MILD COGNITIVE IMPAIRMENT: WHAT'S NEW ABOUT?

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Summary

Mild Cognitive Impairment (MCI) is a diagnostic entity describing patients affected by cognitive deficits that are not yet severe enough to impair their abilities of daily living. For a long time it has been considered part of normal ageing, so that scientists initially talked about "benign senescence forgetfulness". Subsequently, MCI has been recognized as a pathological condition, and many researchers have focused their attention to the identification of its diagnostic criteria; different subtypes of MCI, with relative etiologies and outcomes, have been then identified, and nowadays it is widely assumed that those patients have a major risk to develop dementia. Moreover very recent researches have been focused on the identification of new diagnostic criteria for Alzheimer's disease (AD), and it has been hypothesized that amnestic MCI may already represent a prodromal AD.

Keywords: Mild Cognitive Impairment (MCI), Alzheimer's Disease (AD), AD New Diagnostic Criteria

Introduction

The term "Mild Cognitive Impairment" (MCI) characterizes those subjects having some cognitive damage which is not yet severe enough to impair their autonomy in everyday life[(1)]. MCI is considered the transitional state between normal ageing and very early dementia, and consequently it receives nowadays an increasing attention. Longitudinal studies showed indeed that MCI subjects are at high risk for developing Alzheimer disease[(2)], and more generally dementia[(3)]. Recently the concept of MCI has been reconsidered and a proposal has been done to revaluate it. This paper aims at offering an updated information on the topic. We report in Table 1 the general terminology about the topic.

Table 1: Terminology

Mild Cognitive Impairment: individuals with memory or both memory and cognitive impairment, and unaffected activities of daily living. AD criteria are not currently fulfilled.

Amnestic Mild Cognitive Impairment: A specific subtype of MCI characterized by an isolated memory deficit, and unaffected activities of daily living. AD criteria are not fulfilled.

Preclinical AD: The long and asymptomatic period between the first brain lesions and the first symptoms. Includes normal individuals that will later fulfill AD criteria

Prodromal AD: The symptomatic predementia phase of AD, included in the MCI category: symptoms are not severe enough to fulfill AD criteria.

Material and methods

Initially scientists talked about "benign senescence forgetfulness" to identify people with mild memory impairment but having no significant impairment in other cognitive domains. The idea was that memory loss was essentially due to the normal ageing process[4]. Subsequently the International Psychogeriatric Association proposed the term of "age-associated cognitive decline" referring to a multiple cognitive domain impairment presumed to decline during the normal ageing. The Canadian Study of Health and Aging[5] preferred the term "cognitive impairment, no dementia", to underline that the impairment severity was mild and did not allow the term "dementia". Up to now MCI is considered a pathological condition and not a more consequence of normal ageing.

The typical MCI patient shows a memory impairment going beyond the physiological decline of ageing, but no damage in other cognitive domains. Consequently the neuropsychological assessment will show low scores in memory tests with normal results in other. This pattern reflects the criteria first described by Petersen[1, 6]. According to this interpretation MCI is essentially characterized by:

- Memory complaint, preferably corroborated by an informant.
- Objective memory impairment for age.
- Relatively preserved general cognition for age.
- Essentially intact activities of daily living.
- Not demented.

Subsequently different clinical subtypes of MCI were found and the concept was extended beyond memory. Nowadays the term MCI include (Table 2: scheme of the different subtypes of MCI with etiology and outcomes):

- a-MCI : amnesic MCI, that is the isolated memory damage.
- Md-MCI: multi domain MCI, that involves various cognitive domains, such as language, executive functions, visuospatial skills, with or without a memory impairment. If there is a memory impairment the label is of md-MCI-a, otherwise, if memory is not impaired the label is of md-MCI –na.

- na-MCI: the third and less common type. Here there is a single no memory damage as language , praxis, or visuospatial impairment without any other dysfunction.

Of course, all MCI clinical subtypes have a minimal impairment in functional activities[7]. The causal factors of each subtype seem different: while a-MCI has a presumed degenerative etiology preluding to AD, the other subtypes more probably progress towards non-AD dementias. Amnestic MCI is obviously the main focus of research, particularly because we already have some drugs for AD which might be of more benefit if employed earlier.

The NINCDS-ADRDA (1984) criteria required the impairment of two or more cognitive domains (that is a pathological performance had to be found in multiple domains at neuropsychological tests) and to have a gradual worsening of everyday life autonomy (Table 2: NINCDS-ADRA and DSM-IV-TR criteria for Alzheimer's Disease).

Table 2: NINCDS-ADRDA criteria and DSM-IV-TR criteria for Alzheimer's Disease

NINCDS-ADRDA criteria, 1984	***Limits***
Documented dementia: MMSE&Tests	
Deficit in two or more cognitive domains	Sensibility: 65-96%
Progressive worsening	
DSM-IV-TR criteria	Specificity: 23-88%
Memory impairment	
One or more associated cognitive deficits	
Daily impairment	

Coming from this perspective and recently the International Group driven by Dubois[8] proposed the New Criteria for Alzheimer Disease diagnosis (Table 3: The new proposed diagnostic criteria for Alzheimer's Disease).

Table 3: The new proposed diagnostic criteria for Alzheimer's Disease (Dubois et al.)

A plus one or more supportive features B,C,D, or E:

Core diagnostic criteria

A. Presence of an early and significant episodic memory impairment hat includes the following features:
   1. Gradual and progressive change in memory functions reported by patients or informants over more than 6 months
   2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled
   3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances

Supportive features:

B. Presence of medial temporal lobe atrophy: Volume loss of hippocampi, enthorinal cortex, amygdala evidenced of MRI with qualitative ratings using visual scoring (referenced to well characterized population with age norms)
C. Abnormal cerebrospinal fluid biomarker: Low amyloid β concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three. Other well validated markers to be discovered in the future.
D. Specific pattern on functional neuroimaging with PET; Other well validated ligands, including those that foreseeably will emerge such as Pittsburg compound B or FDDNP.
E. Proven AD autosomal dominant mutation within the immediate family

Exclusion criteria

History

- Sudden onset
- Early occurrence of the following symptoms: gait disturbances, seizures, behavioural changes.

Clinical features

- Focal neurological features including hemiparesis, sensory loss, visual field deficits
- Early extrapyramidal signs

Other medical disorders severe enough to account for memory and related symptoms:

- Non-AD dementia
- Mayor depression
- Cerebrovascular disease
- Toxic and metabolic abnormalities, all of which may require specific investigations
- MRI FLAIR or T2 signal abnormalities in the medial temporal lobe that are consistent with infectious or vascular insults

Criteria for definite AD

AD is considered definite if the following are present:

- Both clinical and histopathological (brain biopsy or autopsy) evidence of the disease, as required by the NIA-Reagan criteria for the post-mortem diagnosis of AD; criteria must both be present
- Both clinical and genetic evidence (mutation on chromosome 1, 14, or 21) of AD; criteria must both be present

The main difference between these criteria and those previously employed consists in the number of impaired domains required for the diagnosis. Following Dubois' Alzheimer disease may be already diagnosed if there is an isolated memory impairment of hyppocampal type. It means, in practice, that what was previously called amnesic MCI may be now called early dementia. Dubois observes that NINCDS-ADRDA and DSM-IV-TR criteria are today inadequate as they do not consider some biomarker as those obtained through structural MRI, PET, and cerebrospinal fluid (CSF). All of them are indicated as support features in Dubois criteria. Brain MRI may show a reduction of hyppocampal volume, PET hypometabolism or hypoperfusion in temporoparietal areas, and cerebrospinal fluid may disclose different biomarkers. All these features give further elements to the diagnosis in its earliest stages that is before the full-blown dementia develops. As a consequence the Prodromal AD, the symptomatic predementia phase included in MCI category, may be identified. Infact there is accruing evidence that, years before the onset of clinical symptoms, there is an AD process evolving along a predictable pattern of progression. The new criteria are reported in Table 3. The nodal point of them is the importance of the distinction between MCI subjects and Prodromal AD subjects. The distinction divides people having a major risk for developing AD from those being yet AD and who might benefit of disease-modifying therapies. Probably they would be in fact more effective in a stage where amyloid and tau have a lower burden and influence positively the subsequent cascade of events (inflammation, toxicity, and apoptosis).

From the neuropsychological perspective the new criteria introduce a new test to employ. This is the Free and Cued Selective Recall Reminding Test (FCRST)[9] which has the advantage to give an accurate evaluation of memory impairment. This test allows in author's opinion the important difference between the memory impairment due to a medial temporal lobe dysfunction, which is typical of AD from that of healthy controls or other dementias[10]. Other patients with non-AD disorders seem to perform not differently than control subjects. The hyppocampal impairment, than, identifies a prodromal AD. Buschke and co-workers, who first introduced this paradigm, indicated that the sensitivity and specificity to discriminate AD patients from healthy controls were of about 93% and 99% respectively. Grober and Buschke[11] gave a further confirmation of the memory difference between AD and other dementias impairments employing the same paradigm.

Discussions

The NINCDS-ADRDA criteria for AD indicated a two step diagnostic process consisting first in the identification of a dementia syndrome, and then in the individuation of the specific phenotype of AD. DSM-IV-TR criteria also required the presence of both disorders and that the condition had to interfere with the social and daily living activities of the individual. In this scenario the new criteria of Dubois et al suggest to consider the recently developed diagnostic biomarker coming from imaging and CSF analysis and introduce as a core element the neuropsychological results at the Free and Cued Selective Recall Reminding Test (FCRST). This test gives an accurate evaluation of the memory impairment and allows the accurate diagnosis of the "medial temporal lobe memory deficit" being then the most adequate to define the characteristics of the memory impairment. Its advantage is that it evaluates if the memory dysfunction is due to an encoding impairment (which is typical of AD) or not. The test requires the subjects to use semantic cues in the coding phase, so that if forgetting is found, it cannot be attributed to a simple attention impairment, but is essentially due to the inability of codifying. The principle aim of these new criteria is to obtain earlier the diagnosis which might offer potentially useful therapies in a phase where the disease is at his beginning. Even if both the new diagnostic criteria and the FCRST require more studies, this perspective seems to represent the next future of the clinical research about AD.

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