

Amnestic MCI or prodromal Alzheimer's disease?

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The concept of mild cognitive impairment (MCI) draws attention to cognitive changes not severe enough to warrant the diagnosis of dementia. As used today, it covers many pathological disorders and characterises a diverse population of patients who attend memory clinics. Our concern is the underlying heterogeneity. We suggest that it will soon be possible (if it is not already) to identify the underlying pathological disorders before the affected patients meet the criteria of dementia, thanks to specific neuropsychological assessments, neuroimaging, and biomarkers. In particular, patients with Alzheimer's disease (AD), the most important subgroup of patients with MCI, can already be identified before appearance of the fully developed clinical dementia syndrome. Accordingly, this paper proposes diagnostic criteria for "prodromal AD".

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Mild cognitive impairment (MCI) is a concept that was introduced by Flicker and colleagues¹ and the Mayo Clinic group^{2,3} to fill the gap between cognitive changes associated with normal ageing—successively called benign senescent forgetfulness,⁴ age-associated memory impairment,⁵ ageing-associated cognitive decline,⁶ and age-related cognitive decline⁷—and those associated with dementia (vascular, degenerative, etc). In this review we consider the advantages and disadvantages of MCI, and offer an alternative view to the usefulness of the concept.

Clinical relevance of the concept of MCI

The concept of MCI draws attention to cognitive disturbances that occur before the clinical diagnosis of dementia. The mild symptomatic phase of AD that precedes the fully developed clinical syndrome of dementia has no official clinical standing. For reasons not fully clarified, but possibly related to regulatory issues, the clinical onset of AD is only when patients meet the criteria for dementia—ie, when they have lost autonomy.⁸ Therefore, MCI characterises many patients at memory clinics and identifies those who are at risk of developing dementia in the future. Additionally, MCI indicates deviation from normal ageing. Hence, MCI may be used in clinical research to assess risk factors for subsequent development of dementia—such as hypertension and traumatic brain injury.

Clinical limitations of MCI

Neuropsychological tests and test scores for the diagnosis of MCI are not fully specified or generally agreed upon. As a consequence, studies of MCI done by different research

groups have divergent results (for example, the number of patients with MCI who develop frank dementia of the Alzheimer's type in follow-up studies).^{3,9,10}

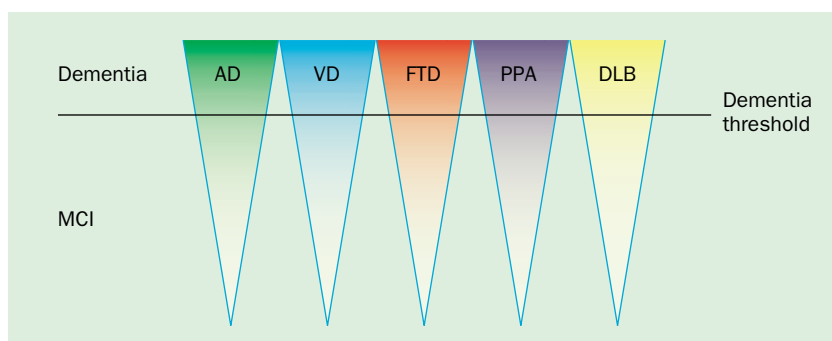
Our main concern, however, is with the concept of MCI itself and its underlying heterogeneity. As used today, MCI is a syndrome; to have full clinical usefulness, an aetiological understanding must follow. As it is, under the label of MCI, various pathological entities share clinical features but have different causes. This aetiological heterogeneity limits the value of MCI for at least three reasons. First, heterogeneity prevents the definition of specific diagnostic criteria, because the diagnostic criteria for MCI must remain sufficiently broad to include disorders of different causes. Second, heterogeneity prevents the development of specific therapeutic approaches because of the large range of possible underlying conditions. Finally, heterogeneity makes it difficult to predict clinical progression for any patient with MCI. In this review, we argue that MCI has full clinical usefulness only when it communicates prognostic information.

What is the disease behind the syndrome?

Although the concept of MCI may be useful in large-scale epidemiological studies, it seems less beneficial when a clinician is facing a patient. In such a situation, the main question that the clinician must address is this: should we label a syndrome or should we try to identify the disease causing the syndrome? To establish, for example, that a person with high body temperature has a fever is only a first step toward the more important definition of the underlying disease, such as tonsillitis or meningitis, which then and only then has implications for prognosis and treatment. Indeed, the approach we are proposing for MCI already prevails for dementia: neurologists no longer diagnose a general dementia, but rather try to identify the underlying disorder causing the dementia (ie, AD, vascular dementia, etc) on the basis of well defined criteria, because each disorder has a specific prognosis and treatment (figure).

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Diseases that cause MCI. In most cases, the disease can be identified before the stage of clinical dementia. VD=vascular dementia; FTD=frontotemporal dementia; PPA=primary progressive aphasia; DLB=dementia with Lewy bodies.

The same approach should be applied to MCI. To isolate and label a syndrome with multiple potential causes is clinically irrelevant. Why not instead try to isolate the specific causes of mild cognitive impairment? The argument that early identification of such diseases is impossible no longer seems convincing. When confronted with apathy or behavioural disinhibition coupled with a progressive disturbance in executive functions and a perfusion defect in frontal areas on single-photon emission CT, neurologists can already identify frontotemporal degeneration well before the stage of clinical dementia.¹¹ We can recognise primary progressive aphasia¹² on the basis of anomia with speech apraxia and phonetic disintegration with limited atrophy of the left perisylvian region well before dementia, which generally occurs later. Diffuse Lewy-body disease is associated with precocious hallucinations, cognitive fluctuations, and extrapyramidal signs early in the course of the illness, before the development of clinical dementia in many patients.¹³ Furthermore, the cerebrovascular origin of cognitive disorders may be recognised in their early stages by the appropriate combination of clinical history, neurological examination, and neuroimaging. Why should each of these easily recognisable disorders be included, in their early stages, under the single label of MCI, as is so common in practice today?

Indeed, the argument we are proposing here—that MCI should be subdivided, according to its specific underlying disorders—has already been proposed elsewhere. The

concept of “prodromal Alzheimer’s disease (AD)” was introduced in 2000 to refine the concept of MCI.¹⁴ In 2001, an international group of experts suggested the subdivision of MCI into three subcategories.¹⁵ In a recently published book on MCI, the subdivision of MCI by aetiology was recommended.¹⁶

MCI of Alzheimer-type or prodromal AD

By way of example, we comment on one of the subtypes of MCI, the one which leads to AD, because it is now possible to identify AD before the

occurrence of the fully developed clinical dementia syndrome,¹⁴ thanks to neuropsychology and newly developed memory tests, neuroimaging, and biomarkers.^{17,18}

Long before the onset of clinical dementia, AD is already at work on the brain, following a rather predictable route. Neuropathological changes are already present in mesial temporal regions (hippocampal formations, parahippocampal gyrus, and entorhinal cortex), areas critical for long-term episodic memory. The presence of AD in its earliest, predementia stages, may be detectable by use of specific memory tests aimed at distinguishing the characteristic pattern of memory disorders associated with the disease. Deficits of free recall are common in many disorders. Different mechanisms cause these deficits: impaired registration, as in disorders of attention due to depression, confusion or drugs; impaired consolidation and storage, as in diseases associated with lesions of the hippocampus and related structures, such as AD; and impaired retrieval of stored information, as in executive dysfunction. Therefore, before deciding that a patient has a true amnesic syndrome (ie, putative AD), one needs to establish that information has been registered and cannot be retrieved, even with the use of facilitation techniques (cueing or recognition).

Thus, impaired free recall, when associated with a limited effect of cueing on recall (ie, low total recall), many intrusions and false positives on recognition tasks is highly suggestive of AD (if effective encoding of information has been previously controlled).¹⁹ This neuropsychological profile of memory deficit, which can be called “amnesic syndrome of the hippocampal type”, contrasts with that seen in depression, where encoding deficits are predominant, and with that seen in frontotemporal dementia, vascular dementia, or even normal ageing, where impaired free recall is greatly improved or normalised with cueing or recognition.^{20–22} Interestingly, the same memory profile “of the hippocampal type” has also been shown in early stages of disease in patients with AD and a mini-mental state examination score greater than 25 and in a prospective study of elderly people who became demented within 5 years,^{19,23} probably because episodic memory is a constant, precocious, and reliable neuropsychological marker of the disease in relation to early involvement of mesial temporal structures.²⁴

Diagnostic criteria for “MCI of Alzheimer-type” or “prodromal AD”

- Memory complaints by the patient or by the family
- Progressive onset
- Normal or mildly impaired complex activities of daily living
- Amnesic syndrome of the “hippocampal type” defined by:
 - very poor free recall despite adequate (and controlled) encoding;
 - decreased total recall because of insufficient effect of cueing or impaired recognition;
 - numerous intrusions
- Persistence of memory changes at a subsequent assessment
- Absence of the fully developed syndrome of dementia
- Exclusion of other disorders that may cause MCI, with adequate tests, including neuroimaging and biomarkers

Indeed, most studies that have addressed the issue of neuropsychological prediction of AD in MCI patients have emphasised the diagnostic value of recall deficits.^{25,26} It should therefore be possible to identify patients with prodromal AD, even today, if one uses specific neuropsychological tools to demonstrate an “amnesic syndrome of the hippocampal type”.

Conclusion

We have no doubt that, in the future, the diagnosis of the predementia stage of AD will benefit from the combination of neuropsychology and structural and functional neuroimaging, focused on the hippocampal formations and related structures,^{27–30} together with measurement of selected biomarkers, such as CSF concentration of the 42 amino-acid residue amyloid- β peptide, tau, and phosphorylated tau protein.^{31,32} Such multimodal studies—involving clinical evaluation, neuropsychological measurements, structural and functional imaging, and biomarkers—are already starting to provide useful clinical guides toward the refinement of the concept of MCI, especially in regard to AD.^{17,18}

We assert that MCI represents different subtypes of clinical disorders, several of these are dementing disorders, many of which can be identified at an early stage, and that, therefore, the concept of MCI may actually interfere with

clinical progress. If, despite these arguments, a compelling urge is felt to maintain the term MCI, we propose that it be qualified as “MCI of the Alzheimer type” or MCI of the X, Y, or Z type. With this qualification, MCI would represent a stage of severity for specific disorders that have not yet reached the dementia threshold. We propose clinical diagnostic criteria that have a high specificity for “MCI of the Alzheimer type” or “prodromal AD” (panel). This may help clinicians identify the most important subgroup of patients with MCI.

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Authors' contributions

Both authors contributed equally to the writing and preparation of the panel and figure.

Conflict of interest

We have no conflicts of interest.

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