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The Mild Cognitive Impairment (MCI) in Searching for its Clinical Identity, Comment of the NEDICES Cohort Data

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Abstract

Elderly cognitive decline is a well-known disorder that affects many people. One of the first medical definitions for this clinical reality was Kral's "benign and malignant senescent forgetfulness". After Kral, many authors proposed other entities of memory impairment or cognitive decline in the elderly: "Age-associated memory impairment", "Age-related memory decline", "Ageing-associated cognitive decline", Mild Cognitive Impairment (MCI) and "Cognitive Impairment Non-Dementia" (CIND) of the Canadian Study. And very recently, the DSM-V defined the elderly cognitive decline as a "Minor Neurocognitive Disorder". By large, MCI had far more citations than any other predementia state in MEDLINE (more than 8,000 reviews in this medical database). This success in the medical literature is rather the expression of a controversy than a well-defined clinical disorder. In fact, its medical birth, near 30 years ago, was as a research entity that precludes dementia. The theoretical definition of MCI is quite clear (A cognitive decline with an increased dementia risk); the problem is the operational definition of this cognitive decline in many elderly that have produced, along the time many definitions and subtypes. In summary, MCI is defined as cognitive decline (of one or more cognitive domains, mainly memory) with normal or near normal functional activities of the patient, and obviously, no dementia. According to the type and extension of the affected cognitive domain, MCI has received several subtyping: Amnestic- only memory affected, non-amnestic- deficit in another cognitive domain different from the memory, such as executive capacities. Both of them could be shown alone or in combination (only amnestic MCI, only non-amnestic, or amnestic o non-amnestic plus other cognitive domain affected.

There are several well-known characteristics of this entity. First, it is prevalent in the elderly, more prevalent (about 10-15%) that the dementia states (5-10%). Obviously, in both conditions, its prevalence oscillates with the operational definitions used and with the population demographic characteristics studied: age, sex and education. Second, MCI involves an increased risk of dementia and mortality in relation to the normal cognition elders. Third, it is an unstable disorder, many MCI cases do not evolve to dementia, and many others change to normal cognition in a period of 2-3 years. Fourth, MCI is a heterogeneous entity with many risk factors and aetiologies; it is not always the predementia state of the main neurodegenerative disorders of the elderly: Alzheimer disease (AD), Parkinson disease (PD) and others; cerebral vascular diseases, depression and elderly co-morbidities underpinning many MCI cases.

From an epidemiological point of view, it is interesting to comment the MCI definition in three different scenarios: the clinical setting, the population-based surveys, and the trial studies because in these three scenarios, MCI had different characteristics and evolution.

Keywords: Mild cognitive impairment; Alzheimer's disease neuroimaging initiative; Population based survey; Trials; NEDICES; Cognitive decline; Dementia

Introduction

MCI in the clinical setting

There are hundreds of studies on MCI in a clinical setting. In a brief review, it is very difficult to summarize its results. Perhaps it is more interesting to describe some MCI studies in relation with two diseases: AD and PD [1-7].

The first is the "Alzheimer's Disease Neuroimaging Initiative (ADNI)" project. This big research is going on, investigating the evolution of AD from an initial population of cognitively normal subjects (n=200), MCI (n=400) and AD patients (n=200) with sophisticated CSF biomarkers (beta-amyloid, tau) and neuroimaging (MRI, PET) [7-11]. The study begins in 2005 with the enrollment of 800 participants from 56 clinical sites of the United States and Canada. The ADNI project had successive participant inclusions (2009, 2011), and it will be finished in 2021 [12-14]. Other ADNI studies from Europe, Australia and Japan had shared the ADNI primitive aims and methods [12]. The database of this project is open to investigators and more than 1,800 recognized investigators had applied to use its databases. ADNI has generated hundreds of scientific papers [12-14]. I would like to underline some findings. 1) Subjective memory loss (SML) does not have a clear risk of dementia in the short-term (3-5 years); the NEDICES cohort determines similar findings [14,15]. In the long run of two decades, possibly, SML had a minimal dementia risk [16]. Cognitive normal subjects (some of them have clear biological risks of preclinical AD) and MCI are biologically heterogeneous [14]. One ADNI work divides the MCI into four groups of subjects: one, clinically stable and without AD physiopathology

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(¿vascular?¿hippocampal sclerosis?), another MCI group had no relationship with AD physiopathology, and the other two groups have a relationship with the AD physiopathology, although in a different way [17]. Moreover, the ADNI study needs to divide the MCI cases into early and late MCI, separate from the classical (amnestic and non-amnestic) to better understand the MCI evolution [13,14]. The AD longitudinal evolution is complex and it is out of this brief revision. The majority of ADNI works have postulated that multiple data: clinical, psychometric and biomarkers (biochemical and neuroimaging) are the most informative way to predict the MCI evolution [14]. However, an ADNI investigation sustains that the psychometric evaluation is the most indicative to predict the MCI evolution [18]. With this tremendous amount of information, the ADNI study will need more than two decades of investigation to obtain firm conclusions to eliminate). The addition of sophisticated biomarkers to the clinical evaluation does not clarify the subject at the moment. In conclusion, the words of Weiner et al, 2017, are informative: "…mounting evidence suggests that AD progression is a far more complicated tale" [14].

In the MCI-PD field, there is not a so great study such as ADNI investigation, but there is an interesting "Task Force" agreement on this theme with two publications. Their conclusions, in summary, are: 1) PD-MCI in PD patients is common; 2) PD-MCI has a significant heterogeneity; 3) it has a risk of progressing to PD-dementia; and 4) formal diagnostic criteria for PD-MCI in PD patients are proposed in the last paper [19]. A recent review of this theme insists in the necessity of the formal diagnostic criteria of MCI-PD to advance in this field [20].

MCI in population-based surveys: The NEDICES cohort

Farias et al. demonstrated that not only the methods of evaluation of MCI cases are different in the clinical setting versus the population-based scenario, but the conversion to dementia could be four times greater in the clinical setting [21]. It is known that a selected population applies for clinical assistance everywhere.

There are many well-known long evolution population-based cohorts that studied MCI (e.g. the Framingham Heart Study and the Mayo Clinic Study of Aging) in the USA, or in Canada, the Canadian Study of Health and Aging [8,22]. Also, there were similar studies in Europe: PAQUID cohort in France, the MCR CFAS in the UK, and ILSA in Italy, or the Sydney Memory and Ageing Study in Australia are good examples [23-26]. I will comment only the main data of the NEDICES cohort.

The NEDICES cohort population and methods and main findings have been described [27-29]. In brief, the NEDICES population was sampled from the census of three sites of Central Spain with different socioeconomic backgrounds: Las Margaritas, a working-class neighborhood in Getafe (Greater Madrid); Lista, a professional-class neighborhood in Salamanca district (downtown Madrid); and 38 villages of the Arévalo county in Castile (125 km northwest of Madrid), a rural area. All participant had 65 years or older at the baseline wave and signed an informed consent to be enrolled in the cohort.

The ethical committees of two university hospitals from Madrid approved its methods [27-29]. The baseline wave (1994-1995) of the NEDICES cohort included 5,278 participants and had two incidence evaluations (in 1997-1998 and 2003-2004, only completed adequately in the rural area). The diagnoses of dementia were performed by neurologists or geriatricians, after two phase's methods (Phase I, screening; Phase II, diagnosis by specialists). All participants underwent a complete evaluation of their health status and lifestyle behaviors [27-29]. The date of death of and its main causes were obtained by a link with the official Spanish Registries from 1994 until 2008.

In the NEDICES-MCI study, the MCI diagnosis was made by an algorithmic retrospective definition according to the International Working Group recommendations [6,10]. The presence of cognitive impairment was based on performances obtained from the MMSE-37 at baseline [30,31]. Accordingly, the MCI cases showed evidence of cognitive impairment on MMSE-37 (a Spanish adaptation of the Folstein's MMSE) with preserved or 'minimally impaired' activities of daily living (score on Pfeffer-11 ≤ 5), but did not meet conventional diagnostic criteria for dementia [5,7,32]. Several MCI subtypes were also retrospectively performed to evaluate its predictive capacity of future dementia and mortality; one is a "global cognitive deficit" obtained from the MMSE-37. [For this approach, two cut-off points; 1.5 standard deviation (SD): "moderate cognitive impairment" (MCI-1.5) (n=145) and 1.0 SD: "mild cognitive impairment" (MCI-1.0) (n=462) below the mean score of non-dementia, cognitive normal (CN) participants; n=2,949]. The other subtypes were categorized when it was deficit in any of the five "specific cognitive domains" obtained from the MMSE-37: spatial-temporal orientation; attention-concentration (serial subtraction 7 from 100 and digits backwards); memory (word recall); language (naming, repeating, comprehension and writing); and visuoconstructive abilities (visual reproduction of the two figures). This classification required the presence of at least one affected cognitive domain (cut-offs 1.5 SD below the mean of the baseline non-dementia cases). According to this paradigm the four MCI subtypes based on "specific cognitive domains" were: amnestic MCI (a-MCI) (n=259); amnestic-multidomain-MCI (aMd-MCI) (n=193); non-amnestic-MCI (na-MCI) (n=517); non-amnestic-multidomain-MCI (naMd-MCI) (n=116). Cox proportional-hazards models to estimate hazard ratios (HRs) were used to calculate the risk of dementia in every MCI subgroup. The predictive values for incident dementia (sensitivity, specificity, positive and negative predictive value, likelihood ratios, accuracy and positive and negative clinical utility) were also calculated using all MCI subtypes.

The main results of the NEDICES MCI study can be summarized [10]:

1. The different MCI definitions determine variable MCI prevalence (4.5%–31.8%).
2. The MCI subgroups were cognitively heterogeneous and generated frequent overlap between them (e.g. the MCI-1.5 and aMd-MCI showed an overlap higher than 40%).
3. At follow-up, the MCI subgroups determined higher dementia conversion in all MCI subgroups than in their corresponding CN subgroup ($p>0.01$) and higher mortality, but the non-amnesic subgroups had low predictive dementia conversion and death risk (the naMd-MCI did not reach statistical significance).
4. The different MCI subtypes did not determine specific dementia subtypes at follow-up, with the exception of a-MCI (very high conversion to AD).
5. The MCI risk factors for dementia conversion were age and years of education, not sex (like in the NEDICES dementia study -33). Neither disease, nor comorbidity was risk factors for dementia conversion, with the exception of self-rated health.
6. Our MCI definitions demonstrated low sensitivity (0.19-0.71). Two MCI subtypes (aMd-MCI and MCI-1.5) had an elevated

specificity (higher than any other MCI definition), but low sensitivity. This finding is relevant for preventive dementia trials (rule- out diagnosis).

7. The aMd-MCI has the best dementia predictive accuracy. The aMd-MCI subgroup showed a high positive likelihood ratio: 9.54 (CI 95%: 6.93-13.12) (high clinical utility when negative). For AD preventive trials, the need is to obtain a MCI subtype with high diagnostic specificity or to add clinical data, biomarkers or neuroimaging to the MCI clinical subtype [7].

The most interesting finding of this study is the high rate of dementia conversion in the subtype: aMd-MCI. These findings are analogous in other studies [10,24,34-38].

Several surveys with similar MCI definitions to our study, but with a more extensive psychometric evaluation also showed similar results [10,39-41]. The aMd-MCI is the only stable MCI subgroup in our longitudinal clinical investigation [evolution to more cognitive decline or dementia (15.6%), persistent MCI (35.7%), evolution to CN (10.1%), the rest were dead or ineligible subjects]. This observation has biological plausibility showing that the temporal lobe gray matter atrophy has a continuum: from normal cognition, amnesic MCI, aMd-MCI to mild AD [42].

The main limitation of this study is the retrospective MCI diagnosis, the elemental cognitive evaluation in the baseline wave (MMSE-37 and Pfeffer-11), the evaluation of MCI with the same dementia screening instruments, and also the need to explore a selected non-dementia sub-cohort (younger and more educated) of total NEDICES cohort because we eliminated all subjects with abnormal Pfeffer-11 [33]. We had several strengths: the high number of participants, the adequate definition of dementia cases the mortality data (link with the official Spanish Death Registries), and the low-moderate rate of non-respondent participants in NEDICES [33,43-45].

MCI in clinical and population trials

The initial aims of the MCI entity were the possibility to postpone (or to eliminate) the onset of dementia (mainly AD) by means of pharmacological trials in the MCI individuals. Hundreds of trials, in the last two decades, mainly pharmacological, but also with non-pharmacological methods have been performed without a clear success [46,47]. But the there are many ongoing trials and many more drugs are in the pipeline waiting for new trials. Two points deserve to be commented. First, the need for more homogeneous definitions in the trials of MCI and second, the new preventive trials in a population-based scenario with multimodal methods (pharmacological and non-pharmacological) are going on in Europe [48-50].

Conclusion

Elderly cognitive decline affects many people. This cognitive decline in many cases is a predementia state as MCI. But MCI must be subtyped to achieve the better dementia risk prediction. In the NEDICES cohort, the clinical based amnestic-multidomain MCI has the higher risk of future dementia and it is the better MCI subtype for clinical trials in the NEDICES cohort as in others studies.

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