Review Article

Are Guidelines Needed for the Diagnosis and Management of Incipient Alzheimer’s Disease and Mild Cognitive Impairment?

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Current research is aiming to push the boundaries of the point at which a diagnosis of Alzheimer Disease (AD) can be made. Clinical syndromes such as Mild Cognitive Impairment (MCI) and various clinical and biological markers of AD may help to identify people in the early stage of AD, before a full dementia syndrome is present. In the first part of this paper, we discuss whether MCI represents incipient AD, and examine some of the methods currently used in research to identify AD patients in the preclinical phase. In the second part, we discuss whether specific guidelines are needed for the diagnosis and management of MCI and incipient AD, and consider the potential impact of this on clinical practice and public health from the perspective of patients, caregivers, and healthcare providers.

1. Introduction: The Concept of MCI and Incipient AD

Currently, dementia of the Alzheimer type is diagnosed clinically according to diagnostic criteria [1]. These criteria include deficits in memory and other cognitive functions, and the symptoms have a gradual onset and progressive deterioration. The H. Braak and E. Braak [2, 3] staging describes an increasing burden of the neuropathological hallmarks of Alzheimer disease (AD), neurofibrillary tangles, and amyloid plaques, with increasing dementia severity, mainly starting in the brain regions associated with memory functioning such as the hippocampus and entorhinal cortex. Evidence now clearly shows that the disease starts before the symptoms of a full dementia syndrome are present. AD related pathology, such as beta amyloid deposition, may already begin occurring even ten to twenty years before a clinical diagnosis of dementia can be made [4]. Furthermore, deficits in cognitive functioning may start to appear three [5], six, or even up to ten years [6] before a clinical diagnosis of AD.

Several syndromes that identify patients at high risk of developing dementia—or “preclinical, early AD” syndromes—have been proposed, including Mild Cognitive Impairment (MCI) and others; for a review see Mariani and colleagues [7]. A decade ago, Petersen et al. [8] proposed diagnostic criteria to describe patients who were neither normal nor demented, but had a mild form of cognitive impairment characterized by memory deficits. The MCI paradigm is based on the assumption that patients with AD develop symptoms, particularly memory impairment, gradually and, therefore, there may be an intermittent stage between normal aging and dementia characterized primarily by episodic memory deficits. These MCI patients have a high risk of progressing to a full dementia syndrome within a few years [8], although, as discussed later, the evolution is heterogeneous.

In the last decade, much focus has been paid to identifying clinically diagnosable syndromes of incipient AD. Criteria for MCI, and other syndromes, have been revised several times [9–11], with interest in identifying specific characteristics of MCI patients who are at the highest risk of progressing to AD. People with MCI progress to dementia at a rate of about 6% to 15% per year [7, 8, 12, 13], although the condition is heterogeneous and some MCI patients do not develop dementia. As discussed in
a recent systematic review of MCI [7], a number of factors have been suggested to further predict conversion to AD in MCI patients, and it is becoming increasingly evident that biomarkers, such as cerebrospinal fluid (CSF) markers including beta-amyloid1–42 and total tau protein, may have a good accuracy for identifying impending AD in MCI patients [14] compared to healthy controls. Although the differential diagnostic capacity of using CSF markers between the preliminary states of various dementia disorders has not yet been thoroughly studied, the discoveries regarding AD are pushing the boundaries as to when AD can be identified and diagnosed in individuals.

2. Guidelines for AD and Dementia

Guidelines for the diagnosis and management of AD and other dementias are regularly published, updated, and revised in the USA and elsewhere in the world [15–19]. The latest European recommendations for the diagnosis and management of AD were published by the European Federation of Neurological Societies (EFNS) [17]. These evidence-based guidelines were created through a consensus process to provide guidance for physicians concerning diagnostic evaluation and management of dementia, including pharmacological and nonpharmacological treatment, management of behavioral and psychological symptoms of dementia (BPSD), counseling and support for caregivers, and so forth. The EFNS guidelines state that the recommendations are relevant only to dementia, and do not include MCI. Recently, Dubois et al. [20] published new diagnostic criteria for the early detection of AD. These were proposed as research criteria, rather than for clinical diagnosis and patient management, and incorporate clinical evidence of episodic memory loss (isolated or with other cognitive deficits) with biomarkers (CSF, neuroimaging, genetic) to identify patients in an early, predementia stage of AD. The criteria are novel because rather than focusing on the dementia syndrome they focus on clinical, biological, structural, and biochemical presence of AD in a predementia phase. These, and other, criteria for syndromes of early preclinical phases of AD raise controversial questions in the scientific and medical world. Should physicians diagnose MCI or incipient AD? Should MCI patients be treated? How should physicians and healthcare workers manage the healthcare of patients with MCI? Should dementia guidelines be revised to incorporate MCI? In this paper, we will discuss the disadvantages and advantages of omitting MCI and incipient AD from dementia guidelines, and discuss the potential impact on clinical practice and public health from the perspective of patients, caregivers, and healthcare providers.

3. Does MCI Represent Incipient AD?

The first relevant question to ask in this discussion is whether syndromes such as MCI truly represent an early preclinical phase of AD. Research both from clinical- and population-based samples suggest that MCI patients have a high risk of progressing to a full dementia syndrome; a meta-analyses
particularly CSF, for identifying patients in the early, prede- 
mentia, phase of AD. A multicenter study of the CSF markers 
MCI patients has shown innovative results concerning the 
use of beta-amyloid_{1-42}, total tau protein, and tau 
phosphorylated at position threonine 181, which was found 
to have a good accuracy for identifying impending AD in 
MCI patients [14]. This was one of the first studies to pool 
the data from a large range of single center studies. It showed 
that the positive predictive value of these CSF markers for 
identifying incipient AD in MCI patients was 62%, with a 
sensitivity of 83%. However, despite these promising results, 
the findings should be viewed with caution. An editorial 
by Petersen and Tojanowski [27] highlighted the clinical 
variability of the MCI patients as well as the variability in 
CSF measurements in the different centers in Mattsson and 
colleagues’ work. Further, they acknowledged that although 
the sensitivity and specificity of the CSF markers were 
adequate for screening, they did not have high enough 
accuracy to be used as diagnostic tests, although they may be 
useful for use in clinical trials [27]. Interestingly, the positive 
predictive value showed that 62% of MCI patients developed 
AD when a combination of the three CSF markers was used 
[14]. However, this positive predictive value needs to be 
compared with other markers and clinical syndromes. Before 
taking into consideration other markers, the cumulative 
conversion rate from MCI to AD across studies is 31.4% [13]. 
Furthermore, other studies have shown that this positive 
predictive value can be increased by combining other, less 
invasive, markers. For example, a prediction model using 
five factors (functional and olfactory markers, cognitive 
testing, and MRI measures of hippocampal volume and 
temporal cortex volume) had a positive predictive value of 
more than 80% for identifying incipient AD in MCI 
patients [25].

There are important limitations to consider when exam- 
ining clinical and laboratory markers in MCI patients. First, 
laboratory samples are mainly taken from clinical patient 
populations, which may not be representative of the general 
population. Consequently, the sensitivity of a laboratory 
measure evaluated in a clinical sample does not reflect the 
level of sensitivity of the test if used at the population level. 
Second, a study in the general population showed that half 
of AD patients have no subjective complaints about their 
memory performance up to one to three years before AD 
diagnosis, and one fifth show absolutely no cognitive deficits 
[24]. This highlights the heterogeneity of patients in the 
preclinical phase of AD. It is likely that patients who seek 
medical advice for cognitive problems are at a more advanced 
stage of cognitive impairment, closer to the diagnosis of AD, 
which will affect the accuracy of measurements of sensitivity 
and predictive values in markers such as CSF values. Finally, 
the multicenter study by Mattsson et al. [14] found that 
the diagnostic validity of CSF markers had less accuracy 
in the multicenter analysis than the accuracy reported in 
single-center settings. This highlights the importance of 
replicating positive results from single centers, which are 
often conducted on small study populations, and the need 
for more multicenter trials and meta-analyses to determine 
the accuracy of biomarkers for identifying incipient AD.

4. Do We Need Guidelines for the Diagnosis and 
Management of MCI?

MCI is a frequently occurring syndrome in the elderly. 
A European longitudinal study [28] reported an incidence 
rate per 1000 person years of between 11.4 for amnestic- 
MCI and 33.8 for other types of cognitive impairment, 
and prevalence data suggests that cognitive impairment 
syndromes in younger nondemented elderly actually exceed 
dementia prevalence [29]. Given that MCI is a frequent 
syndrome in older people, and that individuals with MCI 
have a high risk of progressing to AD [7, 12], this raises 
the question of what should be done with such patients. 
As mentioned earlier, guidelines for the management of 
dementia often do not include recommendations for patients 
with MCI. However, many of the issues regarding both 
diagnosis and management of dementia may also be relevant 
to the large number of elderly persons suffering from MCI, 
who may or may not be in the early stage of AD. Clinically, 
MCI could be viewed, not as a disease or disorder per se, but 
as a risk factor for AD. Risk factors such as this are commonly 
addressed in other areas of medicine. Many conditions have 
been shown to predispose an individual to a higher risk of 
developing another medical condition, such as hypertension 
for stroke and myocardial infarction, dyslipidemia for stroke 
and other vascular disease, diabetes for osteoporosis and so 
forth. In good clinical practice, clinicians explain the risks 
associated with such conditions with their patients, and plan 
appropriate care and management. In this way, MCI should 
be viewed as a clinical syndrome that has a high risk of 
progressing to AD. Thus, if clinicians were to consider MCI, 
not as incipient AD, but as a risk factor for developing AD, 
certain issues concerning management and treatment that 
have been raised for dementia, may be relevant also to MCI.

5. Treatment of MCI

First, although dementia disorders such as AD are currently 
not curable, there are a number of symptomatic phar- 
maceutical treatments that are recommended in guidelines 
for dementia [17, 30]. Conversely, there are currently no 
approved drugs for the treatment of MCI or early preclinical 
AD. Clinical trials on MCI patients have had limited success; 
none of the trials, including donepezil, rivastigmine, rofe- 
coxib, galantamine, and vitamin E, have demonstrated con- 
vincing effects for delaying progression from MCI to AD [31, 
32]. However, other trials are ongoing, and data on subsets of 
MCI patients have identified potentially promising avenues 
for future research. For example, although randomized- 
control trials on cholinesterase inhibitors such as donepezil 
have shown little or no reduction in the risk of conversion 
from MCI to AD [33–35], the results of one trial suggested 
that MCI patients with depressive symptoms treated with 
donepezil had a lower risk of conversion to AD [36]. Without 
the availability of effective treatment strategies, and in the 
absence of approved drugs for the treatment of MCI or 
incipient AD, one may question the benefits of diagnosing 
such syndromes. Thus, dementia guidelines, such as those 
proposed by EFNS, might be right to avoid discussing
disease-specific treatment strategies for MCI, since MCI per se is not a disease, and currently there are no approved drugs for MCI. However, pharmacological treatments are not the only recommendations suggested in current guidelines for dementia, and the other recommendations might be of relevance to MCI patients as well as those with dementia, including suggestions for diagnosis, management of BPSDs, and support for families and caregivers.

6. Nonpharmacological Treatment and Interventions

Although there are no currently approved pharmacological treatments for MCI, nonpharmacological interventions have also been the focus of recent research. Management of risk factors and somatic disorders, lifestyle changes, and cognitive intervention programmes may be beneficial to certain patients, and may be advantageous as they might have less side effects and risks than pharmacological drugs. Cognitive rehabilitation studies in MCI [37–39] have showed improvement in ADL functioning, mood, and memory following training, although there is no evidence for delayed progression from MCI to AD. Further, if MCI patients are told of their high risk of developing AD, there are possibilities for modifying risk factors associated with AD, such as diet, somatic, and lifestyle factors [40]. Further, as it has been shown that MCI has heterogeneous risk factors [21] and that MCI may have diverse somatic, psychiatric, and neurological etiologies [11], the modification of somatic and lifestyle factors may be beneficial to the overall health of MCI patients, even those who are not in a preclinical phase of AD.

7. Disclosure of MCI Diagnosis

There is ongoing debate as to whether a formal diagnosis of MCI should be made and disclosed to patients in the clinical setting. The fact is that increasing numbers of elderly people are approaching physicians complaining of memory problems, and there is a high incidence of both MCI and other syndromes of cognitive impairment in the elderly [28]. There may be some benefits to disclosing a diagnosis of MCI to a patient and discussing the associated risk of developing AD. First, it allows patients to plan for their future before their cognitive impairment becomes severe, including financial planning, and the planning of care and living arrangements for the future. Second, in some cases it may be helpful for individuals to have a formal diagnosis that somewhat explains their symptoms. From the physician’s perspective, giving an early diagnosis may be beneficial as the patient will have better cognitive capacities to understand the diagnosis and discuss future treatment and care options; indeed, studies have shown that physicians are often reluctant to disclose a diagnosis of dementia in more severe stages of the disease due to lack of comprehension by the patient [41]. Furthermore, physicians may be concerned that disclosing a diagnosis of dementia may trigger catastrophic events in the patient such as depression or suicide. However, a study by Carpenter et al. [42] examined changes in depression and anxiety both in patients and their relatives before and after the diagnosis of dementia. They found that there were no changes in depression status in either patients or their next-of-kin after a disclosure of a dementia diagnosis, but levels of anxiety decreased substantially after receiving the diagnosis. This supports the idea that receiving a formal diagnosis that explains the symptoms and memory loss can actually be beneficial to a patient.

Interesting lessons can also be learned from studies investigating the effect of disclosing genetic risk of AD to individuals, such as ApoE ε4, a cardiovascular risk factor which is also associated with an increased risk of developing AD [43]. Both MCI and the ApoE ε4 genotype are associated with a higher risk of AD but do not represent a definite risk; that is, not all patients with MCI or ApoE ε4 will develop AD. The REVAL study group [44] investigated the effect of disclosing AD risk (both ApoE genotype and a numeric risk estimate) to family members of AD patients using a randomized-control trial design. They found no differences in short-term psychological symptoms such as anxiety, depression, or distress between people who were told that they had a genetic risk of developing AD (ApoE ε4 carriers) than those who were not told their genotype. However, when questioned after one year, individuals were more likely to recall their genotype than their numerical lifetime risk estimate of AD [45]. The authors suggested that clinicians, therefore, needed to find an appropriate manner to communicate AD risk and probabilities. Most interestingly, however, was that disclosure of genetic AD risk was associated with a change in behaviors; a large proportion of individuals made changes to their long-term healthcare insurance after learning they were ApoE ε4 carriers [46] and more than half made changes to their health behavior, such as vitamin intake and exercise [47]. Although specific studies on the disclosure of MCI diagnosis are needed, the results of there studies on disclosing genetic AD risk suggest potentially beneficial effects of informing an at-risk individual that they have a high risk of developing AD.

8. Recommendations for the Management of BPSD

Although there are no approved treatments for MCI, patients with this syndrome might have other related symptoms that can be treated. The EFNS guidelines for dementia stipulate that physicians should be aware of the importance of treating behavioral and psychiatric symptoms for the potential benefit of the patients and carers. This may also be relevant to MCI patients. Studies both from clinical- and population-based samples consistently report a high burden of BPSD in MCI patients, particularly depression, anxiety, and irritability (for a review see Monastero and colleagues [48]). Indeed the pattern of BPSD in MCI are similar to those observed in patients with dementia, and symptoms have been observed in more than one third of patients, with many studies reporting a higher prevalence [48], even up to 85%. Nevertheless, the role of BPSD in MCI remains unclear and,
thus, treatment of specific symptoms or psychiatric disorders in this group of patients is controversial. A population-based study showed that anxiety in MCI patients was associated with an ongoing AD related neurodegeneration [49], and clinical-based studies suggest a similar role for apathy [50–52]. In contrast, depression in MCI is generally not associated with progression to AD [49, 53]. There are currently no clinical trials investigating the effect of treating BPSD and psychiatric disorders in MCI patients, and thus it is not known whether pharmacological treatments are effective either in slowing the progression from MCI to AD or in reducing the severity of neuropsychiatric symptoms in these patients. Indeed, the situation is similar for patients already in the stage of clinical dementia; current guidelines for dementia [17] highlight these controversies.

9. Patient Guidelines and Advice

Guidelines on MCI for healthcare workers as well as patients have already been published in America. In 2010, the American Academy of Physician Assistants [54] published guidelines for physician assistants, stating that they should be able to recognize and treat MCI and dementia. Specific suggestions were made for screening tools, cognitive and somatic evaluation of at-risk patients, as well as tentative recommendations for treatment strategies. A Patient Page, published in the Journal of the American Medical Association [55], aims to provide patients and families with general information about MCI, including possible conditions associated with MCI, a description of diagnostic techniques, and some recommendations for prevention, mainly the management of high blood pressure and other chronic conditions, as well as social activities and dietary changes. A patient and family fact sheet on MCI, published in The Neurologist [56] describes potential causes of cognitive impairment in the elderly, rather than focusing specifically on AD, and describes diagnostic procedures and examination that might be conducted on patient with suspected cognitive problems. It also makes suggestions for life style changes, including social and dietary changes.

10. Conclusions

In conclusion, MCI is not a disease or disorder, but a risk factor for developing dementia and AD. Although studies examining biological markers and other factors in MCI patients have identified markers that further increase the risk of developing AD in these patients, we are still not at a stage where we can accurately identify with 100% accuracy which patients are in the early phase of AD. Consequently, current guidelines for the diagnosis and management of AD and dementia often do not include specific suggestions for MCI. Despite this, many of the recommendations made for patients with dementia, may also be relevant to people with MCI. Therefore, peer-reviewed, consensus guidelines for the diagnosis and management of incipient AD or MCI might be beneficial in the future. However, it is imperative to focus future research on identifying more accurate diagnostic markers to define incipient AD, and to study the effect of informing patients that they have a high risk of developing AD, in terms of psychological reactions and potential benefits for planning appropriate management and prevention strategies in MCI patients.

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