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Research Article

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Objective Cognitive Dysfunction Assessment in Patients with Subjective Cognitive Complaints: Does it Allow an Early Differentiation between Dementia and Mild Cognitive Impairment?

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Abstract

The term “mild cognitive impairment” was adopted by Petersen in 2004 to describe a period in the course of neurodegenerative disease where cognition is no longer normal relative to age expectations, however, daily functions are not satisfactorily to correlate with the diagnosis of dementia. A recent meta-analysis indicated that about 45% of MCI patients maintained stable, 28% progressed to AD and 15% return to normal status without recurrence. Predicting progression from MCI to dementia has received much attention in the literature. This work has aimed to improve the detection of the early stages in AD dementia and improve the methods used to identify individuals with MCI who are at high risk of developing AD dementia.

Keywords: Dementia, Mild Cognitive impairment, Neuropsychological assessment

Introduction

Dementia is a chronic pathological neurodegenerative process leading, to progressive decline in cognitive and functional abilities. The estimated prevalence of all-cause dementia varies from 4.7% in Central Europe to 8.7% in North Africa/Middle East, with North America falling between at 6.4%. Currently, over 46 million individuals live with dementia worldwide and this number is projected to increase to 131.5 million by 2050.

The risk of Alzheimer increases with age and women seem to be more easily affected. Age is considered the most important risk factor for the disease. Dementia is not an inevitable or normal part of ageing (World Health Organization, 2017). Dementia is one of the major causes of disability in later life, and the prevalence doubles in every five-year increment in age after 65 years of age (World Health Organization, 2012)

The MCI is the stage between the cognitive decline expected in normal aging, and the more severe one, found in dementia. It is characterized by deficits that may involve: memory, language, thought and judgment. MCI has become an important topic in clinical practice and research. Numerous randomized, controlled studies for the MCI subtype due to AD are ongoing, and doctors need to be aware of these research opportunities for their patients. As treatable etiologies of ICMs (such as those due to psychiatric conditions, medications, or medical comorbidities) are identified, cognitive deficits can be reversible. The development of biomarkers should provide the clinician with new tools to identify and hopefully cure ICM (1).

Mild Cognitive Impairment: definition

Identifying cognitive impairment at an early stage has become an increasingly important challenge: decades ago, it was satisfying to distinguish dementia from typical cognitive aging, but in recent years the desire to make a deeper decision on the incipient disease has taken hold. Precisely for this reason, the clinical spectrum from dementia has extended to "Mild Cognitive Impairment" (MCI).

The MCI is considered the boundary land between cognitive changes of aging and very early dementia; but, although conceptually reasonable, the construct poses difficulties in clinical practice (1).

According to Petersen (2016), Mild Cognitive Impairment (MCI) is a neurological syndrome characterized by a state of mild cognitive impairment that afflicts subjects who have a greater cognitive deficit than the one statistically expected based on age and level of education, but who are still able to carry out their daily activities.

This condition is connoted by the objective evidence of a memory impairment not yet such that it can be included in the definition of declared dementia. The MCI has received multiple alternative definitions: incipient dementia, isolated memory deficit, age-related memory deficit, mild cognitive disorder and cognitive impairment in the absence of dementia.

Mild Cognitive Impairment is therefore considered a form of pre-dementia, placing itself in a transition phase between normal aging and actual dementia (2).

Epidemiology

Numerous international population studies have been conducted to document the frequency of MCI, estimating its prevalence between 15% and 20% in people aged 60 years or older. The annual rate at which MCI progresses to dementia varies between 8% and 15%, which shows how mild cognitive impairment is an important condition to identify and treat.

The Mayo Clinic Study of Aging, through a population study in Olmsted County, Minnesota, found that the overall prevalence of MCI is 16% in residents aged 70 years or older. ICM is clearly an age-related condition and, to the extent that the assessment suggests a degenerative etiology, AD is very likely.

Also the same Institute, followed subjects aged 70 years or older for a median of 5 years and found that the progression rate was between 5% and 6% per year. Rates are lower in younger subjects and increase significantly with age (1).

The reviews of the multiple studies conducted on the subject show how subjects suffering from ICD have an increased risk of developing Alzheimer's disease ranging from 1 to 28% per year. This great variability demonstrates the variety of: diagnostic criteria and tools; as well as the fact that until now only small study groups have been used to investigate the subject. Progression towards dementia reaches 20- 50% in 2-3 years; and according to one estimate it could reach 60-100% in 5-10 years (2).

Classification

Over the years, there has been the evolution of various classification categories for the MCI. The Mayo Clinic criteria, previously formulated, focused mainly on memory disorder and were developed to clarify the early symptomatic stages of AD. However, it soon became apparent that not all intermittent cognitive states represented an incipient AD, nor did all patients only have impaired memory. To address this situation, the Key Symposium held in Stockholm in 2003 and 2004 has published more far-reaching criteria.
These criteria have achieved two objectives:
Extend the classification scheme beyond memory
Recognize that MCI could derive from a variety of etiologies and not just from AD

This characterization of the MCI led to the distinction between the amnestic form of the MCI and the non-amnestic form of the MCI, since these clinical syndromes seem to be aligned with the etiologies in a differential way and also, can have variable outcomes.

In addition, it must be taken into account that, based on the domains involved, we distinguish: the single domain impairment form (sd-MCI) in which a single cognitive domain is involved and the multi-domain form (multi-domain impairment, md-MCI) in which several are involved Cognitive domains; this is a more common typology than the superscript. This results in the presence of 4 subtypes of MCI:
Amnestic MCI single domain or Isolated Memory Impairment: isolated memory impairment, in which only the cognitive domain of memory is involved that is maximally correlated with an evolution in Alzheimer's Disease (Alzheimer's Disease, AD); it has been shown that it is a tendency to be a rare form.
Amnestic MCI multiple domain: in which the cognitive function of memory is involved together with one or more cognitive domains; this is the statistically prevalent form.
Non-Amnestic MCI single domain: in which only one cognitive domain that is not the mnesic one is involved.
Non-Amnestic multiple domain: in which two or more cognitive domains other than mnesic ones are involved.
Amnestic MCI is generally considered as the typical prodromal stage of Alzheimer's dementia, but other phenotypes can also be associated with this form of MCI: such as logopenic aphasia, posterior cortical atrophy (also known as a visual variant) or disecutive frontotemporal dementia. The key concept is that not all forms of MCI precede an AD: it can in fact also evolve into frontotemporal degeneration, Lewy body dementia and vascular dementia.

In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association convened working groups to develop the criteria for the full spectrum of AD. The latter, as far as the criteria for the MCI are concerned, essentially adopted those of the Symposium, while making some of the diagnostic features more explicit. They added biomarkers for the pathophysiology of AD, in an attempt to perfect the underlying etiology and, therefore, predict the outcome. The substantial difference is that these criteria did not distinguish between amnestic and non-amnestic forms.

The Diagnostic and Statistical Manual of Mental Disorders - Edition 5 (DSM - 5), published in 2013, (3) in the general category of neurocognitive disorders, presents, among the criteria, a "predementa" phase called "Mild Neurocognitive Disorder". The construct is very similar to the criteria for the Symposium's MCI and suggests that, in addition to the syndromic classification, some characteristics would allow the sub-classification of the clinical presentation in pathological etiologies. The category of mild neurocognitive disorder due to AD is very similar to the classification of the MCI due to AD formulated by the working groups of the NIA and the Alzheimer's Association.

In conclusion, over the course of several years, the prodromic AD construct has evolved thanks to a more in-depth observation of amnestic ICM. It has been seen in fact that,

When the amnestic MCI is coupled to certain biomarkers (amyloid or amyloid and tau), it approached the first symptomatic stages of the AD process (1).

Risk factors

Currently the data to determine the MCI are limited, but it is necessary to detect and deepen the risk factors that determine it. Although the latter are in fact numerous, the real cause is still unknown. Currently, the main risk factor for cognitive decline is age. Other possible risk factors are:
Somatic factors: metabolic conditions: hyperomocysteinemia, chronic renal failure, vitamin B12, B6, D and E deficiency, folate deficiency, endocrine problems (testosterone deficiency, subclinical thyroid dysfunction, reduced estrogen level), cardiovascular problems (hypertension, hyperlipidemia), age, vision and hearing loss, lower physical activity, diet, education level, socio-economic status, sleep disorder, substance abuse, environment, chronic pain, ethnicity, living alone, sex, fatigue, depression, neurosis, smoking habit, alcohol consumption, Down syndrome, excessive exposure to aluminum and head injuries.

Genetic factors: apolipoprotein E, paraoxonase, catechol-O-methyltransferase, brain-derived neurotrophic factor and non-coding RNAs (as micro RNAs).

The identification of genetic risk factors is important because it increases the ability to identify people at higher risk of developing cognitive impairment and/or its progression to dementia. Progression to dementia is faster when there are concomitant medical conditions and severe pathological changes. ICM proceeds to dementia when amyloid plaques and neurofibrillar tangles are deposited in the neocortex of the brain.

The vector Epsilon 4 of apolipoprotein E (ApoE) may also increase the risk of conversion from MCI to Alzheimer's, in subjects with cognitive impairment. Due to environmental effects and genetic complexity, finding a single responsible gene or allele to generate MCI is still difficult. So far, only a small part of cognitive impairment in old age related to genetics has been identified (4).

Clinical characteristics: signs and symptoms

In the MCI there is generally a pejorative change in menesic abilities. The presence of a subjective memory deficit reported by the patient, in the first person, or by a family member/lose acquaintance, which is greater than at least 0.5 SD than what is expected for age and education, is necessary. The subjective deficit is always good that it can then be objectivable with psychometric tests. The subject with ICM more often and easily forgets acquired information, does not remember socially important events, easily loses the thread of his thoughts or a book he is reading or an ongoing conversation; the patient is also overwhelmed by the idea of making decisions, planning, performing a given task or completing instructions given to him. An individual affected by MCI can end up no longer recognizing the familiar environment. He proves to be more impulsive or with loss of judgment and thoughtfulness.
In the MCI, both visual, visual-spatial and verbal memory are affected, variously and in a pejorative sense; it seems that non-verbal memory is the most strongly affected.

With regard to the remaining cognitive domains, in the MCI it is possible to overimpose the presence of:
Preeminent language disorder up to the evolution into a primary progressive aphasia
Preeminent visual-spatial disorder (especially in dependence of a Lewy body dementia)
Selective practical deficit, which can lead to corticovascular degeneration.

The studies have concluded that a high prevalence of neuropsychiatric symptoms is detectable; in fact, the estimate of the subjects who have demonstrated one or more psychiatric symptoms is in a range between 35% and 85%. These symptoms include: both depression, anxiety, irritability, apathy, agitation, as the most common symptoms; both euphoria, disinhibition, hallucinations and delusions, as less frequent symptoms. Neuropsychiatric symptoms in the MCI are associated with a worsening of the cognitive and functional abilities of patients. Patients with MCI who are suffering from a depressive state have a 2.6 times higher risk of developing AD than patients

Suffering from ICM without depression; in addition, depressed patients develop dementia earlier than those who are not depressed. The growing interest in neuropsychiatric symptomatology in subjects suffering from MCI has suggested that such symptoms can also serve as clinical indices to attest to the presence of a prodromal form of dementia (2).

Clinical criteria and approach to diagnosis

It is assumed that the patient with MCI presents a cognitive concern. There must be evidence of a state of concern related to the change in the condition of the subject with respect to his previous status; this data can be obtained from the patient himself (who notices a worsening of his condition), from an acquaintance who knows how to interpret his health well or by a clinician who has kept him under observation.

This is why it is essential to start from the collection of the subject's history, which must be confirmed by the person directly concerned, by his informant and/or by a clinician. Cognitive anxiety is important because it reflects a change in the person's performance.

This pejorative change can occur at the level of the different cognitive domains: memory, attention, language and visual-spatial abilities. Here the doctor should focus on the type of cognitive change that the patient (and those living around him) has noticed: if for example, the main cognitive concern is the memory domain, he should focus on relatively recent cases of forgetfulness (i.e. appearing approximately in the last 6 months or a year) that involve appointments, visits to friends or conversations. There must therefore be evidence of a reduction in the subject's capacity in one or more cognitive domains that is greater than that expected based on age and level of education. If repeated assessments are available then it is possible to highlight the decline in performance over time. We therefore speak of an investigation into the extent of cognitive change. Patients generally notice cognitive changes related to memory, but in reality, there may also be problems with attention or speech. At this point, the clinician will have to do an examination of the mental state and explore the various cognitive domains. If time is limited, an assessment of the mental state involving a tool such as the Montreal Cognitive Assessment (MoCA) or the Short Test of Mental Status, but the doctor must be aware that these screening tools are insufficient to make the diagnosis; however, it can be useful to isolate the various domains, identify damaged ones and carry out more in-depth evaluations. Other elements to be evaluated are functional performance, which, in a patient with MCI, should be largely preserved (daily functions such as driving, preparing a meal, shopping). In fact, people with ICM commonly show that they have only mild problems in performing complex functional tasks that they were used to performing in the past. They may spend more time and/or be less efficient in these activities; or they may make a greater number of mistakes in the performance. In the end, however, they are still able to perform them without any assistance; in fact, they maintain a certain independence in carrying out everyday actions, with the need, sometimes, of marginal support. They may show minimal changes in the ability to use tools in the context of ADLS (Activities of Daily Living) but do not demonstrate a significant deficit in basic activities (such as: eating, washing, dressing or performing housework). The risk is that this evaluation can be very subjective, so a reliable informant who knows the patient well is useful. In light of all these considerations, the criteria for the MCI will be met, regarding the maintenance of functional performance, and consequently, those for dementia will not be met. This means that the person's cognitive impairments are not severe enough to compromise daily functioning, therefore, the main criterion for dementia is not met (1). It is also important to investigate the cognitive characteristics of the subject. In fact, it is necessary to determine whether there is an objective decline in cognitive functions, and if it is present, it must then be evaluated to what degree it is. The scores that assess the cognitive decline of the patient with MCI are usually 1-1.5 lower standard deviations than the average calculated based on the age and level of education of the subject. Among the tests that can be used for cognitive assessment we have, for example, those for episodic memory (i.e. the ability to learn and store new information). This is because its impairment is commonly

observed in patients with MCI who subsequently tend to switch to a diagnosis of AD. These tests share the characteristic of evaluating both immediate and delayed recall, so that it is possible to determine retention in case of delay. Many of the tests that have proven useful in this regard are learning tests with word lists with multiple tests. These tests record the learning rate over time, as well as the maximum amount acquired during the learning tests.

The neuropsychological evaluation must be as complete as possible by examining the main cognitive functions: executive functions, visual-spatial skills, memory and learning and language.

The MMSE (5) consists of thirty items that assess orientation, short and long-term memory, language, attention, visuospatial skills, and the ability to follow simple verbal and written commands. This easy-to-use and relatively quick neuropsychological test is often employed to assess the overall cognitive status.

Executive functions:
Executive functions (EFs) include high-order cognitive skills such as working memory, inhibitory control, cognitive flexibility, planning, reasoning, and problem-solving
The main neuropsychological tests used to assess executive functions include:

1. Stroop Color- Word Test: is a neuropsychological test that assesses the capacity for selective attention and the components of executive functions such as cognitive flexibility and the ability to inhibit interfering or irrelevant stimuli (6,7).
2. Trail Making Test (TMT): it is a neuropsychological test aimed at assessing attention skills, with particular reference to planning, visual-motor speed and cognitive flexibility,

The Trail Making Test (TMT) (8) measures visual attention and task switching. It consists of 25 circles distributed over a sheet of paper. In part A, the circles are numbered from 1 to 25, and the patient should draw lines to connect the numbers in ascending order. The patient is instructed to connect the circles as quickly as possible without lifting the pen or pencil from the paper. The time to connect the "trail" is measured. If the patient makes an error, the examiner immediately points it out to allow the patient to correct it. Errors affect the patient's score as the error correction is included in the time completion for the task. The test is interrupted if the patient has not completed both parts within five minutes. (7,9).

1. Phonemic fluency test: it is a neuropsychological test that assesses the ability to recall words and investigates the flexibility of the subject.
2. Memory: The Babcock Story Recall Test (BSRT) (9) measures immediate and delayed recall. The examiner reads a brief story, and the participant must provide immediate recall.

Then, the story is repeated, and a delayed recall is obtained after ten minutes.

The Serial Repetition Test of Two-syllable Words (9) measures verbal short-term memory. In this test, the examiner presents a sequence of unrelated two-syllable words that the subject must repeat immediately after the presentation. The test is preceded by an example. The examiner begins with a two-word sequence; if the subject correctly repeats 2 out of 3 stimuli, the examiner moves to a longer set (one more word). The span is given by the longest sequence for which at least 2 out of 3 stimuli are correctly repeated.
Language: The Verbal Fluency Test is a short test of linguistic functioning (11).

It consists of two tasks: category or semantic fluency and letter or phonemic fluency. Semantic verbal fluency is measured by the number of words produced within a restricted category. Name categories are semantic colors, animals, and fruits. Concerning phonemic fluency, participants were instructed to generate words beginning with the test letters F, A, and S, spelled out loud by the examiner in this order. Examinees were given 60 s to name as many words as possible, beginning with the first letter; the procedure was then repeated for the two remaining letters. The participants were informed of inadmissible words (repetitions, proper names, or words with different inflections sharing the same root) to be eliminated from the analysis.

Instructions were followed by examples using the letter P to illustrate correct and incorrect words. The participants are given 1 min to produce as many unique words as possible within a semantic category (category fluency) or starting with a given letter (letter fluency). The participant's score in each task is the number of unique correct words. Constructional praxis: The Constructional Apraxia Test (CAT) (11) was used to measure the ability to consistently copy the elements that constitute the geometric bidimensional models presented by the examiner. The figures derive from those used in the test of Arrigoni and De Renzi. After the run-in, the examiner presents the figures printed on the upper half of the paper; the participant is asked to copy them below as precisely as possible. A score of 4 is given if the reproduction is perfect, 1 if the copy is partially defective, and 0 if the reproduction is unrecognizable or if there is a "closing-in" (despite the instructions, the subject follows the contour of the figure printed above).

Fluid Intelligence: The Raven's Coloured Progressive Matrices (CPM) (10) is a non-verbal intelligence test representative of general intellectual capacity or the "g" factor proposed by Spearman. The CPM was developed to assess children aged from 5 to 11 years old, mentally disabled individuals as well as older individuals. The items are organized in ascending difficulty throughout three sets (A, Ab, and B). On average, set B is more difficult than set Ab, which is more difficult than set A. The items consist of a drawing with a missing part, which the individual needs to complete by choosing one among six alternative responses. There is only one correct answer for each item. The respondents score one for each correct response and zero for each wrong response. The minimum score is 0, and the maximum score is 36.

Visual-spatial skills: Visual-spatial skills consist of the ability to integrate information from perceptual space to develop spatial coordinates that allow the proposed material to be organized and used to adequately perform a task. A neuropsychological test frequently used to assess visual-spatial skills is: Rey's Figure Test: the neuropsychological test assesses visual-constructive spatial skills, planning, organizational skills and problem-solving strategies (12).

Spatial Memory: Spatial memory is the ability to record information about your environment and orientation in space. Working memory allows you to record and process temporary information in order to achieve a goal.
Short-term spatial memory allows you to remember and identify different environments and record spatial relationships between objects in the environment.

Long-term memory allows the individual to record and remember the characteristics of their environments (concept of "cognitive map").

Neuropsychological tests used to assess spatial memory include:
Course tests: or tests for visuospatial MBT Corsi's Block Tapping Test measures visuospatial working memory.
This test consists of nine cubes fastened in random order to a blackboard; each time the examiner taps the blocks in a prearranged sequence, the patient must copy the tapping pattern, which involves a series of blocks of increasing span length to be tapped by the
patient in a forward (memory span) or backward (working memory span) manner (8).
Rey's Figure Test: Verbal Memory Verbal memory is defined as the ability to retain words or abstractions about language in memory. The main neuropsychological tests used to assess verbal memory are:
Rey's Word Test: Assesses short-term audio-verbal memory.
Digit Span: measures the amplitude of short-term verbal memory.

Since other cognitive domains can also be compromised, in addition to memory, it is important to examine them.
It is important to obtain a longitudinal clinical evaluation, if possible, as there is evidence of the possibility of a progressive decline in the clinical condition in the patient. Once the diagnosis is made based on the congruence between the clinic and the psychometric tests, the neurologist must determine the most likely cause that has determined the disease in the patient, The clinician must determine if memory is a salient part of the cognitive impairment (amnestic MCI), if, the person is experiencing a cognitive decline, but the memory is relatively well preserved, the other form will be considered, that is that of non-amnestic MCI. After determining the clinical syndrome, it is necessary to determine its etiology. If the history of the onset of the disorder is slow and gradual, it is likely that it is a degenerative disease, if the patient has a history of vascular risk factors and has had cerebral ischemic events, it is necessary to consider a vascular contribution; in this case we also speak of Vascular Cognitive Impairment.

If there is a degenerative cause at the base, clinical syndromes can be useful in suggesting an underlying diagnosis. If the patient has a typical amnestic syndrome that leads to IM and is in the appropriate age group, AD is a probable consideration, if the patient has attentive and visuo-spatial difficulties, dementia from Lewy bodies could be taken into consideration, while if the person is experiencing behavioral changes, inappropriate behavior, apathy, lack of intuition, attention and concentration it is possible that there is a frontotemporal degeneration. The etiological identification is more difficult in particularly elderly patients (the oldest old, aged ≥ 90 years), because in these an impairment of the general state is added; moreover, in these subjects the pathological criteria for the determination of AD remain obscure, making its distinction from the MCI even more challenging. Among the fundamental steps of the formulation of the diagnosis of MCI, laboratory diagnostic tests (leukocyte and red blood cell count, thyroid hormones, serum electrolytes, serum calcium, blood glucose, vitamin B12), neuroimaging techniques (to evaluate the possible role of an underlying cerebrovascular disease, in patients who present a vascular risk) and neurophysiological evaluation are also included. At the end of these evaluations, it is also possible to proceed with a psychiatric and neurospichiatric evaluation, a clinical cognitive assessment and/or an electrophysiological evaluation by means of EEG.

A screening for MCI should be conducted whenever elderly patients present themselves to the attention of the specialist clinician, with a subjective loss of memory or complains, however, cognitive problems. It is important to focus attention on the following characteristics:
Appearance of the MCI clarifying when the symptoms began
Nature of the pathology to understand its etiopathological basis
Frequency of the disease: how often the symptoms occur
Progression: It is essential to realize if the symptoms are getting worse or if the patient's condition is stable.

Although the diagnosis can make use of laboratory data and psychometric tests, it can only be made thanks to the critical judgment of the clinician. This is because, to date, there is no absolute consensus on the type of cognitive surveys to be used or on how many tests to administer or which thresholds to adopt (2).

Role of genetics in diagnosis
If the presence of an autosomal dominant form of AD (i.e. mutation in APP, PS1, PS2) is known, the MCI development is most likely the prodrome of AD dementia. The vast majority of these cases develop early-onset AD (i.e. onset under 65 years of age). In addition, there are genetic influences on the development of late-onset AD dementia. To date, the presence of one or two ε4 alleles of the apolipoprotein E (APOE) gene is the only genetically variant widely accepted as an increasing risk of late-onset dementia, while the ε2 allele reduces the risk. Evidence suggests that an individual who meets the clinical, cognitive, and etiological criteria for MCI, and is also APOE ε4 positive, is more likely to progress to AD dementia within a few years than an individual without this genetic trait (13).

Biomarkers in the MCI
Most treatment strategies are more effective in the pre-symtomatic phase of dementia, further studies have been conducted on diagnostic strategies for MCI. The use of genetic, proteomic and imaging markers could be essential for predicting the risk of disease. In the preclinical phase of dementia, the degree of cognitive decline is irrelevant and individuals may still have normal cognitive abilities. Among the elderly, preclinical dementia often remains undiagnosed, although it can affect normal aging. Cognitive deficits can be detectable years or even decades before the clinical symptoms of dementia. Changes in the levels of biomarkers in body fluids and in specific regions of the brain can allow these cognitive alterations to be detected even before the appearance of MCI. Several biomarkers can therefore lead to a more accurate prediction of who will develop dementia in the future (14).

The use of biomarkers can respond to two fundamental questions related to individuals with ICM:
Establish support for the basic etiology of clinical syndrome in an individual with MCI, which will have great importance in choosing the correct therapy, when effective treatments are available.

Determine the likelihood of cognitive and functional progression for a single MCI patient at a more severe stage of MCI or dementia, and the likelihood that this progression will occur within a defined period.

The different properties of biomarkers will ultimately determine their use in clinical situations, such as deciding who to treat, as well as research situations that could include the selection of subjects for clinical trials or inclusion in longitudinal research studies. In addition, since the timing of dementia progression is important, different biomarkers can have a differential utility in the short and long term. Biomarkers can be divided into different classes. Some directly reflect the pathology of AD by providing evidence of the presence of key proteins deposited in the brain during AD, such as beta-amyloid protein (Aβ) and tau. Other biomarkers provide less direct or non-specific evidence of AD, monitoring a variety of neural damage indices. These biomarkers can also have a certain specificity for the AD, by virtue of the regional model of anomalies. On the contrary, other biomarker models may be useful in providing evidence of an alternative non-AD underlying cause.

The current pathological criteria for AD require Aβ deposition tests in plaques, along with tau deposition tests in neurofibrillar tangles. Evidence suggests that together, the accumulation of these two proteins in the brain is associated with neuronal damage. The hypothetical framework, according to which biomarkers can be used to increase diagnostic accuracy, is presented in Table 1 below.

Tabella 1. *Biomarkers and diagnostic accuracy in the MCI (Marilyn S. Albert et al., 2011).*

Biomarkers indicating a high probability that MCI syndrome Is due to the AD	A positive Aβ biomarker and a positive biomarker of neuronal damage.
Biomarkers indicating an intermediate probability that MCI syndrome is due to AD	A positive Aβ biomarker in a situation where neuronal damage biomarkers have not been tested or cannot be tested or a positive neuronal damage biomarker in a situation In which Aβ biomarkers have not been or cannot be tested. Individuals who fall into one of these categories show An important aspect of the pathological process of AD, but without The full evidence of both Aβ deposition and neuronal damage Downstream that characterize The AD.
Biomarkers That Suggest This is unlikely that the syndrome MCI is due to AD	Negative biomarkers for both Aβ and neuronal damage. The definitive absence of Aβ deposition or damage Neuronal strongly suggests that the MCI syndrome Is not due to AD. In such situations, the search for biomarkers that reflect alternative pathological processes should be considered. These biomarkers are not as well established as those for The AD.

Basic clinical criteria

The possibility that the patient with MCI has a basic AD pathology is presented in the classification proposed in Table 2.

Table 2. Basic clinical criteria MCI (Albert et al., 2011).

MCI due to AD: Intermediate probability	If the subject meets the basic clinical criteria for MCI, but in addition has a positive biomarker that reflects the deposition of Aβ with an untested biomarker of neuronal damage, or a positive biomarker that reflects neuronal damage with an untested biomarker of Aβ, then there is a greater probability that the result will be AD dementia. Therefore, in the absence of one of these categories of biomarker information, the situation is still consistent with an intermediate level of certainty that the individual will switch to AD dementia over time. Therefore, patients who meet the criteria for this diagnosis have an intermediate level of certainty of Have MCI due to AD.
MCI due to AD: High probability	If the subject meets the basic clinical criteria for ICM and also has positive biomarkers for both Aβ and neuronal lesions, this provides the highest level of certainty that over time the individual will pass to AD dementia.
MCI due to AD: Unlikely	Patients with negative biomarkers for both Aβ and neuronal lesions are considered to have the lowest probability of underlying AD pathophysiology. Although such individuals may still have AD, research is justified Of an alternative cause of MCI syndrome.

The possibility of early identification of patients suffering from ICM is particularly important in the prevention phase. In fact, for subjects who have already developed dementia, currently there are only drugs that act mainly at a symptomatic level, while the intervention in the MCI phase would allow to prolong the time of active life, while maintaining a good quality of life (Maddalena, 2012). With regard to drug treatment, most efforts in this regard have been made on a-MCI and its evolution towards AD dementia. Currently, there are no drug treatments for MCI approved by the FDA, the European Medicines Agency or the Pharmaceuticals and Medical Devices Agency in Japan. Numerous randomized control trials have been conducted in the MCI spectrum, but none has been successful in demonstrating efficacy in delaying the progression from MCI to AD dementia. Rehabilitation (non-drug) treatment in the patient suffering from MCI is distinguished in two main types of intervention: physical exercise and cognitive intervention; the latter in turn includes: Cognitive Stimulation and Cognitive Training (2).

Prospective studies have revealed that subjects with IMI who are physically active have a lower risk of developing dementia than those who are less physically active.

A systematic review and a subsequent meta-analysis of 16 prospective epidemiological studies concluded that physical activity reduces the risk of incurring dementia by 28% and that of developing AD by 45% (15).

A comparison on how often subjects exercised by recruiting 198 participants suffering from MCI and 1126 subjects enrolled as controls, found that any frequency of moderate physical activity (even walking at a sluck pace) is associated with a reduction in the probability of incurring the MCI: 39% reduction in the probability, if the exercise is performed by middle-aged subjects (50-55 years) and 32% reduction in the probability, if the exercise is performed at a later age (16).

Studies show how interventions aimed at physical training can also guarantee a benefit for cognitive abilities in patients suffering from ICM. In fact, an RCT (Randomized Controlled Trial) found that 6 months of aerobic activity improve performance in tasks inherent in executive functions (Trails B, Stroop test and fluency in speech), with effects that have proven more pronounced in women than in men (17).

At present, according to the CCCDTD3 (3rd Canadian Consensus Conference on Diagnosis and Treatment of Dementia) there is not enough evidence to conclude that exercise can ensure that progression from MCI to AD is avoided. However, the CCCDTD3 itself has also established that there is sufficient evidence for clinicians to recommend and promote physical activity at any level of intensity compatible with the subject's age, as an integral part of a healthy lifestyle. Cognitive Stimulation consists of an involvement of patients in activities that are created to increase cognitive and social functions in a non-specific way. It is based on a self-assessment, in which the enrolled subjects indicate their degree of participation in a series of voluptuous or social activities.

Cognitive Training includes the individual teaching of strategies and skills, in order to optimize the cognitive functions of the subject and his independence in daily activities; we include among these: training in the use of memory techniques and support in learning without errors, the recovery of what has been learned after a time (space retrievals), relaxation exercises, training in attentive abilities and planning of daily life.

Cognitive Training can be carried out in a variety of ways: individually or in groups, by hand (with paper and pencil) or on the computer or it can include the performance of activities that are reminiscent of those of the subject's daily life.

Longitudinal studies involving healthy elderly subjects have suggested that recruitment into Cognitive Stimulation activities is associated with a reduction in cognitive decline and the risk of developing both a-MCI and AD. Therefore, it could have a protective effect on the possible development of cognitive deficits related to aging. Improvements in cognitive activity and quality of life, identified by Spector et al. (2004) in a large randomized trial, proved effective in patients with moderate dementia. As for research on Cognitive Training, they highlight how this can maintain or increase cognitive functions in older patients. The studies focused mainly on individuals subject to normal aging and on the population affected by dementia. A systematic review of 15 studies showed that at the end of the training there were significant improvements in 44% of memory tasks, according to objective measurements compared to a 12% improvement in non-mnemonic cognitive tasks; in addition, a significant improvement was recorded in 49% of subjective measurements related to memory, quality of life and mood, after cognitive training sessions. According to the CCCDTD3, however, the evidence is insufficient to conclude that organized cognitive interventions can prevent the progression of the MCI or to guarantee prescription, but there is sufficient evidence to promote an enrollment of older subjects in cognitive activities as an integral part of the healthy lifestyle. The future orientation of research in the field of therapy should therefore be aimed at establishing the duration of therapy, measuring more sensibly the results regarding the cognitive state and the overall condition of the patient and ensuring more homogeneous patient groups at the entrance to the studies (2).

Discussion

ICM is a neurological syndrome characterized by a mild cognitive disorder, or by the alteration of a single cognitive function in the absence of impaired autonomy in activities of daily life. The diagnosis of MCI is complex and is formulated based on multiple criteria. From a cognitive point of view, the performance of these subjects, relative to a single domain (or several domains compromised in a nuanced way) are lower than the reference values of the population having the same demographic variables. Secondly, it is essential that functional skills must be substantially intact or, at most, minimally compromised. The cognitive problem must result from the detailed anamnesis with the patient and the caregiver and must be associated with objective deficit performance in cognitive tasks and/or evidence of a decline over time in neuropsychological tests. The diagnostic process begins when the patient, or any other person close to him, expresses concern about his cognitive state. Once the clinician, based on the anamnesis and neurocognitive examination, has established that the subject does not fall within the dementia diagnosis, but at the same time does not have normal performance, he will objectively evaluate cognitive functions. The clinical presentation of the MCI can be variable, depending on the number and type of deficient neuropsychological functions. To define the specific subtype of ICM, a detailed cognitive examination is necessary, using a battery of neuropsychological tests, although at present there are still no specific instruments unanimously accepted, moreover, biological markers can be used mainly for research purposes and, in particular cases, for the purpose of identifying, together with other means, subjects at risk of evolving into AD. Regarding this deficiency in the field of biomarkers for the identification of MCI, this study has the merit of emphasizing the importance of an adequate neuropsychological examination, as it can potentially prove to be an excellent aid in the diagnosis of subjects with MCI, in order to discriminate against them from healthy subjects. It is therefore necessary to validate neuropsychological scales and screening tools in order to evaluate the MCI and identify pre-clinical dementia situations. The results that emerged from the literature examination have a relevant value. First of all, from the evaluative point of view, it reiterates the importance of an adequate selection of specific tools for a complete neuropsychological examination, in the face of the scarcity of information associated with biomarkers for the diagnosis of IC, together with the role of cognitive rehabilitation aimed at subjects with ICM, which can help a better quality of life for both the patient and the caregiver.

Conclusion

An adequate test battery could allow to identify those patients who are going to develop dementia and to distinguish them from those presenting with a depressive disorder only. This distinction, of course, has obvious therapeutic implications. The literature data supporting that an adequate psychometric assessment of patients with subjective memory disturbances can help in differentiating early candidates to develop dementia or those who do not.

Appropriate strategies for the treatment of MCI and the prevention of the progressive decline of cognitive functions are: periodic monitoring of patients, providing indications on lifestyle, treatment of lifestyle-related diseases and training on cognitive function.

Cognitive activities and training programs can also improve cognitive abilities or slow cognitive decline. The contribution of family and friends to the treatment is essential, thanks to their support, encouragement, patience and respect. The promotion of independence in communication and activities of daily living, the control of vascular risk factors, a healthy lifestyle, together with mental exercises, are effective factors for treatment. In addition, periodic medical care of patients at intervals of 3-6 months will help improve cognition and delay disease progression into dementia (18).

Before, the MCI was not seen as a condition conducive to rehabilitation due to its likely progressive course towards dementia. However, to date, there has been a growing interest in whether individuals with MCI can benefit from rehabilitation techniques. Reviews of cognitive interventions in the MCI have been more than positive, noting hopeful results on cognition and daily life after cognitive rehabilitation (1) Petersen, 2016).

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