Mild cognitive impairment of vascular origin: Proposal for an empirical approach in primary care

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Abstract

The incidence of mild cognitive impairment of vascular origin is increasing continuously among individuals with cardiovascular risk factors. The etiology of this kind of impairment is related to cerebrovascular pathologies, with the presence of silent cerebral infarctions the most relevant etiology. The incidence of cognitive impairment affects around 22% of patients at 3 months after an ischemic stroke, and this incidence is maintained or increased even 5 years after the stroke. Silent infarction should be considered the first clinical suspicion in patients with cardiovascular risk factors (such as hypertension, diabetes and dyslipidemia) who are attending a consultation for cognitive complaints, not only memory complaints. There are various tools for detecting such cognitive problems during the examination, such as brief cognitive tests and neuropsychological evaluations (for example, MMSE, SPMSQ or MoCA), and to assess its development. For a patient with cardiovascular risk factors and cognitive complaints, it should be possible to carry out an empirical treatment and assess the development of the cognitive deficits before referring the patient to the specialist. This review outlines various attitudes and therapeutic possibilities that might be useful in the scope of Primary Care. As a conclusion, there are enough tools to detect mild cognitive impairment at Primary Care level, and to initiate an adequate therapeutic strategy to avoid the evolution of the cognitive decline.

Keywords: Mild cognitive impairment. Cardiovascular risk factors. Evaluation. Therapy. Algorithm. Diagnosis.

Introduction

Cognitive impairment and dementia are among the most widespread health problems in developed countries and their incidence is increasing in parallel with the progressive increase of life expectancy. It is increasingly evident that early identification of cognitive impairment in older adults presents opportunities for interventions that aim to mitigate the impact of cognitive symptoms on daily function and that attempt to delay (or ultimately prevent) progression from mild cognitive impairment (MCI) to dementia (Kelley, 2015).

Mild cognitive impairment is a syndrome defined as cognitive decline greater than that expected for an individual's age and education level (Petersen et al., 1999), but which does not interfere notably with activities of daily life (Gauthier et al., 2006; Petersen et al., 2001). But there is a growing body of evidence that subtle deficits in instrumental activities of daily living (IADL) may be present in MCI (Jekel et al., 2015).

In the last years, there has been a paradigm shift towards a new concept, that of vascular cognitive impairment (VCI), and this is now widely accepted as a more appropriate concept than the old concept of vascular dementia. Thus cognitive impairment that is caused by or associated with vascular factors has been termed "vascular cognitive impairment" (VCI) (Hachinski & Bowler, 1993).

Patients who do not have dementia but who may not be "normal" remain diagnostic challenges. In fact, the concept of "normality" in an elderly person is itself controversial. Patients who do not have dementia but who may not be "normal" remain diagnostic challenges. In fact, the concept of "normality" in an elderly person is itself controversial. Although most elderly people note subtle changes in their memory and cognition since youth, most feel that their memory performance and daily functioning is similar to that of others their age. The majority of experts view this as normal "cognitive aging" and that normality must be determined with a particular age group. The label "mild cognitive impairment" is applied to elderly people with short- or long-term memory impairment who have no significant daily functional disability. The initial criteria for mild cognitive impairment require a subjective report of cognitive decline from a former level, gradual in onset, and present for at least 6 months. This subjective report is supplemented by objective evidence of the decline in memory and learning on brief or extensive cognitive testing. Other cognitive domains remain intact. But controversy still surrounds their characterization, definition and application in clinical practice (Chertkow et al., 2008), despite the fact that the National Institute for Neurological Disorders and Stroke and the Canadian Stroke Network convened on standards for the description and study of VCI (Hachinski et al., 2006).

Cognitive impairment is associated with increasing age and low education levels (Ranlall et al., 2013), and, also, female gender is an associated factor (Sun et al., 2014). Another point to consider is that MCI can act as a transitional level of evolving dementia with a range of conversion of 10-15% per year (Eshkoor et al., 2015; Kaduszkiewicz et al., 2014).

In multi-domain MCI patients, 59% of patients progressed in 2 years, whereas only 18% of amnestic MCI patients become demented in this period (Mitchell et al., 2009). The interaction between the vascular component and other components more than doubles the rate of progression when compared to pure Alzheimer disease alone (Hachinski & Bowler, 1993). Thus it is crucial in protecting older people against MCI and developing dementia (Eshkoor et al., 2015) and, for this reason, the early detection of MCI has become important for better healthcare management and more favorable outcomes for affected patients and their families and caregivers (Cordell et al., 2013; Luna-Lario et al., 2015; Mora-Simón et al., 2012).

Pathophysiology

Mild cognitive impairment, especially of the amnestic type, is often considered the earliest clinical sign of probable Alzheimer disease (AD) (Schneider et al., 2009). Studies of the pathologic basis of MCI have shown AD-type pathology. It has also been postulated that a cerebral cholinergic deficit underlies the memory loss and other cognitive deficits (Morris, 2002) and, in this respect, the activity of the choline acetyltransferase is relevant (DeKosky et al., 2002).

Although there are many risk factors (Table 1), in practice, many people with mild cognitive impairment have vascular risk factors (Chertkow et al., 2008). For example, hypertension was associated with an increased risk of cognitive decline (HR 1.20; 95% confidence interval (CI) 1.04, 1.39; P = 0.02) (Haring et al., 2015). Joosten et al. (2013) demonstrated, in a large population–based cohort, that a worse overall cardiovascular risk profile was associated with poorer cognitive function and that this association was already present in young adults aged 35 to 44 years. Zhao et al. (2014) presented a new method for the early diagnosis and assessment of mild cognitive impairment in elderly individuals with hypertension. Elderly hypertensive patients with cognitive impairment were assessed by the Montreal Cognitive Assessment (MoCA) and Clinical Dementia Rating Assessment (CDR). Cognitive results were compared to apparent diffusion coefficient (ADC) values from magnetic resonance-diffusion weighted imaging. Systolic and diastolic blood pressure values increased as cognitive function declined ($P<0.001$). Cognitive function declined as ADC values increased, and they differed between elderly people with and without hypertension ($P<0.001$). Among elderly hypertensive participants, ADC values were significantly increased in the cortex and hippocampus. The MoCA and CDR tests were sufficiently sensitive to evaluate cognition. Blood pressure was closely related to cognition, as well as to functional and structural changes in the brain. Greater cognitive decline was observed in elderly participants with hypertension compared to those without.

Unmodifiable factors:

- Age
- Sex
- Ethnicity

Modifiable factors:

- Metabolic conditions:
  - Hyperhomocysteinemia
  - Chronic renal failure
  - Deficiency of vitamins (B_{12}, B_6, D, E)
  - Folate deficiency
  - Diabetes
- Endocrine problems:
  - Testosterone deficiency
  - Subclinical thyroid dysfunction
  - Reduced level of estrogens
- Cardiovascular problems:
  - Hypertension
  - Hyperlipidemia
  - Diabetes
  - Peripheral vascular disease
- Vision and hearing loss
- Lower physical activity
- Diet
- Educational level
- Socioeconomic status
- Sleep disorders
- Substance abuse (ilegal drugs, alcohol)
- Environment
- Chronic pain
- Living alone
- Stress
- Depression
- Fatigue
- Smoking habit
- Excess exposure to aluminum
- Head injuries

Genetic factors:

- Apolipoprotein E
- Paraoxonase
- Catechol-O-methyltransferase
- Brain-derived neurotrophic factor
- Non-coding RNAs, such as miRNA

Table 1. Mild cognitive impairment risk factors in the elderly (modified from Eshkoor et al., 2015).

VCI defines a continuum of disorders ranging from mild cognitive impairment to full-blown dementia, attributable to cerebrovascular causes. Cognitive decline is commonly caused by widespread small cerebrovascular lesions (CVLs) affecting regions/networks essential for cognition, memory and behavior. CVLs often coexist with Alzheimer-type and other pathologies, which interact in promoting dementia, but in many non-demented elderly individuals, mixed brain pathologies are also present (Jellinger, 2014). The prevalence of post-stroke cognitive impairment ranges from 20% to 80%, which varies with country, race, and diagnostic criteria (Sun et al., 2014). Douiri et al. (2013) concluded that the overall prevalence of cognitive impairment 3 months after stroke and at annual follow-up remained relatively unchanged at 22% (24% [95% CI, 21.2–27.8] at 3 months; 22% [17.4–26.8] at 5 years to 21% [3.6–63.8] at 14 years). In multivariate analyses, the post-stroke prevalence ratio of cognitive impairment increased with older age (2% [1–3] for each year of age), ethnicity (2.2 [1.65–2.89]-fold higher among black group) and socioeconomic status (42% [8–86] increased among manual workers). A significant, progressive trend of cognitive impairment was observed among patients with small vessel occlusion and lacunar infarction (average annual percentage change: 10% [7.9–12.8] and 2% [0.3–2.7], respectively, up to 5 years after stroke). But even 11 years after ischemic stroke in young adults, a substantial proportion of patients must cope with permanent cognitive deficits (Schaapsmeerders et al., 2013). Also, more than 35% of patients with TIA had impairment of ≥1 cognitive domain. The presence of silent brain infarcts was related to worse executive functioning but did not explain the whole relationship between TIA and cognitive impairment (van Rooij et al., 2014).

Microinfarcts are described as attenuated lesions of indistinct shape occurring in both cortical and subcortical regions involving a small vessel at its core but are foci with pallor, neuronal loss, axonal damage, and gliosis (Kalaria, 2012). They appear robustly associated with cognitive impairment and predict poor outcome in the elderly with cerebrovascular diseases (Arvanitakis et al., 2011; Kalaria, 2012). Lacunar strokes might be less likely to affect cognition than more severe, larger cortical strokes, except that lacunar strokes are associated with cerebral small vessel disease (SVD), which is the commonest vascular cause of dementia. Cognitive impairment appears to be common after lacunar strokes despite their small size, suggesting that associated SVD may increase their impact (Makin et al., 2013).

Thus, even with no presence of macroscopically visible lesions in brain parenchyma, microvascular lesions are one of the most important factors associated with vascular cognitive impairment.

Evaluation of MCI

Diagnosis of MCI is based on subjective complaints of memory loss, memory impairment based on brief cognitive or neuropsychological testing, the decline in normal function, and unchanged basic daily functioning. In patients with a cardiovascular risk profile, we can assume that the diagnosis could be vascular MCI. The basic diagnosis relies on asking questions about memory, medications,

health status, and comorbidities. This could be complemented by interviews with family members and close friends. Other complementary diagnostic tools are the various neuroimaging techniques (such as CTscan and MRI) and the use of biomarkers (such as amyloid beta and tau). The combination of MRI and CSF tau/Aβ42 can provide a better prediction of MCI and its progression to AD that is extremely helpful in developed countries compared to the developing world. This difference is due to resource limitations and different cultural values, which limits the utility of MRI and CSF tests (Eshkoor et al., 2015).

Clinical assessment is used along with other methods to determine cognitive decline. Clinical tests are based on interviews to be used in clinical judgment and third-party information. There are many different neuropsychological tests to detect and evaluate cognitive impairment, such the Short Portable Mental Status Questionnaire (Pfeiffer, 1975), the MiniMental State Examination (Folstein et al., 1983), the Clock-drawing test (Dal Pan et al., 1989), the Memory Impairment Screen test (Buschke et al., 1999), the Montreal Cognitive Assessment test (Nasreddine et al., 2005) or the Try Your Memory test (Brown et al., 2009), among many others. Among these scales, probably the most common screening test is the MMSE. The MMSE evaluates memory, orientation, language, praxis, and construction, but lacks an evaluation of executive control functions. The MoCA includes this evaluation of executive control functions and for this reason is considered the most suitable tool for the screening and evaluation of patients with MCI.

Another important tool for the assessment of patients with MCI is the use of the Informant Questionnaire on Cognitive Decline in the Elderly or IQCODE (Jorm & Jacomb, 1989). The IQCODE is a questionnaire that asks an informant about changes in an elderly person's everyday cognitive function. The questionnaire aims to assess cognitive decline independent of pre-morbid ability, providing very useful information for the evaluation of the progress of the cognitive impairment.

The main differential diagnosis should be made to discard the presence of delirium or depression.

Management

Given the high risk of progressing from mild cognitive impairment to dementia, it is important for clinicians to have knowledge of the definition, diagnosis, and treatment of mild cognitive impairment. And this is especially applicable to clinicians at Primary Care level. A suitable treatment is based on choosing the effective and appropriate strategies for the specific etiology of the cognitive disorder, in this case, the vascular etiology. Pharmacological and non-pharmacological treatments can be used to prevent cognitive decline in MCI (Kelley, 2015; Sherwin, 2000).

The first level of action should be focused on the modifiable risk factors (Cooper et al., 2015). Haring et al. (2015), in a large study, demonstrated that women with antihypertensive treatment and uncontrolled BP showed highest risk estimates for developing cognitive decline compared to non-hypertensive women. Soon, the FINGER study will provide important information on the effect of

lifestyle intervention to prevent cognitive impairment among at-risk persons (Ngandu et al., 2014).

At the same level, we can use non-pharmacological therapies to stop the cognitive decline. Fiatarone Singh et al. (2014) demonstrated that a program of resistance training significantly improved global cognitive function, with a maintenance of executive and global benefits over 18 months. The study of Intzandt et al. (2015) supports cardiac rehabilitation exercise programs as a feasible model of exercise for patients with MCI with vascular risk. Also, the efficacy of cognitive intervention programs has been recently demonstrated, with positive effects for both objective and subjective outcome variables, and these effects persisted from 1 month up to 5 years (Yi et al. 2015).

Table 2 lists the pharmacological agents suggested for the treatment of patients with MCI. The most recent data suggest that cholinesterase inhibitors and memantine should not be prescribed for patients with MCI (Schneider et al., 2011; Cooper et al., 2013; Russ, 2014). COX-2 inhibitors were also ineffective (Cooper et al., 2013). Thal et al. (2005), in their MCI study, concluded that the results did not support the hypothesis that rofecoxib would delay a diagnosis of AD. In conjunction with the lack of effects observed in previous AD studies, the findings suggest that inhibition of COX-2 is not a useful therapeutic approach in AD.

Regarding vitamins, there is no convincing evidence that vitamin E is of benefit in the treatment of AD or MCI (Farina et al., 2012). Recently, Douaud et al. (2013) demonstrated that B-vitamin supplementation can slow the atrophy of specific brain regions that are a key component of the AD process and that are associated with cognitive decline.

Testosterone treatment may modestly improve verbal memory and depression symptoms in men with both MCI and low testosterone levels (Cherrier et al., 2015). Also, it would appear that estrogen hormone therapy in women could have a positive effect on cognitive performance (Kim & Jung, 2015).

In a recent systematic review about the use of selective serotonin reuptake inhibitors for MCI, Dixon & Mead (2013) concluded that patients receiving treatment with fluoxetine had better cognition at the end of treatment compared to the placebo group. However, the sample size was small and further randomised clinical trials are needed to confirm whether fluoxetine in MCI reduces the rate of cognitive decline and whether any beneficial effects are sustained after treatment ends.

With regards to the so-called neurotonic drugs, there are some positive data for actovegin (Mikhaĭlova et al., 2013), cerebrolysin (Boksha et al., 2014), ginkgo biloba (Tan et al., 2015), and piracetam (Waegemans et al., 2002) in the treatment of MCI patients.

Both nimodipine (López-Arrieta & Birks, 2002) and nicardipine (Amenta et al., 2009) can be of some benefit in the treatment of patients with features of MCI. Mahmoudi et al. (2013) concluded that prescription of low dose ω-3 PUFAs for 6 months had no significant beneficial effects on improvement of cognition or prevention of cognitive decline in older people. The use of cholinergic precursors

such as citicoline and choline alphoscerate is associated with a modest improvement of cognitive dysfunction (Parnetti et al., 2007). In 2003, De Jesus Moreno Moreno suggested the clinical usefulness and tolerability of choline alphoscerate in the treatment of the cognitive symptoms of dementia disorders of the Alzheimer type. Citicoline is a drug with a pleotropic effect on the central nervous system and with an excellent safety profile (Secades, 2011). Fioravanti and Yanagi (2005), in their systematic review,

Cognitive enhancers:
Cholinesterase inhibitors (Cooper et al., 2013; Russ, 2014)
Memantine (Schneider et al., 2011)
COX-2 inhibitors:
Rofecoxib (Thal et al. 2005)
Celecoxib (Cooper et al., 2013)
Vitamins:
Vitamins B (Douaud et al. 2013)
Vitamin E (Farina et al., 2012)
Hormone replacement:
Testosterone (Cherrier et al., 2015)
Estrogens (Kim & Jung, 2015)
Selective serotonin reuptake inhibitors (Dixon & Mead, 2013)
Neurotonics:
Actovegin (Mikhaĭlova et al., 2013)
Cerebrolysin (Boksha et al., 2014)
Gingko biloba (Tan et al., 2015)
Piracetam (Waegemans et al., 2002)
Calcium channel blockers:
Nimodipine (López-Arrieta & Birks, 2002)
Nicardipine (Amenta et al., 2009)
Omega 3 fatty acids (Mahmoudi et al. 2013)
Cholinergic precursors:
Choline alphoscerate (Parnetti et al., 2007; De Jesus Moreno Moreno, 2003)
Citicoline (Fioravanti and Yanagi, 2005; Alvarez-Sabín et al., 2013; Cotroneo et al., 2013)

Table 2. Proposed pharmacological treatments for patients with MCI

concluded that there was some evidence that CDP-choline has a positive effect on memory and behaviour in at least the short to medium term. The evidence of

benefit from global impression was stronger, but is still limited by the duration of the studies. Further research with CDP-choline should focus on longer term studies in subjects who have been diagnosed with currently accepted standardized criteria, especially mild vascular cognitive impairment or vascular dementia. More recent studies, following these recommendations, have demonstrated the beneficial effects of longer periods of treatment with citicoline in patients with post-stroke vascular cognitive impairment (Alvarez-Sabín et al., 2013) and in patients with MIC of vascular origin (Cotroneo et al., 2013).

With the proposed algorithm (Figure 1), the general practitioner should be able to evaluate and effectively treat patients with MCI.

As conclusion, there are enough tools to detect mild cognitive impairment at Primary Care level, and to initiate an adequate therapeutic strategy to avoid the evolution of the cognitive decline.

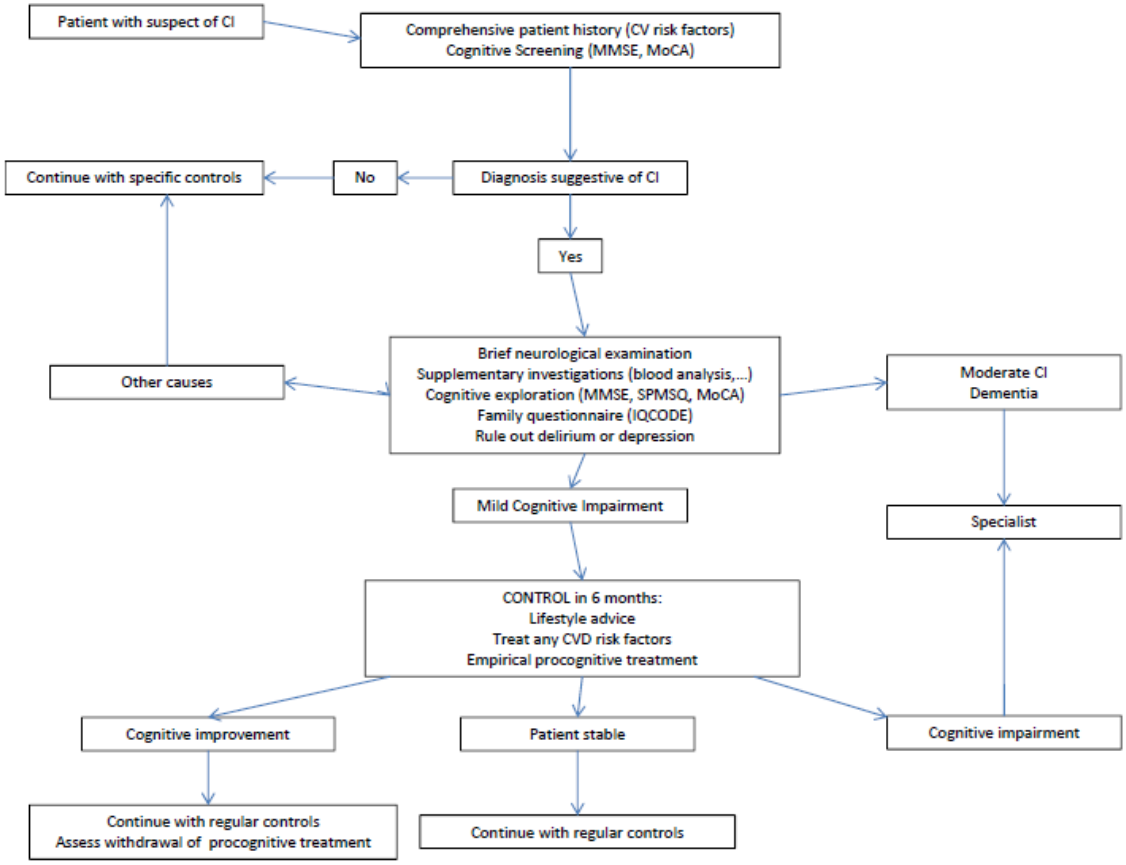

Figure 1. Proposal for an empirical approach to MCI patients in primary care

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