Review article
Mild cognitive impairment: a comprehensive review

V N Mishra, V Singh

*Department of Neurology, Institute of Medical Science, Banaras Hindu University, Varanasi-221005, UP (INDIA).

ABSTRACT

Background: Mild cognitive impairment (MCI) is an intermediate stage between normal cognitive alterations associated with aging and dementia. MCI individuals identified as having a faster rate of progression to dementias. Main body: There is different type of risk factors for MCI progression include greater cognitive deficits at baseline, ApoE4 carrier status, brain volume changes, cerebrospinal fluid (CSF) changes, and the presence of behavioral and psychological symptoms. Refinements in the diagnostic criteria for MCI and the identification of biomarkers result in the development of possible prevention and treatment strategies. Conclusion: In the present study, we summarize the epidemiology, neuropsychological aspect, management and preventive treatment for MCI. As, better understanding of MCI could help in minimizing risk of MCI.

1. Introduction

Mild cognitive impairment (MCI) or Neuro Mild cognitive disorder (MCD) consider as a transitional state between the cognition of normal aging and mild dementia. It is a clinical term, which describes individuals, have mildly impaired performance on objective neuropsychological tests but relatively intact global cognition and daily functioning (3). MCI validated as qualitatively different from both normal aging and dementia and has been a matter of debate regarding whether or not it is a risk factor for the development of dementia (3). The advancement of healthcare 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 (1). Memory impairment is the usual consequence of the aging process in the elderly and can be a marker of Alzheimer’s disease (AD) and dementia. The AD presents with diminished episodic and immediate memory. Episodic memory refers to the ability to recall recent experiences and events, and it decreases in the early stages of adulthood. Immediate memory also decreases with increasing age, and recognized by a lower ability to think and deciding (2).

1. National Institute on Ageing and Alzheimer’s Association (2010) revised the criteria of MCI as: a) concern regarding change in cognition, b) preservation of independence in functional abilities, c) impairment in one or more cognitive domains and d) not demented (7,8).

2. “Diagnostic and Statistical Manual of Mental Disorders” (DSM-5) includes MCI under the category of mild neurocognitive disorders (9).

2. MCI is classified into two subtypes

Based on cognitive features, MCI is classified into amnestic and non-amnestic. Further into single domain or multiple domains, based on the involvement of the number of cognitive domains affected. Amnestic MCI is a clinically significant memory impairment that does not meet the criteria for dementia. It was stated that mini-mental state examination (MMSE) scores of less than 26 in uneducated individuals and less than 28 in educated individuals warrant assessment for MCI (10).

In studying the prodromal phase of dementia, another group observed, known as “mild behavioral impairment” (MBI) that presented only with behavioral symptoms and yet progressed toward dementia. Thus, Taragano et al. (11) proposed another classification: 1) MCI with neuropsychiatric symptoms, 2) MCI without neuropsychiatric symptoms, 3) MBI with cognitive symptoms, and 4) MBI without cognitive symptoms.

Based on etiopathology, it can be neurodegenerative (pre-Alzheimer’s, Lewy body, fronto-temporal) or vascular. The nonamnestic type is probably less common than the amnestic type.
type and may be the forerunner of non-Alzheimer’s Disease in the text such as fronto-temporal dementia or dementia with Lewy bodies (12).

3. Neuropsychiatric manifestations

MCI frequently presents with neuropsychiatric symptoms. The most comprehensive studies of behavioral manifestations have documented with at least one neuropsychiatric symptom in 35-75% of MCI patients (11). Depression, apathy, and anxiety are consistently among the most common behavioral abnormalities in MCI (13). Of the neuropsychiatric manifestations of MCI, depression is the most widely studied. Cardiovascular Health Study Cognition Study depicted prevalence of depression was 20% in MCI (14). Of the entire neuropsychiatric symptom in AD, apathy is most prevalent. It commonly starts during the MCI stage and progressively increases as AD progresses, and related to worsening on tests of memory and executive control. Psychotic symptoms such as delusions and hallucinations reported to be less than 5% in MCI patients (15). A number of varied results found for euphoria, aberrant motor behavior, and irritability in MCI (16).

1. Epidemiology

MCI prevalence rates vary from 3 to 17% (17). There is 3% MCI at the age of 60 years and 15% at the age of 75. The rate of development of MCI was about 5.3% per year (3.5% in the seventh decade of life and 7.2% in the eighth decade) (18). According to previous studies, men seemed to found more affected with MCI in comparison with women. Vas and Pinto et al. (2001) showed that the prevalence of 0.25% AD in the population with it increasing to 1.5% for those 65 years and older (19). An Indian study from Calcutta reported 14.89% prevalence of MCI of which the amnestic type (more seen in men) was 6.04% and the multiple domain types (more seen in men) was 8.85% (20). The study from Cochin also reported the prevalence to be about 14.89% (21). Satishchandra and group (22) on the other hand reported an incidence in a clinical setting to be as high as 47.1%. Mridula, Alladi et al. (23) in their clinic sample reported a rate of 59% with MCI. Conversion rates from MCI to the AD found to be 10-15% as reported by Peterson in his sample at a specialty clinic, whilst it was 8-10% in the general population, by his estimate (24). Alladi et al. (23) in their clinic sample, showed 11% conversion rate to AD, during a 13 month follow up.

2. Stability of diagnosis and outcome

MCI may not always convert to dementia. Around 20-40%, cases appear to improve over time on retesting. After diagnosis, the subtype may change on follow-up. Single domain particularly seems to be at risk of this shift (25). However, some have found that all MCI subtypes either convert to dementia or retain their MCI status.

MCI may have different outcomes (26). Multi-domain amnestic MCI appear to be at the greatest risk of dementia. Amnestic MCI has the highest risk for conversion to Alzheimer’s dementia, whereas multi-domain presentation to vascular dementia (27). A non- amnestic subtype with multiple domain involvement more likely converts to non-AD, with the single domain at particular risk of progressing to fronto-temporal dementia (28). Rates of progression from MCI to dementia vary in the range of 20-40% (10-15% per year) with a few outliers at the lower and higher ends of the spectrum (29).

3. Risk factors for progression of MCI

Progression of MCI may be determined by the following factors includes, older age, fewer years of education, Multi-domain amnestic MCI, High fat diet, Medical comorbidities. Medical comorbidities involving metabolic syndrome, chronic inflammatory diseases, vascular disease, thyroid disorders, and elevated homocysteine levels, Excessive alcohol intake, Stressful lifestyle, Untreated depression, Presence of apolipoprotein E (ApoE), E4 allele and Magnetic resonance imaging (MRI), with volumetric measurements of the hippocampus at or below the 25th percentile for matched age and sex (30).

4. Evaluation of a patient suspected of MCI

Any patient suspected of having MCI should undergo detailed clinical and investigatory evaluations. A thorough history and physical examination focusing on the status of cognitive functions, a status of activities of daily routine, medications, neuropsychiatric evaluation, and laboratory testing are important components of this assessment (31).

A. Taking history: Taking history of the patient provides, details about the onset of disease, duration, nature, and progression of cognitive symptoms.

B. Functional status: Cognitive paired patient functional status was gained by taking information from family members, the previous level of functioning, both personal as well as instrumental, in order to differentiate MCI from dementia. The Functional Activities Questionnaire used for assessing these, using data from an informant. A Score of 6 or more has >85% accuracy in differentiating MCI from dementia (32).

C. Information to rule out potentially reversible causes of MCI (depression, vitamin B12/folate deficiency, thyroid diseases, and medication).

D. Presence of neurological or psychiatric symptoms (to rule out Parkinson’s disease, normal pressure hydrocephalus, stroke, or neuropathy).

E. History of substance use disorders, family history of cognitive disorders, and psychosocial history.
8. EXAMINATION

A. Thorough Neurological and Psychiatric Evaluation: A complete psychiatric evaluation and neurological examination including orthostatic hypotension, extraocular movements, vision, hearing, speech, focal weakness, ability to stand from a chair, and gait are useful for identifying potential contributors to cognitive decline including stroke, parkinson disease, normal-pressure hydrocephalus, or neuropathy due to toxins or vitamin deficiency. Depression associated with cognitive impairment in the elderly can assessed using the Geriatric Depression Scale (GDS), on which a score of 6 or more suggests depression (33).

9. INVESTIGATIONS

1. Laboratory Testing: Testing complete blood count, electrolytes, glucose, calcium, thyroid function, vitamin B 12, and folate is recommended to identify potentially reversible forms of MCI including infection, renal failure, hypomagnesemia or hypermagnesemia, hyperglycemia, hypocalcemia or hypercalcemia, hypothyroidism or hyperthyroidism, and vitamin B 12 or folate deficiency. Laboratory testing for liver function, syphilis, and human immunodeficiency virus (HIV) may reveal rarer causes. About 9% of the causes of dementia seem to be reversible. While studies have suggested that levels of biomarkers in the cerebrospinal fluid (e.g., Aβ42 and tau protein) may help to identify patients with MCI who are more likely to progress to AD, a routine lumbar puncture is generally recommended for clinical evaluation (34).

2. Neuroimaging

A. Structural neuroimaging

The National Institute of Aging-Alzheimer's Association (NIA-AA) diagnostic guidelines do not recommend routine neuroimaging in the assessment of MCI but suggest that it may help in determining MCI etiology and prognosis. Structural MRI may be useful for identifying MCI and those at greater risk for progression from MCI to dementia. Decreased medial temporal cortex, especially in the entorhinal and hippocampal volumes, are well-established risk factors in an AD (35). However, decreased size of the hippocampus on volumetric measures is suggestive of MCI and correlated with the likelihood of progression to dementia. MRI in nonamnestic MCI revealed a significant reduction in the dorsolateral and dorsomedial prefrontal cortices and reduction in the volume of caudate nucleus; meanwhile, in amnestic MCI, atrophy in bilateral posterior temporoparietal cortices, medial temporal cortices, posterior cingulate gyrus, and right inferior parietal cortex were noted (36). However, the lack of standardization and validation for these measures limit their usefulness in clinical practice, and they are not currently recommended for informing prognosis. Nevertheless, they may rule out other potential causes for cognitive decline such as subdural hematoma, stroke, normal pressure hydrocephalus (NPH), or tumor, if suggested by history and physical or laboratory studies. Diffusion tensor imaging produces in vivo images of biological tissues weighted with the local microstructural characteristics of water diffusion. Higher diffusivity in the left centrum semi-ovale and right parietal regions and left hippocampal region seen in cognitively affected subjects. The combination of MRI and DTI hold promise in the future (38). Diffusion imaging makes use of the variability of "Brownian motion" of water molecules in brain tissue. Cell membranes, axon cylinders, and vascular structures restrict or limit the extent of diffusion. In addition, macromolecules and chemical interactions of water affect diffusion properties. Therefore, in the brain, water diffusion referred to as "apparent diffusion." Higher Apparent Diffusion Coefficient’s (ADC’s) have found in the hippocampus, temporal lobe gray matter, amygdala, posterior cingulated and corpus callosum of patients with MCI compared with that of controls (39).

A. Functional neuroimaging

Magnetic resonance spectroscopy (MRS) assess cognitive changes on the basis of metabolite ratios. A host of researchers has found a reduction in the N-acetylaspartate to creatinine ratio particularly in the temporal and parietal lobes in an AD. However, the evidence in MCI is yet lacking. Some researchers have been able to show posterior cingulate involvement in MCI (37). Increased activation in the medial temporal lobe with decreasing activation in the posterior medial cortices seen in Functional MRI. The revers found while performing fMRI after exposure to galantamine, suggesting a clear involvement of the cholinergic system in declining cognition. With 4T fMRI subjects with MCI showed decreased magnitude of activation in bilateral frontal cortex regions (on encoding and retrieval), the left hippocampus (on retrieval), and the left cerebellum (on encoding) compared with the magnitude of activation in control subjects. Mild cognitive impairment patient showed increased activation in the posterior frontal lobes (on retrieval). Reduction in hippocampal activation during retrieval was the most significant correlate of clinical severity of memory loss in mild cognitive impairment (40). Reduced glucose metabolism (in PET) and reduced blood flow (in SPECT) reported in the tempo-parietal association cortices, posterior cingulate and hippocampus in MCI. Similarly, gray matter loss in the entorhinal and hippocampal areas and hypo-metabolism or hypoperfusion in the posterior cingulate cortex and precuneus has also observed (41).

3. Neuropathology

It is only in patients where progression from MCI to AD occurs, that the gross pathology can accurately assessed. In these patients, there is evidence of neuritic plaques and neurofibrillary tangles (particularly in the entorhinal cortex and hippocampus), along with amyloid deposition (42). Braak
and Braak in autopsies conducted on a number of patients in various stages of cognitive change demonstrated that plaques and tangles are prior to the appearance of amyloid, and this might be significant while following up patients of MCI to AD (43).

There are variety of microscopic changes, which are:

1. Neuronal loss: Decreased neuron number and volumes are mainly in the entorhinal cortex (which forms a nerve relay) and hippocampus (memory storage) (44).

2. Beta-amyloid deposition: Though the deposition of beta-amyloid in MCI is intermediate between normal elderly and those with an AD, this is not of statistical significance.

3. Neurofibrillary tangles and tau proteins: Phosphorylated tau protein within the neurofibrillary tangle is in the vulnerable regions. The presence of amyloid does tend to accelerate the tangle formation (45).

4. Down-regulation of trkA RNA: There is evidence that both those with MCI and those with AD had a significant loss in the number of trkA-containing neurons, (46% decrease for MCI, and 56% for an AD). The alterations in the number of nucleus basalis neurons containing trkA immunoreactivity occur early and not accelerated from the transition from MCI to AD (46).

5. Loss of Choline Acetyl Transferase (ChAT): In individuals with MCI and mild AD, ChAT activity was unchanged in the inferior parietal, superior temporal and anterior cingulate cortices. On the contrary, ChAT activity in the superior frontal cortex was significantly elevated above normal controls in MCI subjects, whereas the mild AD group was not different. ChAT activity in the hippocampus was significantly higher in MCI subjects. The up-regulation in frontal cortex and hippocampal ChAT activity could be an important factor in preventing the transition of MCI subjects to AD (47).

4. Biological markers

The advent of a prodrome to Alzheimer’s disease, and the possibility of early intervention, led to a number of researchers looking for tangible, quantifiable means of assessing the changes. The most commonly studied biomarkers can divided into the following groups: 1) Related to the gross pathological changes of neurofibrillary tangles and amyloid sheets, are the cerebrospinal fluid biomarkers. Recent advances further support a notion that plasma A-beta levels, expressed as an Abeta-42/Abeta 40 ratios could also be of value particularly in the progression of MCI to AD (48). 2) Another biomarker of importance, related to lipid peroxidation is isoprostane, which found, elevated in the urine, CSF, and blood of AD patients (49). 3) Measurement of a protein biomarker complex that may include one or two of trans-thyretin protein and/or a prostaglandin-H2 D-isomerase protein, (50). 4) In AD and MCI patients, there is a significant rise in the percentage of monocytes producing cytokines (IL-1β, IL-6, IL-12, and TNF-α), as well as a decreased response of these cells to inflammatory challenges, when compared with controls (51).

5. Genetic testing

The presence of mutations in A4 precursor protein (APP) and PS1 and PS2 genes are likely predictors of the conversion of MCI to early Alzheimer’s dementia (52). In addition, there is an increased risk for the development of dementia in an individual with MCI, in the presence of apolipoprotein (Apo) E4 allele. On the other hand, an E2 allele is associated with decreased risk. In an Indian study, frequencies for ApoE2, ApoE3, and ApoE4 alleles found to be 0.25, 0.35, and 0.4 in Alzheimer’s patients and their first-degree relatives. ApoE4 was present in 71% of the patients with Alzheimer’s and their relatives that was 2.7 times higher than the controls. However, the cost and availability of the testing have limited its use in the Indian context. The complex genetics of AD and also MCI are proving to have makes it difficult to pinpoint a single gene or allele which may be responsible. Many researchers have put forth their various hypotheses. 1) In cognitively impaired patients without dementia, the utility of Apolipoprotein E (ApoE) genotyping is unclear. What known is that ApoE epsilon 4 carrier status was associated with conversion to an AD. Its role in MCI may be limited. 2) Lindsay Farrer and colleagues have data collected from the Multi-Institutional Research in Alzheimer’s Genetic Epidemiology (MIRAGE) study, which supports the idea that risk factors for vascular disease and AD are common (53). One of the families of genes they have investigated is those that encode paraoxonase (PON - an enzyme that expressed in the liver) which show polymorphisms in MCI (54). 3) The same group of researchers is studying the Wadi Ara tribe in Israel, who has a high incidence of an AD, perhaps due to inbreeding. They are studying polymorphisms on the ACE gene, and they believe that though this is more predictive of vascular dementia - this cascade of the A-beta amyloid accelerated through the vascular events. 4) Matay and colleagues from the National Institute of Mental Health (NIMH) have a unique technique of research called “Imaging Genetics” (55). They use imaging techniques to capture genetic polymorphisms. Their main area of work revolves around catechol-methyltransferase (COMT) and brain-derived neurotrophic factor (BDNF) on age-related changes in cognition. The met allele of a frequent polymorphism (val66met) in the gene for BDNF if present shows reduced hippocampal use during memory processing. 5) Giulio Pasinetti and his team use cDNA microarray and proteomic technologies to assess and quantify changes in cognition (56).

6. Neuropsychological testing

Assessment of cognition in the elderly can be a challenging task. There are a variety of tests that can be used for the
assessment of MCI; however, tests such as MMSE, clinical dementiaring (CDR) scale, repetition, fluency, and digit span are the ones that are handy, easy, and quick to administer and can be readily used by the clinicians (60). The commonly used tests are as follows:

A. Brief cognitive tests

A comprehensive set of tests applied when there is suspicion of having MCI. However, there are no clear-cut guidelines, the following tests commonly used for screening.

i. MMSE: It is probably the most widely used test for bedside memory testing. It has sensitivity and specificity of 70% with a cutoff score of 26. The scores of 26 (in non-educated individuals) and 28 (in educated individuals) warrant further assessment, follow up and surveillance for MCI. Addition of a recall after a longer delay improves the sensitivity and specificity to >80% (57).

ii. Montreal Cognitive Assessment (MoCA): developed specifically for the detection of MCI and takes approximately 10 min to administer. It has a high sensitivity as well as specificity. It assesses orientation, attention, immediate and delayed recall, executive function and language, etc. (58).

iii. DemTect: This evaluates immediate and delayed recall of word list, number transcribing, verbal fluency, and reverse digit span. It has a sensitivity of 80% and specificity of 92% in differentiating MCI from normal controls (59).

iv. Clinical Dementia Rating (CDR) Scale: It considers six domains - memory, orientation, judgment and problem solving, community affairs, home, and hobbies, and personal care. A score of 0.5 on this scale is of diagnostic importance for MCI, according to Peterson's modified criteria. American Academy of Neurology (AAN) accepts this score as equivalent to the presence of MCI. It has a high inter-rater reliability and appears to be a reliable and valid tool for assessing and staging dementia (60).

v. Global deterioration scale: A score of three considered to indicative of MCI (61).

vi. Neuropsychological tests: These are helpful but not definitive for the diagnosis of MCI. Various cognitive domains can be tested and tests used include tests for recall (Hopkins verbal learning test, Wechsler's memory delayed recall), verbal category and semantic fluency, attention (digit span forward and backward), processing speed (trail making test A), visuoconstructual function (clock drawing test and Rey-Osterricht complex figure test), and executive functioning (trail making test B and symbol digit substitution) (62).

B. A typical battery assessing these domains is more sensitive than routine office tests and can provide a thorough profile of deficits, differentiating between amnestic from the nonamnestic and single domain from multiple domains MCI.

i. Neuropsychiatric Inventory (NPI) and short questionnaire form of the NPI (NPI-Q): The presence of psychiatric symptoms and caregiver distress can be assessed (63).

ii. Addenbrooke's cognitive assessment: It assesses five domains - orientation/attention, memory, verbal fluency, language, and visuospatial. At the cutoff of 82, the likelihood of dementia is 100:1. It has a high sensitivity of 0.94 and specificity of 1 and correlates well with CDR (64).

iii. AD assessment scale-cognitive subscale (ADAS-Cog): It assesses 11 domains in cognition, along with 10 clinician-rated items for psychosis, depression, agitation, etc. Its results can range from MCI to severe impairment, and is a good tool for longitudinal assessment; however, it takes a long time to administer (65).

iv. Informant questionnaire on cognitive decline in the elderly ([CODE]) addresses the objective reporting by the caretaker on the day-to-day behavior of the person. It requires a very well informed caregiver for the same (66).

v. Assessment By definition and the clinical presentation, one can easily conclude that memory testing would be the most important single means of accurately assessing MCI. However, it becomes essential to have a comprehensive set of tests accurately reach the suspicion that an individual may have MCI. Of historical importance are the CAMDEX (Cambridge Mental Disorders of the Elderly Examination) where "minimal dementia" is suggestive of MCI, and "limited cognitive disturbance" on the CARE (Comprehensive Assessment and Referral Evaluation) (67). Although presently there is no clear guideline, the following are the commonly administered tests to aid the diagnosis: Mini-mental status examination (MMSE) is probably the most widely used test for bedside memory testing. Interpretation, however, can pose to be an issue. It has both high floor and ceiling effect. These tests also used during PET activation procedures. It is of course, not possible to use all tests, however, as far as possible, these tests give a good guideline for assessment of MCI.

10. Management of MCI

There have been no specific recommendations for the treatment of MCI but the management can divided into pharmacological and non-pharmacological (that are mostly the preventive factors for MCI) for the sake of simplicity.

A. Pharmacological:

Although no drug is approved for treating MCI, the following have been the focus of interest:

i. Acetylcholinesterase Inhibitors

The AD Cooperative Study favored donepezil at 1 year but not at 3 years follow-up. Its effect was greater in ApoE4-positive individuak that seemed to be an important predictor
for progression. Based on these studies, the screening of patients with amnestic MCI for ApoE4 allele recommended and only if an ApoE4 allele is present the patients should give AChEIs (68).

ii. Piribedil

It is a dopamine receptor agonist, having acetylcholine release in the hippocampus and the frontal cortex as a putative mechanism of action. Piribedil improved cognition over 3 months on the primary outcome in the placebo-controlled study at National Institute of Mental Health and Neurosciences (NIMHANS) by Nagaraj et al. (69).

iii. Memantine

Memantine has not reported to benefit patients with MCI (70).

iv. Cyclooxygenase (COX)-2 inhibitors

Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce brain neurotoxic inflammatory responses and so was assumed to improve cognition. Rofecoxib increased incident cases of Alzheimer’s dementia in the study and has a fair evidence against its use. Triflusal (COX-1 and COX-2 inhibitors) had no effect on cognition but was associated with a reduced risk of conversion to AD (71).

v. Nicotine

Brain nicotinic receptors are important for cognitive function. Nicotine patches improved attention, but not global functioning, over 6 months (72).

vi. Gingko Biloba

The proposed mechanisms of action include increasing brain the blood supply, modifying neurotransmitter systems, and reducing oxygen-free radical density. However, the results of its use have been inconsistent (73).

vii. Vitamin B

Higher homocysteine plasma concentrations are associated with cognitive impairment, the levels of which decreased by B vitamins. Immediate memory did not improve; however, attention and executive functioning had varying results (74).

viii. Antioxidants such as vitamin E, vitamin C, and curcumin (from turmeric) hypothesized to reduce oxidative stress and aging, yet work in this field is largely in the incipient stages (75).

ix. Omega-3 polyunsaturated fatty acids (PUFAs)

With PUFAs, cognition, in terms of verbal fluency and depressive symptoms improved at 6 months follow-up (79).

x. Antiamyloid therapies

Secretase inhibitors reduce amyloid production by inhibiting the secretase activity. Similarly, fibrillogensis inhibitors (alzhmed and clioquinol) are also under research, along with the vaccines that would prevent amyloid plaque formation.

xi. Neurotonics

The use of piracetam has not met with any evidence (78).

xii. Estrogens

These have found actually increase the risk for MCI and AD (77).

xiii. Others

Huannao Yicong responded on a cognition and social functioning measure but the result was not significant. CDP choline, Calcium channel blocker nimodipine, and testosterone supplementation seem partially effective (76).

xiv. Drugs on trial for MCI include vasoactive intestinal peptide (AL-208), a selective metabotropic glutamate receptor antagonist (C-105), a novel L-type calcium channel blocker (MEM-1003), a phosphodiesterase inhibitor (MEM-1414), a gamma-aminobutyric acid B receptor antagonist (SGS-742), and a selective serotonin receptor (5HT6) antagonist (SGS-518).

B. Non-pharmacological

Although, the outcome of MCI still a matter of debate, efforts made to prevent progression of the disorder and much emphasis given for its prevention at the first place. The following are some non-pharmacological measures that have discussed, which have a role in preventing MCI and reducing the risk of its progression.

i. Treatment of vascular and other comorbidities such as hypertension, diabetes, atrial fibrillation, obesity, vitamin deficiency, hypothyroidism, depression, and sleep disturbances. Abstention from heavy alcohol, smoking, and other substances of abuse (80).

ii. Diet: A Mediterranean diet (with high intake of cereals, fruits, fish, legumes, and vegetables) reduces the risk of cardiovascular disease, increases the concentration of plasma neutrophils, limits proinflammatory cascades, thereby helping in preventing cognitive decline. Second dietary factor that has implicated is curcumin (a pharmacologically active ingredient in the Indian spice "haldi") that was a probable contributory factor mentioned for the lower prevalence of MCI in India than in developed countries.
iii. Socialization with people, apart from one's immediate family members, e.g., friends, being part of a senior citizen's group, etc. (81).

iv. A spiritual activity of some form is also of importance in maintaining cognition (82).

v. Physical exercise/activity: It has favorable effects on neuronal survivability and function, neuroinflammation, vascularization, neuroendocrine response to stress, and brain amyloid burden. Inconsistent results of improvement in fluency, memory, and trail making observed. It has claimed that any frequency of moderate exercise reduced the odds of having MCI (83, 84).

vi. Computer-assisted cognitive training: It involves teaching individuals empirically supported strategies and skills in order to optimize current cognitive functioning and independence in daily life. Its effect was on objective and subjective measures of memory, quality of life, and mood (85).

vii. Cognitive stimulation: It involves activities designed to increase cognitive and social functioning in a nonspecific manner (e.g., reading, board games, and group discussions) (86).

1. REGULAR FOLLOW-UP: Given the uncertainty of prognosis in this population, it has recommended that MCI patients should every 6-12 months for follow-up. Follow up would consist of repeat cognitive screening, functional inquiry, and careful history taking (including family collateral) to assess for conversion to dementia. It is also important to educate patients and families about the kinds of warning signs that would suggest the possibility of progression and warrant the need for follow-up (87).

2. Other relevant issues

A. Informant reliability: The informant reliability is a matter of grave consideration in MCI. A recent study by et al. demonstrated a discrepancy on the financial domains of checkbook management, bank statement management, and bill payment, and on overall financial capacity, as reported by patients and informants, informants being laxer about the abilities. This could have important implications for case management and treatment (88).

B. Ethics: The diagnostic entity of MCI is one by exclusion. The validity and reliability of the entity still have to stand the test of time. Further, treatment becomes an ethical dilemma in view of the weak current evidence, and the apparent stigma attached to the same (89).

13. Conclusion and future directions

All data from different studies reflects the diversity of MCI in relation to demographic and cultural influences. This information can be beneficial for both clinical and educational purposes. Present study has the potential to improve the knowledge of a large group of people, including healthcare providers, policy-makers, MCI patients, and family members. Moreover, it can increase the ability to identify variations in the utility of clinical diagnostic criteria. Present study 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 for the future to determine standardized definitions and the diagnostic criteria for MCI and prodromal stages of an AD in population-based studies and clinical trials. It is a crucial to find specific biomarkers, which help for correct diagnose MCI and MCI converters to dementia. Clinical evidence 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.

References


