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Mild Cognitive Impairment

Marina Janelidze and Nazibrola Botchorishvili

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Abstract

Mild cognitive impairment (MCI) refers to cognitive decline from a previous level of functioning, both subjectively and by objective evidence. MCI is an intermediate stage of cognitive impairment between the normal cognitive aging and dementia. The concept of mild cognitive impairment originally evolved with an intention to characterize the pre-dementia phase of cognitive impairment. MCI is a known risk factor for dementia. Patients with MCI may represent an optimal target population for pharmacological and non-pharmacological interventions. The following chapter provides an overview of the concept of mild cognitive impairment, epidemiological data, current diagnostic criteria, clinical approach and management of MCI.

Keywords: mild cognitive impairment, prodromal dementia, mild neurocognitive disorder, cognitive decline, Alzheimer's disease

1. Introduction

Mild cognitive impairment (MCI) represents an intermediate stage of cognitive impairment between the normal cognitive aging and dementia. The development of the concept of MCI was stimulated by the clinical awareness of the existence of an intermediate level of cognitive impairment that was not captured by any clinical definition on the one hand and by the rising awareness of dementia as an important area of public health on the other [1]. The concept of MCI permits timely identification of patients at high risk of developing dementia, thus opening a potential therapeutic window and increasing the significance of controlling modifiable risk factors.

2. History of the concept of mild cognitive impairment

During the last few decades various terms and definitions have been proposed to determine intermediate stage between normal aging and dementia. In 1962, V.A. Kral first described two types of age related cognitive changes in his works. One of them is "benign senescent forgetfulness" (BSF), which is characterized by mild and non-progressive memory decline and presumably implies non-specific histopathological changes in the brain. The second form, "malignant senescent forgetfulness" (MSF) includes progressive cognitive and behavioral changes which involves specific brain histopathology [2]. Introduction of the term "benign senescent forgetfulness" was the first attempt to conceptualize MCI [3].

In 1986, the working group at National Institute of Mental Health proposed the diagnosis of age-associated memory impairment (AAMI) to identify age-related memory changes [4]. The concept was based on the comparison of older persons to young adult norms on a variety of memory tests. The idea was criticized by the WHO and International Psychogeriatric Association, because it included only memory assessment and did not imply diversity of age-sensitivity of memory tests [5]. The concept of AAMI did not develop further. Alternatively, in DSM-IV it evolved in the term aging-associated cognitive decline (AACD) [5, 6]. The AACD diagnosis is similar to age-associated memory impairment. However, the AAMI diagnosis is based on a less comprehensive evaluation which takes into account memory function only [7]. Subjects are classified as having AAMI if they score 1 SD below the mean of younger adults (not people of their own age) in a standardized memory test [4].

In 1989, Blackford and La Rue proposed modified version of age associated memory impairment, "late life forgetfulness" (LLF) [8]. LLF was defined as slight deterioration of memory compared with aged-match persons, but the absence of Dementia [5].

Before the introduction of MCI concept elderly persons with cognitive complains who were not demented were categorized as having questionable dementia [5]. In the 1980s, global clinical staging scales have been developed to classify the wide spectrum of cognitive dysfunction in geriatric population. Among them Global Deterioration Scale (GDS) and Clinical Dementia Rating (CDR) are the most frequently used [9]. These scales differentiate a type of cognitive impairment which is intermediate between dementia and normal cognition function. Subjects with GDS 3 or CDR stage 0.5 are classified as having "questionable," "borderline" or "preclinical" AD. Other terms, such as "minimal dementia," "limited cognitive disturbance," "isolated memory loss," "mild cognitive disorder," "mild neurocognitive disorder" and "cognitive impairment-no dementia" (CIND) have been used to reflect the similar intermediate level of cognitive performance [9].

The term "cognitive impairment no dementia" was introduced in the Canadian Study of Health and Aging [10]. It was a multicenter study evaluating epidemiological aspects of cognitive impairment among Canadians aged 65 and older. In this study individuals with some degree of cognitive decline, who did not meet criteria for dementia, were classified as having "cognitive impairment no dementia". Cognitive impairment no dementia is a broad concept and involves cognitive decline of any etiology, including delirium, alcoholism, drug addiction, depression, psychiatric disorders [11]. The prevalence of CIND among the Canadian elderly was reported to be twice that of all dementias combined [5, 10].

At the same time, in the medical literature of dementia and aging, the term "mild cognitive impairment" has emerged. In 1988 Reisberg and colleagues used this term to characterize subjects with the Global Deterioration Scale Score 3 [12]. The GDS is a seven-point rating instrument for the staging of the magnitude of cognitive and functional capacity from normal aging to severe dementia [13]. Points in GDS range from 1 to 7. A score 3 indicates mild but obvious cognitive decline leading to difficulties in handling complex situations and tasks - e.g. lack of orientation while traveling to unfamiliar places, failure to recall names of new acquaintances, concentration deficit, troubles with retaining large amount of information, word and name finding deficit.

In 1995, in an observational study of aging at Mayo clinic, R.C. Petersen and colleagues adopted mild cognitive impairment as an independent diagnostic entity to categorize persons with memory complaints, who were not demented, retained global cognitive function and daily living skills, but scored below the age-adjusted norms on memory tests (Although, it was in 1991, when the term MCI first appeared in the headline of the article by Flicker et al., "Mild Cognitive Impairment in the elderly: predictors of dementia") [14, 15].

Petersen R.C. and colleagues provided Mayo clinic criteria for mild cognitive impairments: 1. Subjective complaint on memory disturbance (preferably supported by the informant); 2. Objective evidence of memory deficit: 3. Generally preserved cognitive functions; 4. Intact activities of daily living; 5. Absence of dementia [16].

In 2001, the American Academy of Neurology (AAN) incorporated new diagnostic criteria in a guideline on mild cognitive impairment. The AAN criteria for MCI were as follows: 1. An individual's report of his or her own memory problems, preferably confirmed by another person; 2. Measurable, greater-than-normal memory impairment detected with standard memory assessment tests; 3. Normal general thinking and reasoning skills; 4. Ability to perform normal daily activities [17]. Early detection and monitoring of persons with mild cognitive impairment was recommended, due to the high risk of progression to dementia.

Based on clinical observations, it became clear that mild cognitive impairment is not limited to memory loss. In 2003, the first key symposium was held in Stockholm, with the aim to integrate clinical and epidemiological perspectives on the topic of mild cognitive impairment [18]. The proposed MCI criteria were no more focused on memory impairment alone and included the following features: 1. The person is neither normal nor demented;

2. There is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; 3. Activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired.

At the same time a comprehensive classification of MCI was proposed that categorizes individuals by the type or domain of cognitive deficit (memory vs. non-memory such as language, visuospatial, speed of processing or executive function) and the extent of the deficits (single domain vs. multiple domains). Based on these criteria, four MCI subtypes have been proposed: Amnestic MCI-Single Domain (a-MCI-sd), Amnestic MCI-Multiple Domain (a-MCI-md), Non-Amnestic MCI Single Domain (na-MCI-sd) and Non-Amnestic MCI-Multiple Domain (na-MCI-md) [19].

Presumably, the cognitive phenotype of MCI (a-MCI vs. na-MCI) and the number of cognitive domains affected (single vs. multiple) determine the future outcome of mild cognitive impairment. Amnestic single or multiple domain MCI is supposed to be precursor of Alzheimer disease, whereas persons with na-MCI likely progress to a non-AD dementia, such as dementia with Lewy bodies, fronto-temporal dementia, Huntington's disease or Parkinson-Dementia [20] (**Table 1**).

In the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V) the term dementia is replaced by the term neurocognitive disorder. DSM-V recognizes the pre-dementia stage of cognitive impairment and defines it as mild neurocognitive disorder (NCD) [21, 22]. Diagnostic criteria for mild NCD are almost identical to MCI criteria and include the following: 1. Clinical concern raised by the patient or an informant, or observations made by the clinician; 2. Cognitive impairment in one or more cognitive domains preferably relative to appropriate normative data for that individual; 3. Preservation of functional independence and 4. No dementia

In 2011, National Institute of Aging (NIA) and Alzheimer's Association (AA) developed diagnostic criteria for symptomatic pre-dementia phase of Alzheimer's disease [23]. The working group proposed two sets of criteria: core clinical criteria and clinical research criteria incorporating biomarkers. The NIA-AA criteria for MCI due to AD are as follows:

1. **Concern regarding a change in cognition.** Concern about a cognitive decline compared to the previous level should be obtained from the patient, form an informant, or from a clinician observing the patient.

2. **Impairment in one or more cognitive domains.** Evidence of dysfunction in one or more cognitive domains (memory, executive function, attention, language, and visuospatial skills) should be objectively demonstrated.

MCI subtypes and etiology			
Amnestic single domain	**Amnestic multiple domain**	**Non-amnestic single domain**	**Non-amnestic multiple domain**
Memory only	Memory plus ≥ 1 of the following: *Language* *Attention* *Executive function* *Visuospatial function* *Processing speed*	One of the following: *Language* *Attention* *Executive function* *Visuospatial function* *Processing speed*	>1 of the following *Language* *Attention* *Executive function* *Visuospatial function* *Processing speed*
Alzheimer's disease	**Alzheimer's disease** **Vascular dementia**	**Frontotemporal dementia**	**Lewy body dementia** **Vascular dementia**

Table 1. MCI classification.

3. **Preservation of independence in functional abilities.** Individuals with MCI usually experience some difficulties with handling complex situations, such as performance of financial operations, cooking, shopping. They may need more time, be less efficient, or make more errors during such activities. Nevertheless, they preserve functional independence.

4. **Not demented.** Observed cognitive dysfunction is usually mild and doesn't affect social or occupational activities. Objective demonstration of intra-individual change of cognitive function via the history or clinical assessment is required for the diagnosis of MCI.

The *Clinical Research Criteria* which incorporate the use of biomarkers, are intended to be used only in research settings to assess the underlying etiology of MCI and the likelihood of progression to dementia. According to the NIA-AA recommendations, concomitant application of clinical and research criteria can increase the diagnostic certainty. For this purposes 2 main types of biomarkers are investigated: Biomarkers of beta-amyloid deposition and biomarkers of neuronal injury/neurodegeneration. Biomarkers of beta-amyloid accumulation are: low CSF concentration of amyloid β42 and PET (positron-emission tomography) evidence of amyloid deposition. Biomarkers of neuronal injury are: High concentration of Tau/ Phosphorylated protein in CSF; Hippocampal, or medial temporal lobe atrophy on MRI, and temporoparietal/ precuneus hypometabolism or hypoperfusion on PET or SPECT [23, 24].

Based on biomarkers we can assess the risk of development of Alzheimer's disease. Currently, CSF $A\beta_{42}$ and tau measures, the ratio of CSF tau/$A\beta_{42}$, PET amyloid measures, and other biomarkers of neuronal injury such as hippocampal atrophy and temporoparietal hypometabolism have all been shown to predict progression of MCI to dementia [5, 24].

- The evidence of positive Aβ biomarker and a positive biomarker of neuronal injury indicate a high likelihood that the MCI syndrome is due to AD. In addition, individuals with this biomarker profile are more likely to decline or progress to dementia due to AD in relatively short periods.

- The probability that MCI is due to AD is moderate in cases in which one of the biomarkers is positive and the others have not been or cannot be tested.

- In a situation, where the biomarkers are negative, the likelihood of development of AD is low.

3. Epidemiology of mild cognitive impairment

Since MCI imposes a health burden of its own and increases the risk of dementia, it is important to reliably estimate the prevalence of MCI around the globe [25]. However, reported prevalence of MCI significantly differs across studies and ranges between 3 and 54% [5]. It is thought that this difference can be explained by the difference in research methodology, such as employed diagnostic criteria for MCI, variability of used neuropsychological tests, selected cut-off scores (≥1 SD or ≥1.5 SD), subjects of trials - population based or clinic based. Some of the variation may be associated with regional and/or ethnic differences. For example, MCI prevalence in India is 5 times higher than in China, despite standardization for age, sex

Study	Country	Years	N	Age	Prevalence
Purser et al.	US	1981–1991	3673	74	24.7
Lopez et al.	US	1991–1999	3608	≥65	18.8
Solfrizzi et al.	Italy	1992–1995	4521	73.4	3.2
Ravaglia et al.	Italy	1994–1996	34	≥ 65	7.7
Pioggiosi et al.	Italy	1999–2004		≥ 90	32.4
Huang et al.	China	2005	920	≥ 55	3.0
Choi et al.	Korea	2005–2006	1215	≥ 65	32.9
Choi et al.	Korea	2005–2006	1215	≥ 65	32.9
Artero et al.	France	2008	6892	≥ 65	42.0
Manly et al.	US	2008	1313	≥ 65	28.3

Table 2. Selected epidemiological studies in MCI.

Study	Country	Years	N	Age	Incidence
Larrieu et al.	France	2002	1265	≥ 65	9.9/1000
Busse et al.	Germany	2003	684	≥ 75	8.5/1000
Trevo et al.	Finland	2004	550	60–76	25.9/1000
Trevo et al.	Finland	2004	550	60–76	25.9/1000
Solfrizzi et al.	Italy	2004	2963	≥75	56.5/1000
Palmer et al.	Sweden	2004	379	≥75	34–168/1000
Carraciolo et al.	Sweden	2008	1070	≥75	13.7/1000 a MCI
Manly et al.	US	2008	1800	≥65	2.3–5.1%
Luck et al.	Germany	2010	2331	≥65	18.8

Table 3. Selected epidemiological studies in MCI.

and education [25, 26]. According to Einstein aging study, prevalence of MCI in the same geographical zone is higher in Negroid population compared with Caucasians. According to Mayo clinic study of aging, MCI prevalence was 16%, among them 11.1% was amnestic MCI and 4.9% non-amnestic MCI [5]. Single domain amnestic MCI was the most frequent type, based on Mayo clinic study of aging. MCI prevalence is increasing with age, is more frequent in males and *APOE e3e4* or *e4e4* allele carriers. The estimated prevalence of mild cognitive impairment in non-demented cohort of 65 years old or older in the Cardiovascular Health Study was 19% and it increased with age [27].

Recently an international consortium—Cohort Studies of Memory in an International Consortium (COSMIC) harmonized data from 11 studies from USA, Europe, Asia and Australia and applied

uniform diagnostic criteria to more reliably estimate MCI prevalence across different geographical and ethno-cultural regions. They have applied three different diagnostic criteria, such as performance in the bottom 6.681%, Clinical Dementia Rating of 0.5 and Mini-Mental State Examination (MMSE) score of 24–27. Prevalence rates before standardization varied between 5.0 and 36.7%. These estimates were reduced with all definitions ranging between 1.8 and 20.7%. The lowest crude prevalence (5.9%) was obtained with the first definition and highest (12%) with MMSE score of 24–27 [25] (**Table 2**).

The overall incidence of MCI based on various trials is in range of 21.5 to 71.3 per 1000 person/year and significantly depends on age. In addition, cardiovascular disease, stroke, Diabetes type 2, Negroid and Hispanic ethnicity are associated with high frequency of MCI. The incidence of aMCI is lower in most of the studies and ranges from 8.5 to 25.9 per 1000 person-years [5, 25, 28, 29] (**Table 3**).

4. Clinical diagnosis of mild cognitive impairment

All patients with suspected MCI should undergo detailed physical, neurological, cognitive, psychological and functional status evaluation. It is important to identify potentially reversible causes of MCI, such as depression, thyroid diseases, vitamin B12 and foliate deficiency. Special attention should be given to the prescription history. Some medications, including sedatives, narcotic pain medications, anticonvulsants or anticholinergics have potential to affect cognitive function. An accurate *neurological* assessment is essential to determine potential etiology of cognitive impairment [13, 30].

For the accurate diagnosis it is highly important to interview patient's family member or close acquaintance, which is familiar with their functioning in daily activities, requiring planning, organization and communication skills. Ideally, an informant should know the patient for years to adequately recognize deterioration from a baseline of functioning. Information received from different sources should be integrated properly [13].

Clinician should be aware, that cognitive impairment is often accompanied by anxiety, which interferes with cognitive performance; therefore, interview should be held in relaxed and conversational manner.

Examiner should inquire about patient's ability to handle technical devices. For example, patients with MCI can drive cars normally, but they might experience episodes of disorientation when they are driving in an unknown environment, or have a tendency to make wrong turns. Patients with MCI can have particular difficulties while planning a trip or social activities and they might need more time to perform complex activities that require planning and organization [13].

Information should be collected about patient's ability to manage financial operations. Individuals with MCI may require more time to perform monetary transaction, or periodically make careless mistakes.

Cognitive assessment should be performed at the end of the interview, preferably without an accompanying person. Objective demonstration of cognitive dysfunction is obligatory to

diagnose MCI. Therefore, examiner should conduct one or more cognitive batteries. Cognitive assessment should incorporate memory, attention, executive function, language and visuo-spatial function evaluation in order to precisely differentiate MCI subtypes. There is no consensus on the type and number of neuropsychological tests that should be used to assess individuals with MCI. Various cut-off points are used to define abnormal cognitive performance (1.0, 1.5 and 2.0 SD). Commonly a deterioration cut-off point of 1.5 SD is adopted. There is no single recommended "gold standard" battery, but rather a set of valid cognitive tests [31]. Commonly used tests are represented in the **Table 4**.

Cognitive screening tests are helpful in clinical practice as a first step to evaluate patients with MCI, followed by formal neuropsychological assessment in selected cases. Andrew J Larner has reviewed data from several diagnostic test accuracy studies [32]. Summarized data on diagnostic validity are shown in the **Table 5**.

In 2016, a workgroup meeting was held at the Institute of Memory Impairments and Neurological Disorders of the University of California, Irvine, USA with the aim to provide recommendations for the diagnosis of mild cognitive impairments. According to the recommendations, workup with standard laboratory tests, neuropsychological assessment, and structural brain imaging is required to diagnose MCI. Assessment of cognitive performance with specific cognitive tests should be considered by the clinicians when delivering the MCI diagnosis. patients should be provided with a written summary of the diagnosis and treatment recommendations that include referral to appropriate supportive services and other local resources; Amyloid imaging may allow a physician to give the patient additional information about potential causes of MCI, improve prognostic information, and reduce the ambiguity and uncertainty associated with the diagnosis. Communication of negative scan results should include that patients with MCI who have a negative scan results remain at risk for dementia and that negative scans, while informative, do not indicate a specific diagnosis or unambiguously signify the absence of disease. Negative amyloid imaging result reduces the possibility that MCI is due to Alzheimer's disease. It also reduces the risk of MCI progression to dementia. Although the likelihood of underlying Alzheimer's disease or any

Cognitive domains	Tests
Memory and learning	Rey Auditory Verbal Learning Test
	Logical Memory Subset of WSM-R
	The New York University Paragraph Recall Test
	Buschke Cued Recall Selective Reminding Test
Language	Semantic and phonemic fluency
Executive function	Trial-Making test
Praxis	The Rey-Osterreith complex figure
	Mimicking the use of objects and Symbol gestures of communication (e.g. inserting a sheet of paper into an envelope; the correct one hand movements designed to wave "goodbye"; cutting a sheet of paper with a pair of scissors; and brushing teeth)

Table 4. Selected cognitive instruments.

Cognitive screening tests	Cut-off	Sensitivity	Specificity
Mini Mental State Examination (MMSE)	≤22/30	1.00	0.28
Mini Mental Parkinson (MMP)	≤20/32	0.92	0.61
Montreal Cognitive Assessment (MoCA)	≥26/30	0.93	0.60
Test your memory (TYM)	≤42/50	0.79	0.54
Mini-Addenbrooke's cognitive examination (M-ACE)	≤25/30	1.00	0.43
Mini-Addenbrooke's cognitive examination (M-ACE)	≤21/30	0.77	0.82
Six item cognitive impairment test (6CIT)	≤9/28	0.66	0.70

Table 5. Selected screening tools in MCI [32].

other neurodegenerative disease can't be fully excluded. Positive amyloid PET scan results in patients with MCI are associated with an increased risk for developing AD dementia. It is important to discuss the risk for cognitive and functional decline and the need for additional monitoring and planning in these patients. Volumetric brain imaging and detailed neuropsychological examination in combination with PET scan results help clinician to determine MCI prognosis and outcome [33].

5. Neuroimaging of mild cognitive impairment

Early radiological studies in MCI were focused on the assessment of the entorhinal cortex (ERC) and hippocampus. Volume of the ERC and the hippocampus in MCI patients tends to be smaller and is either intermediate between normal controls and patients with AD, or similar to AD. Some studies demonstrated higher sensitivity of the entorhinal cortex compared with hippocampal volume. The annualized rate of the hippocampal and entorhinal cortex atrophy has been shown to be more prominent in the MCI patients relative to normal controls [5, 34].

Apart from medial temporal lobe atrophy, decrease in gray matter volume was reported in the lateral temporal, parietal, and frontal lobes, amygdala, fusiform gyrus, cingulate, parietal and occipital lobes and insula. Several studies have documented that the whole brain volume loss rate is associated with objective cognitive decline over time.

Apostolova et al. followed a cohort of MCI subjects clinically and neuropsychologically for 3 years. They found that smaller hippocampal volumes predict conversion of MCI to AD and patients with MCI who convert to AD have greater atrophy in the CA1 and subiculum regions of the hippocampus [35].

Several studies reported significant alterations on diffusion weighted MR imaging (DWI) measures in the hippocampus, thalamus, posterior cingulum (PC) and several regions in posterior white matter in MCI patients. Kantarci et al. found that on the follow up, elevated hippocampal diffusivity predicts MCI progression to AD better than hippocampal volumetry [5, 36].

Study by Delano-Wood et al. showed that diminished white matter integrity of PC was strongly predictive of MCI status. Additionally, patients with amnestic MCI demonstrated lower PC white matter integrity relative to those with non-amnestic MCI [5, 34].

FDG-PET ([18F]-2-fluoro-2-deoxy-D-glucose-positron emission tomography) studies have found substantial reduction in brain activity in some cortical regions (HC limbic system, medial thalamus, and posterior cingulate). These findings are consistent with structural MRI findings [5, 37].

SPECT studies have reported reduced cerebral blood flow (CBF) in the parietal cortex, posterior cingulated cortex and precuneus in persons with MCI. Longitudinal SPECT studies showed that the presence of AD-like hypoperfusion in the posterior posterior cingulate cortex of patients in MCI was predictive of conversion to AD [37].

Accumulation of amyloid-β (Aβ) fibrils in the form of amyloid plaques is a neuropathological hallmark of dementia caused by AD. Amyloid deposition appears an early event in AD, possibly occurring up to 20 years before clinical symptoms. Amyloid imaging has become one of the central biomarkers of AD and predictor of cognitive decline. There is evidence that a positive amyloid PET scan result in patients with MCI will help in predicting conversion to AD. Amyloid-PET may help to differentiate between different etiologies of cognitive dysfunction and in the future it may help to appropriately select patients for anti-amyloid therapy [5].

6. Treatment of mild cognitive impairment

The aim of MCI treatment is to reduce existing clinical symptoms or to delay progression of cognitive dysfunction and prevent dementia. Unfortunately, at present there is no effective pharmacological therapy of mild cognitive impairment. Clinical trials on the effectiveness of Cholinesterase inhibitors didn't prove that they can delay the onset of Alzheimer's disease (AD) or dementia in individuals with MCI. Cooper et al. performed systemic review of studies on MCI treatment. They summarized results of 9 clinical trials on Cholinesterase inhibitors. Reduction in incidence of Alzheimer's disease has not been proven with 4 high quality trials (two evaluated galantamine, one donepezil and one rivastigmine). In one of the trials donepezil and galantamine showed improvement in global cognitive functioning. However, global cognition did not improve in other five large trials of Cholinesterase inhibitors. Donepezil improved immediate memory and delayed progression to AD in MCI patients with depression without affecting their symptoms of depression [38].

In a 2-year, double-blinded, placebo-controlled study, 232 MCI patients were administered 16 mg. galantamine combined with 20 mg. memantine, galantamine only, or a placebo. The amnestic MCI subgroup in the treatment arm combining galantamine and memantine demonstrated a significant positive effect on cognition. Discontinuation of galantamine, but not memantine led to a decline in cognitive functioning [38].

Ginkgo biloba is a natural medicine widely used to enhance memory. Yang et al. conducted meta-analysis of randomized clinical trials on Ginkgo biloba in treating mild cognitive impairment or Alzheimer's disease. Data from 21 trials with 2608 patients have been analyzed [39].

Compared with conventional medicine alone, Ginkgo biloba in combination with conventional medicine was superior in improving Mini-Mental State Examination (MMSE) scores for patients with Alzheimer's disease and mild cognitive impairment. When compared with placebo or conventional medicine in individual trials, Ginkgo biloba demonstrated similar but inconsistent findings. Adverse events were mild.

The Ginkgo Evaluation of Memory (GEM Study) study was a randomized, double-blind placebo-controlled multicenter trial, which was held in 2000–2008 years in the United States. Out of 3069 participants of the clinical trial, most of them (n=2587) didn't have cognitive dysfunction, and 15.7% (n=482) were diagnosed with mild cognitive impairment on the basis of Peterson's criteria. After completion of the 6 -year observation period no significant effect of Ginkgo biloba on the incidence of dementia could be demonstrated [40].

There is an evidence, that inflammation plays an important role in the pathophysiology of Alzheimer's disease. Several epidemiological studies showed negative association between usage of anti-inflammatory nonsteroidal medications and development of Alzheimer's disease. For example, the Canadian Study of Health and Aging involving 5276 cognitively normal subjects demonstrated that there is an association between NSAID use and a lower incidence of AD and cognitive impairment no dementia (CIND) [38].

One large multicenter study on the efficacy of the COX-II inhibitor in preventing dementia has been conducted. In the trial participated 1457 subjects with mild cognitive impairment, half of them were taking Rofecoxib, approximately for 4 years. Trial revealed significantly high frequency of Alzheimer's disease in the group that used Rofecoxib [38].

A randomized, double-blind, placebo-controlled trial of Triflusal in patients with amnestic mild cognitive impairment reported no significant effect of Triflusal treatment on cognition, although it was associated with a reduced risk of conversion to AD [38].

Centrally acting angiotensin-converting enzyme inhibitors (CACE-Is) have demonstrated positive effect on cognitive function in a study including 361 patients with AD, vascular dementia, or mixed dementias, regardless of blood pressure levels at the time of their hypertension diagnosis.

Piridebil is an antagonist of dopamine receptors. Based on experimental trials it increases acetylcholine release in hippocampus and frontal cortex. Piribedil improved cognition over 3 months in individuals with MMSE of 21–25, in one small placebo controlled study.

The role of B vitamins was studied in few clinical trials. However, the data does not yet provide adequate evidence of an effect of vitamins B on general cognitive function, executive function and attention in people with MCI. Similarly, B vitamins are unable to stabilize or slow decline in cognition, function, behavior, and global change of AD patients.

Twelve-week treatment with dietary supplementation containing an oily emulsion of docosahexaenoic acid (DHA)-phospholipids demonstrated considerable improvement in cognitive function in 25 elderly patients with MCI in a randomized controlled study. Studies support the effectiveness of omega 3 fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) on cognitive function, depressive symptoms and general functioning in persons with MCI [41].

Cochrane review on the use of vitamin E in the treatment of mild cognitive impairment and AD did not identify evidences that alpha-tocopherol prevents MCI progression or that it improves cognitive function in people with MCI due to AD. However, there is moderate quality evidence from a single study that it may slow functional decline in AD [42].

Meta-analysis of prospective trials revealed, that Mediterranean diet reduces risks of development of Alzheimer's disease and also progression of mild cognitive impairment into dementia. Mediterranean diet could potentially exert neuroprotective effects via different mechanisms, such as reduction of inflammation and oxidative stress.

Non pharmacological treatment of MCI involves management of modifying risk factors, social and cognitive rehabilitation and physical activity.

There is growing evidence that cognitive interventions may be associated with small cognitive benefits for patients with MCI and dementia. Based on recent trials, computer training program has particular positive effect on cognition and mood. Cooper at al. reviewed two long term group psychological intervention studies. They found that 20 sessions of memory training, reminiscence, cognitive stimulation, psychomotor recreation and social interaction improved global cognition on a primary outcome in a single, very small, 6-month placebo-controlled trial. However, another trial including ten sessions of memory training, psycho education and relaxation did not improve recall on secondary outcomes in one small 6-month trial [38].

Mayo clinic professionals created a MCI intervention program called Healthy Action to Benefit Independence and Thinking (HABIT). HABIT is a 10-day (50 hours) multi-component program offered to individuals with mild cognitive impairment. The program builds on existing strengths and recognizes that procedural memory can be utilized to promote the highest level of function and independence. The program includes five essential components: Individual memory compensation training; Group supportive therapy; Yoga; Brain fitness; Wellness education. Preliminary program evaluation data suggests positive impact on self-efficacy outcomes for patients and caregivers, as well as positive impact on patient functional outcomes [43].

Exercise has been associated with positive effects on neuronal survivability and function, neuroinflammation, vascularization, neuroendocrine response to stress, and brain amyloid burden. It also helps to improve cardiovascular risk factors. Ohman et al performed systematic review of selected 22 trials examining the effect of physical exercise on cognitive performance. According to the review of studies on older subjects with MCI reported some positive effect of physical exercise on cognition, mainly on global cognition, executive function, attention and delayed recall. However, most studies performed in older subjects with dementia showed no effect of exercise on cognition [39].

7. Prognosis of mild cognitive impairment

Mitchell and Shiri-Feshki analyzed 41 high-quality cohort studies. They have found that the annual conversion rate (ACR) from MCI to dementia is approximately 5–10% and most people with MCI will not progress to dementia even after 10 years of follow-up [39]. The cumulative risk over 10 years ranged between 30 and 50%, depending on whether the studies that were analyzed used a definition of MCI that included subjective memory complaints.

Other meta-analyses of long-term (5–10 years) studies reported lower annual conversion rates of 3.3–4.2% and cumulative conversion rate ~31% over 10 years. In fact, a substantial percentage of individuals with MCI actually revert to normal. Sujuan et al. found that the annual reversion rate from MCI to normal cognition was substantially higher (18.6%) than the annual progression rate from MCI to dementia (5.6%) in a study spanning between 1992 and 2009 [44].

Studies suggest that common factors related to MCI reversion include genetics (i.e., fewer APOE ε4 alleles), preserved global functioning, subtype of MCI (i.e., non-amnestic single domain), cognitive functioning (i.e., higher standard scores on cognitive assessments), and neuroimaging (i.e., larger hippocampal volumes) [45]. Huey et al. found that single-domain executive MCI has a better outcome than amnestic MCI and that executive dysfunction in multiple-domain MCI does not independently increase the risk of progression to dementia [46].

It has been shown that as many as 30% of people with MCI have potentially treatable causes of cognitive decline. The most common of these include hypothyroidism, vitamin B12 deficiency, vascular disease, normal pressure hydrocephalus, and subdural hematoma. Another study concluded that changing the risk factors for stroke and treating depression may have contributed MCI reversion to normal [47].

Nevertheless, the proportion of patients with MCI who convert to dementia still remains significant and it is important to identify factors that facilitate progression for adequate prevention and application of both pharmacological and non-pharmacological therapies. Adequate and on timely identification of MCI in definite cases can help to plan effective strategies for prevention of progressive cognitive decline.

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Conflict of interest

We have no conflict of interest to declare.

Author details

Marina Janelidze[1,2] and Nazibrola Botchorishvili[1]*

*Address all correspondence to: nbphosta@gmail.com

1 Tbilisi State Medical University, Tbilisi, Georgia

2 Simon Khechinashvili University Hospital, Georgia

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