging
Functional MRI
Diffusion tensor imaging
Diffusion weighted imaging
Magnetic resonance spectroscopy
Positron emission tomography
Single photon emission computerized tomography

Abbreviation: MRI, magnetic resonance imaging.

the developing world.³⁷ Such difference is due to resource limitations and different cultural values, which limits the utility of MRI and CSF tests.^{12,35} Clinical assessment is used along with other methods to determine cognitive decline (Table 3).¹² Clinical tests are based on interviews to be used in clinical judgment and third-party information. Such tests can help to recognize any psychosocial impairment and the problems of neuropsychological function involving orientation, aphasia, apraxia, memory, calculation, constructional abilities, verbal abilities, and intellectual abilities.²⁸

All tests are used to identify cognitive decline, brain changes, and transitional phase towards AD, which lead to a proper characterization of disease, and its progressive phase in providing effective interventions.¹² Recognition of MCI makes it possible to delay the onset of dementia or even prevent disease via early diagnosis and probably potential treatment.¹⁶ However, an accurate diagnosis is the key element in the practice of medicine for MCI, although etiological heterogeneity⁴¹ limits the development of specific diagnostic criteria, specific therapeutic approaches, and the predictions of clinical progression.⁴² MCI screening for early clinical dementia is recommended particularly for older persons above 75 years of age using blood tests and simple neuroimaging such as computed tomography brain scans.⁴³

Table 3 List of some clinical tests to diagnose mild cognitive impairment

Clinical tests
Intelligence testing
Mini-mental state examination
Clinical dementia rating scale
Neuropsychiatric inventory
Short form neuropsychiatric inventory questionnaire
Structured interview for diagnosis of dementia
Global deterioration scale
<i>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition</i>
Informant questionnaire on cognitive decline
Clock drawing test

It is, of course, not possible to use all tests; however, as much as possible, these tests give a good guideline for assessment of MCI.⁶

Treatments

MCI has a greater risk of progression to dementia; therefore, it needs to be prevented or lowered.^{1,8} A suitable treatment is based on choosing the effective and appropriate strategies for the specific etiology of cognitive disorder.¹ At this time, there is no cure for MCI that stops or reverses it.⁶ It has been suggested that antioxidants such as vitamin E, vitamin C, ginkgo biloba, and curcumin (from turmeric) are useful at the initial stages to reduce oxidative stress levels and ageing consequences.⁶ For example, vitamin E is a dietary compound that can prevent or treat MCI or AD due to strong antioxidant properties.^{44,45} It seems that intake of antioxidants helps to reduce cognitive decline despite inconsistency among epidemiology data on antioxidants and cognitive function.⁴⁶

Pharmacological and nonpharmacological treatments⁶ are used to prevent more reduction of cognition in MCI¹¹ via focusing better and thinking clearly.⁶ Pharmacotherapy is preferably limited to the patients who are at higher risk of transition to AD.^{11,47} Factors including limited options, medications side-effects, uncertain prognosis, and inappropriate social, psychological, and ethical consequences restrict the pharmacological treatment of MCI.⁴⁷ Some chemicals are suggested to treat MCI and prevent its conversion to AD (Table 4). A medication that is used to improve cognition is galantamine. This medication increases the rate of death and has no effect on the conversion rate from MCI to dementia; therefore, the balance of risks and benefits should be concerned for prescription. Acetylcholinesterase inhibitors are used in ApoE4 allele-positive patients with aMCI, who are at a higher risk of developing AD. However, the more popular treatments of MCI are nonpharmacological⁶ such as autonomic training, eating habits, exercise (aerobic exercise), thinking processes, and social activities.¹¹ Such treatment can control psychological and physical comorbidities by having positive impacts on hyperlipidemia, isolation, depression, sleep quality, weight gain, social networking, and vascular risk factors like hypertension.⁶

Appropriate strategies to treat MCI and prevent the progressive decline of cognitive functions are the periodic monitoring of patients, providing lifestyle guidance, treating lifestyle-related diseases, and training on cognitive function.¹¹ Cognitive activities and training programs such as crossword puzzles, novels, and sudoku can also improve cognitive ability or slow down cognitive decline.⁶ The preventive effect of

Table 4 List of some chemicals suggested for mild cognitive impairment treatment

Chemicals	
Cognitive enhancers	Cholinesterase inhibitors (galantamine) Memantine
COX-2 inhibitors	Rofecoxib Celecoxib
Antioxidants	Vitamin E
Neurotonics	Piracetam
Sex steroid hormones	Testosterone supplements, estrogens
Dopamine agonists	
Cytidine diphosphate-choline	
Omega 3 fatty acids	
Phosphodiesterase inhibitors	MEM-1414
Vasoactive intestinal peptide	AL-208
Calcium channel blockers	Nimodipine
Metabotropic glutamate receptor antagonists	C-105
Serotonin receptor (5HT6) antagonists	SGS-518
G-aminobutyric acid B receptor antagonists	SGS-742
Anti-amyloid therapies	Fibrillogenesis inhibitors Vaccines Secretase inhibitors (rofecoxib)

intellectual activities on MCI or dementia⁴⁸ is achieved by protecting against cognitive impairment,⁴⁹ brain disease, and severe neuropathology. The contribution of family members and close friends in the treatment of MCI is via their support, encouragement, patience, and respect.³⁴ However, the risk of MCI can be reduced by a Mediterranean diet⁵⁰ and moderate exercise as well as by interactive and mentally challenging activities.⁵¹

The promotion of independence in communication and activities of daily living, control of vascular risk factors (hypertension, hyperlipidemia, diabetes mellitus), having a healthy lifestyle (physical activity, healthy diet, enough sleep, limited alcohol intake, smoking cessation), along with mental exercises (practicing puzzles, playing scrabble, reading, learning languages, playing musical instruments) are effective factors in the treatment of MCI.⁵² Furthermore, periodic physician care of patients in 3–6 months intervals will help to improve cognition and delay the progression of disease into dementia.

Limitations and strengths of MCI research

There are some limitations that can affect studies about MCI. First, there is the lack of a specific tool for MCI diagnosis and determining its prevalence, especially in cases who delay or refuse to answer survey questions. Second, the exact

classification of MCI requires more extensive measuring tests that are expensive and time consuming. The distribution of patients in the medical clinics is not equal; hence, it is difficult to categorize disease based on types and prescribed medications. In addition, the large population of patients limits the ability to clinically classify all in one study. Heterogeneity of samples also affects MCI studies due to their differences in origins, locations and cultures. The other limitation is the cross-sectional design of studies, which makes it difficult to identify the exact type and cause of MCI as well as the survival of patients. A confounding factor is the return of disease to a normal situation. The lack of specific criteria and specific cutoff points for MCI operationalization can restrict studies about the impairment of cognition. Thus, a wide heterogeneity in diagnosis, type of prescribed medications, severity of illness, and number of patients, as well as a variety of assessment tools can cause great impacts that limit such research. Despite all limitations, the studies about MCI are important to prevent its progression to dementia in future interventions. Research about MCI can be strengthened by having a large sample size containing a wide range of populations with cultural, economic, and social diversity. Pre-validated and standardized measurements strongly increase internal validity in studies and elevate consistency between countries, which can result in a common algorithm used to define MCI.

Conclusion and future works

All data from different countries can reflect the diversity of MCI in different regions in relation to demographic and cultural influences. Such information can be beneficial for both clinical and educational purposes. Our review has potential to improve the knowledge of a large group of people, including health care providers, policy-makers, MCI patients, and family members. In addition, it can increase the ability to identify variations in the utility of clinical diagnostic criteria. This review sheds light on the fundamental issue of developing MCI, although it seems relatively simple. It is necessary to investigate more on risk factors. It will be necessary in the future to determine standardized definitions and the diagnostic criteria for MCI and prodromal stages of AD in population-based studies and clinical trials. It is also necessary to find specific biomarkers, which help to correctly diagnose MCI and MCI converters to dementia. Clinical evidences and anatomical changes in the brain in specific cognitive deficits promote the improvement of imaging techniques, which results in a better assessment of different stages and types of MCI.

Disclosure

The authors report no conflicts of interest in this work.

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