



Mild Cognitive Impairment- A Conceptual Study

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ABSTRACT

Ageing means growing old, maturing, progressive changes related to the passage of time. .Memory complaints are ubiquitous in our aging population. Mild cognitive impairment (MCI) is considered by many as an intermediary stage for dementia. Many older adults fear that today's forgetfulness will usher in tomorrow's dementia. 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 may act as a transitional level of evolving dementia with a range of conversion of 10%–15% per year. 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. There is no exact cure for MCI and dementia. This is an effort to help to find better ways for prevention and treatment of cognitive impairment worldwide.

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

Introduction

We know of course that cognitive test performance is heavily influenced by age and education, and, in some cases, by gender.^[1] In clinical practice, we find patients or their families talking about cognitive impairment as reflected in impaired functioning, forgetfulness, repetitiveness, difficulty in carrying out tasks that would

have been routine in the past, getting lost in familiar places or becoming disoriented. The term mild cognitive impairment (MCI) has been in use since the early 1990s but about a decade ago it acquired the more specific meaning of a "transitional" or intermediate state between normal cognition and dementia. The precise operational definition of this term has varied

across studies and over time^[2] with some authors claiming that it is simply early Alzheimer's disease and not a separate entity.^[3]

Alzheimer's disease is a primary neurodegenerative disease which appears to be the single most common cause of the dementia syndrome in older adults in most populations which have been studied around the world.^[4]

MCI is a new term and awareness is less in community therefore, study of MCI is necessary. MCI pathology starts 10-15 yrs before signs of AD, so we could catch them early to prevent AD.

The high proportion of dementias caused by Alzheimer's disease has contributed to the terms "dementia" and "Alzheimer's" being used interchangeably. It has also led to the diagnostic criteria for the dementia syndrome being "Alzheimerized" by the requirement of specific impairment in memory.^[5]

Definition⁽⁶⁾

Mild cognitive impairment defines a transitional stage between normal ageing and dementia,. Mild cognitive impairment is important in terms of recognising (and taking seriously) memory loss in older people as well as identifying a group of individuals at high risk of developing dementia and who may benefit from preventive strategies.

Symptoms of MCI

If you or your family members have increasing concerns about your mental abilities and memory, the cause could be MCI. If so, you will be experiencing some or all of the symptoms below:

- More frequent difficulty remembering simple things.
- Difficulty following a conversation or basic instructions
- Frequently losing your train of thought
- Forgetting appointments or scheduled events
- Feeling overwhelmed when you attempt to make plans or decisions
- Losing your way even in familiar locations.

With MCI, these changes do not occur suddenly but worsen over time. In addition to these cognitive symptoms? or perhaps because of them? many people with MCI also experience secondary emotional symptoms such as depression, anxiety, irritability or apathy.

Causes of MCI

The causes of MCI are not clear, but it appears some of the same risks for Alzheimer's disease are risks for MCI. Those risks include:

- Being 65 or older
- Having a family history of MCI, Alzheimer's disease, or another form of dementia
- Having certain medical conditions, such as high blood pressure, diabetes, stroke, high cholesterol, or heart disease, brain disease.
- Substance abuse, alcohol abuse
- Lack of exercise.

Nomenclature

MCI has often been referred to by various names, the commonest of which have been including:

- Benign senescent forgetfulness (BSF),.
- Age associated memory impairment (AAMI)
- Age related memory decline (ARMD),
- Age related cognitive decline (ARCD)
- Mild cognitive disorder/mild cognitive dysfunction (MCD)
- Mild cognitive impairment (MCI)
- Mild neurocognitive disorder (MND)
- Cognitive impairment no dementia (CIND)

Of these the following have stood the test of time, and hence are defined:

- BSF - Individuals have poor retrieval of relatively minor details of an episode but no memory loss of the episode itself.
- AAMI - by NIMH is memory loss of 1 standard deviation on testing with no cognitive impairment in advancing age and normal intelligence.

- ARCD - is memory impairment as in AAMI and objective cognitive decline within normal limits for age now known as CIND (Cognitive Impairment Not Dementia)
- MCI - have definite memory and cognitive impairment with GDS score of 3 and a CDR score of 0.5 also known as questionable dementia.

These have at times been referred to as sub-types of MCI.^[7] Recent efforts have been directed at developing a uniform diagnostic classification for MCI.

Subtypes of MCI:^[8]

A. Based on cognitive features

This can be further divided into:

1. Amnestic MCI - Predominant impairment in memory
2. Multiple domain MCI: Impairment noticed in more than one cognitive domains which can include memory
3. Single-domain non-amnestic MCI: Predominant impairment in any one cognitive domain apart from memory

1 and 2 have an equal risk of progress to AD.

B. Based on aetiopathology

These can be of the following types:

1. Neurodegenerative: (MCI, Pre-Alzheimer's, Lewy Body, Fronto-temporal or focal atrophy)
2. Vascular: Vascular dementia and mixed dementia
3. Dysthymia or dysphoria (anxious and/or depressed states)

Epidemiology

The rates of MCI reported vary from 3 to 17%^[9] it being 3% at 60 years to 15% at the age of 75.^[10] In fact, the rate of development of MCI was about 5.3% per year^[10] (3.5% in the seventh decade of life and 7.2% in the eighth decade). Men seemed to be more affected than women (though we must

remember at this point that AD is more seen in women).^[10]

Among the early Indian studies done for dementia, the one done in 2001 by Vas, Pinto et al. showed a prevalence of 0.25% Alzheimer's disease in the population with it increasing to 1.5% for those 65 years and older.^[11] However, MCI was not studied then.

Recently, an Indian study from Calcutta^[12] showed prevalence of 14.89% MCI-of which the amnestic type (more seen in men) was 6.04% and the multiple domain type (more seen in men) was 8.85%. The study from Cochin^[13] also reported the prevalence to be about 14.89%.

Satishchandra and group^[14] on the other hand reported an incidence in a clinical setting to be as high as 47.1%. Mridula, Alladi et al.^[15] in their clinic sample reported a rate of 59% with MCI, in their elder population.

Conversion rates from MCI to AD were found to be 10-15%^[10] as reported by Peterson in his sample at a specialty clinic, whilst it was 8-10%^[10] in the general population, by his estimate. Mridula, Alladi et al. in their clinic sample, showed 11% conversion rate^[15] to AD, during a 13 month followup

Pathology

Although most reviews of MCI have concentrated on the pathology of cortical and basal limbic forebrain regions, there is mounting evidence suggesting that the brainstem harbors the earliest cellular degenerative events, even before those seen in neo and limbic cortex. Clinical pathological investigations of the norepinephrine (NE) containing locus coeruleus (LC) demonstrate NFTs occur during aging^[16]. In MCI, LC neurons display sequential early and late tau conformational epitopes linked to NFT formation^[16, 17, 18]; abnormal tau aggregates occur within proximal axons of LC projection neurons in the absence of either NFTs or neuropil threads in the transentorhinal cortex^[16]. Since LC cytopathology correlates with overall cognition, noradrenergic dysfunction should be considered among the earliest cytopathologic lesions mediating the onset

of cognitive decline in the aging-MCI continuum^[18]. Most likely this occurs by disrupting ascending LC noradrenergic input to the thalamus, hippocampus and cortex^[16]. Similar to the LC, clinical pathologic investigations reveal the involvement of the brain stem serotonergic raphe cortical projection neurons in AD^[19,20,21]. In the early Braak stages 0, II, and III, phospho-tau cytoskeletal changes occur in the supratrochlear-subnucleus of the dorsal raphe nucleus (ST-DR)^[22,23], suggesting that the ST-DR plays a key role in the induction and spread of AD-related cytoskeletal pathology. Currently, information on the state of raphe neurons in MCI is lacking. Once these regions of the brain are fully investigated in MCI, it may be that the currently accepted stages of the cytopathology of MCI may require reclassification based on the emerging concept of a neuron-to-neuron transynaptic propagation, which maybe initiated in the brainstem and over time spreads to the telencephalon^[16].

Treatment

A. Pharmacological

Till date, no medication has been approved for use in MCI. However, the conversion of amnesic MCI to AD, has led to a surge of research in the field.

1. Acetylcholinesterase inhibitors (AChEI's): There were two historical trials with AChEI's- one using donepezil short term, and the other a long term study using galantamine and donepezil. The results indicated that AChEI's have a transient effect on the conversion of MCI to AD, which does not hold up beyond 18 months^[24]. Thus, the recommendation is that patients with amnesic MCI should be screened for the ApoE4 allele, and only if present should be given AChEI's^[24]. This suggests that the AChEIs have a symptomatic and potentially clinically significant effect, but one that is transient. Placebo-controlled trials have failed to show an effect of rivastigmine on conversion from MCI to dementia while

galantamine was associated with some improvement on secondary measures of cognition but not with any effect on the conversion rate to dementia at 24 months. An unexpectedly high galantamine-associated death rate (or perhaps an unexpectedly low placebo-associated death rate) resulted in concern about the balance of galantamine's risks and benefits for patients with MCI.

2. Memantine: Memantine has not been reported to benefit patients with MCI.
3. COX-2 inhibitors: Like rofecoxib have met with little benefit.^[24]
4. Anti-amyloid therapies: Secretase inhibitors help reduce amyloid production by inhibiting the secretase activity. Similarly, fibrillogenesis inhibitors (alzhmed and cliniquinol) are being explored. Lastly, vaccines which would prevent amyloid plaque formation and actually aid regression are under scrutiny.^[25]
5. Neurotonics: Like piracetam are highly debatable and have not met with any evidence.^[24]
6. Oestrogens: The initial interest in post-menopausal women and also men has died down as it actually may increase the risk for MCI and AD.^[26,27]
7. Antioxidants like Vitamin E, Vitamin C, Gingko biloba and curcumin (from turmeric) are hypothesized to reduce oxidative stress and ageing, yet work in this field is largely in the incipient stages.^[28,29]
8. Dopamine agonists in the NIMHANS study using Piribedil a dopamine agonist. There was an improvement in global cognitive function in mild cognitive impairment significantly as compared to placebo after treatment with Piribedil.^[30] Perhaps other dopaminergic agonists should be considered for appropriately designed research in patients with MCI.

9. Miscellaneous: Like CDP choline, omega 3 fatty acid, Ca channel blocker nimodipine and testosterone supplementation have shown to be partially effective.
10. Drugs on trial for MCI current testing 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 g-aminobutyric acid B receptor antagonist (SGS-742), and a selective serotonin receptor (5HT6) antagonist (SGS-518).

B. Non-pharmacological ^[31]

This will perhaps assume more importance in the near future.

1. Treatment of associated co-morbidities like sleep, depression, etc.
2. Treatment of vascular risk factors: Like hypertension, weight gain, hyperlipidemia, etc.
3. Social networking: Isolation exacerbates cognitive decline. Patients with MCI should be encouraged to socialize.
4. Cognitive activities and training: Cognitive activities like crossword puzzles, novels, su-doku, etc. all help against cognitive decline. Cognitive training as a specialized therapeutic intervention helps too.
5. Physical exercise: Although there is no clear evidence of the same in MCI specifically, physical exercise does improve cognitive ability, or definitely slows down decline

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.

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