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Mild cognitive impairment: Believe it or not?

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Abstract

Mild cognitive impairment (MCI) was previously defined as a transitional state that can precede dementia, but the condition and the rates of conversion remain controversial. MCI is now the focus of natural history studies, along with Alzheimer's disease (AD) prevention. The objective of our review will be to consider the question of whether MCI is a well enough established entity that it can be a diagnosis in medical practice and a valid target of Alzheimer's prevention therapy. MCI was originally defined by Petersen et al. (1999) as progressive memory loss, prodrome of Alzheimer's disease. More recently MCI has been expanded to other cognitive domains with other potential causes like normal aging, fronto-temporal dementia, and vascular dementia. Despite many consensus conferences, experts cannot agree on critical aspects of the MCI, particularly with respect to its clinical utility. Based on neuropsychological studies, a hippocampal memory profile has been proposed for MCI as prodromal AD. Further research is needed to advance these criteria. We have no doubt, however, that in the future, the diagnosis of AD as disease (not only a dementia syndrome) will be made in the early pre-dementia stage and will be drawn from a combination of neuropsychological, neuro-imaging and CSF biomarkers.

Introduction

Alzheimer's disease (AD) is a major public health problem because of its growing prevalence and economic burden (Allegri et al., 2007; Brookmeyer, Gray, & Kawas, 1998; Helmer, Pasquier, & Dartigues, 2006). It is a chronic condition globally widespread that seriously impacts patients, their families and society (Allegri et al., 2006; Rabins, Lyketsos, & Steele, 1999). An understanding of the prodromal states or early clinical presentations of AD is a significant priority since it would aid early detection, facilitate early treatment, and lead to prevention. The diagnosis of AD is currently made in patients who meet specific criteria for dementia (DSM-IV [APA, 1994] and NINCDS ADRDA criteria for AD [McKhann et al., 1984]); however, these criteria do not allow early diagnosis (Dubois et al., 2007).

There is a clinical cognitive continuum from normal aging through to AD. Cognitive decline without dementia has been commonly considered to be a normal consequence of brain aging, but it can also indicate the onset of dementia. The boundary between normal aging and very early AD is becoming a central focus of research. The pre-dementia

diagnosis is intimately connected with the development of therapies to prevent AD.

Many attempts have been made to define the cognitive decline associated with aging. The idea of aging effects versus disease is not new; in 1962, Kral et al. described the 'benign senescent forgetfulness' (BSF) in which fairly unimportant details of an experience (e.g. a name, a place or a date) are not recalled but do not interfere with activities of daily life and does not progress to dementia. Kral (1978) also recognized that 'differentiation of the benign and malignant types of senescent forgetfulness does not necessarily mean that there are two neuropathological processes'. These diagnostic criteria were not precise, and were not validated in controlled longitudinal studies. These cognitive changes in aging have been assigned various terms, such as age associated memory impairment (Crook, Bartus, Ferris, Whitehouse, Cohen, & Gershon, 1986), late-life forgetfulness (Blackford & La Rue, 1989) and aging associated cognitive decline (Levy, 1994). These terms have been used largely to explain the extremes of normal aging, to characterize individuals who are not normal but not demented. Such terms were criticized for their imprecision.

Mild cognitive impairment was initially described in the late 1990s by Flicker and colleagues (Flicker, Ferris, & Reisberg, 1991, 1993) and was related to persons who qualified for stage 3 on the Global Deterioration Scale (GDS) (Reisberg, Ferris, de Leon, & Crook, 1982) or 0.5 on the Clinical Dementia Rating (CDR) (Hughes, Berg, Danziger, Coben, & Martin, 1982). Reisberg et al. (2008) identified mild cognitive impairment as a clinical stage on the GDS. Petersen says it is important to note that GDS and CDR are severity rating scales and not diagnostic instruments. Both stages may correspond to MCI or may describe individuals with very mild dementia (Petersen, 2000). He proposed a clinical continuum from normal aging through mild cognitive impairment to Alzheimer's disease. MCI wasn't normal aging: this construct was supposed to be a clinical description of individuals who were destined to develop AD (Petersen et al., 1999).

The identification of individuals at risk of developing dementia, and Alzheimer's disease in particular, is of major economic importance, particularly if preventive strategies or therapeutic action are to be developed. This challenge explains the popularity of the concept of MCI and its wide application in the epidemiological, clinical, paraclinical and therapeutic domains (Portet et al., 2006).

Mild cognitive impairment was originally defined as the transitional state that can precede dementia but the condition and the rates of conversion remain controversial.

The objective of our review will be to consider the question of whether MCI is a well enough established syndrome to be a diagnosis in medical practice and a valid target of therapy. Data for this review was gathered from searches of PubMed articles published in English. Search terms included 'mild cognitive impairment', 'memory impairment' and 'cognitive impairment not demented'.

Several excellent global reviews on MCI have recently been published (Artero, Petersen, Touchon, & Ritchie, 2006; De Carli, 2003; Dubois & Albert, 2004; Ganguli, 2006; Gauthier et al., 2006; Jelic, Kipivlto, & Winblad, 2006; Laurent & Anterion, 2002; Petersen, 2007; Portet et al., 2006; Whitehouse, 2007; Winblad et al., 2004; Rockwood, Chertkow, & Feldman, 2007) that the interested reader should refer to for a more detailed overview of the subject.

Diagnostic criteria

Mild cognitive impairment applies to individuals who have some cognitive impairment but are not sufficiently debilitated as to warrant the diagnosis of dementia or AD. An individual with MCI typically

develops memory deficit and soon exhibits other cognitive abnormalities without functional impairment. Petersen et al. (1999) provided a landmark in the 'rediscovery' of the entity, as well as the popularization of the terminology.

The original diagnostic criteria for mild cognitive impairment (Petersen et al., 1999) were:

1. Memory complaint, preferably corroborated by an informant;
2. Memory impairment relative to age-matched and education-matched healthy people;
3. Preserved general cognitive function;
4. Intact activities of daily living;
5. Not clinically demented.

The tests to detect memory impairment were not specified but memory impairment was defined as performance more than 1.5 standard deviations (SD) below normative values.

Petersen et al. (1999) used the term MCI to define individuals with symptomatic and progressive memory impairment that share many features with early AD (Morris et al., 2001). More recently, MCI measures have been expanded since clinicians observed non-memory related symptoms in some persons. The Canadian Study of Health and Aging (a longitudinal, population-based study of aging) defined 'cognitive impairment not demented (CIND)' to characterize individuals who are cognitively abnormal but not demented (Graham et al., 1997). In many aspects CIND resembles MCI, but the CIND label includes a broader subset of population with cognitive impairment.

De Kosky and Chertkow (2001) proposed three subtypes of MCI: amnesic MCI (which is said to progress preferentially to Alzheimer's disease), multiple domain MCI (which may represent normal aging or may progress to vascular cognitive impairment or neurodegenerative disorder), and single domain non-amnesic MCI (which may progress to fronto-temporal dementia, Lewy bodies dementia or Alzheimer's disease). It is clear that the chosen definition of cognitive impairment will have a major effect on estimates of prevalence. This impact could also extend to prognosis although these definitions describe syndromes and make no claim as to cause (De Carli, 2003).

Petersen (2004) described original criteria for MCI that were specific to isolated deficits in memory; clinical and research developments have extended these criteria to include a broad range of cognitive deficits and clinical subtypes with many potential causes. This concept has been challenged both by those whose studies suggest that MCI is, in fact, early or incipient AD (Morris, 2006) and by those who find that MCI is an unstable

condition with poor predictive validity for AD (Ritchie, Artero, & Touchon, 2001; Whitehouse, 2007). Supporting studies are underway to determine whether amnesic and non-amnesic subtypes of MCI have different prognoses for progression to dementia and which type of dementia they predict (Petersen & Morris, 2005).

The following symptomatic criteria were formulated and put forth by the International Working Group on MCI (Winblad et al., 2004):

1. The individual is neither normal nor demented;
2. There is evidence of cognitive deterioration, shown by either objectively measured decline over time or subjective report of decline by self or informant in conjunction with objective cognitive deficits;
3. Activities of daily life are preserved and complex instrumental functions are either intact or minimally impaired.

These criteria expand the construct of MCI to cognitive domains outside of memory and present MCI as a prodrome to multiple types of dementia (Gauthier et al., 2006).

Artero et al., 2006 validated the newly revised criteria for MCI, but incorporate the possibility of change in activity level and alteration of non-amnesic cognitive functions. A significantly more reliable detection of transition to dementia was obtained with MCI-R than with previous MCI criteria.

Based on the memory profile (information has been registered but cannot be retrieved, even with the use of facilitation techniques (cueing)), Dubois and Albert (2004), defined one subtype of MCI which leads to AD before the occurrence of the fully developed clinical dementia syndrome.

The presence of AD in its earliest, pre-dementia stages may be detectable by use of specific memory tests like the Free and Cued Selective Recall Reminding Test (Buschke, 1984), which distinguishes the different mechanisms of registration, storage, and retrieval of information. When impaired free recall is associated with even a small amount of cueing on recall, many intrusions and false positives on recognition tasks are highly suggestive of AD – this condition is commonly referred to as ‘amnesic syndrome of hippocampal type’ (Dubois & Albert, 2004; Allegri, Drake, Harris, Serrano, & Taragano, 2005; Harris, Drake, Allegri, 2001; Sarazin et al., 2007).

Based on neuropsychological profiling Dubois and Albert (2004) proposed the following new diagnostic criteria for MCI of Alzheimer-type or prodromal AD: memory complaints by the patients 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 intrusion; persistence of memory changes at a subsequent assessment; absence of the fully developed syndrome of dementia; and lastly, exclusion of other disorders that may cause MCI.

Impaired memory tests are defined by scores 1.5 standard deviation (SD) below normative values. It is important to emphasize that the 1.5 SD limits of MCI means that impairment can only be detected when recall is very low, and impairment is late and severe. Therefore, memory impairment defined by low recall according to recall norms cannot detect pre-symptomatic early cognitive (memory) impairment, when declining performance is still in the normal range, and, by definition, MCI cannot detect early impairment, but can only detect severe late impairment.

Sarazin et al. (2007) found that the Free and Cued Selective Recall Reminding Test for verbal episodic memory (Buschke, 1984; Grober & Buschke, 1987; Grober, Buschke, Crystal, Bang, & Dresner, 1988; Buschke, Sliwiski, Kuslansky, & Lipton, 1997) appears to be the best neuropsychological test for detecting AD at its prodromal stage.

Outcome

In clinically based studies the typical rate at which MCI patients progress to AD is 10% to 15% per year, which contrasts with incidence rates of the development of dementia in normal elderly subjects - 1–2% per year (Petersen et al., 1999). In population-based studies the prognosis of MCI deficits seems much less ominous. Ritchie et al. (2001) found that only 22% of MCI subjects developed degenerative dementia over an 8-year follow-up period.

The predictors and rates of progression are widely discrepant across studies and populations (Ganguli, Dodge, Shen, & De Kosky, 2004; Larrieu et al., 2002; Portet et al., 2006; Ritchie et al., 2001). The discrepancies are partly related to the nature of the population (clinical/referral versus community-based) and length of follow-up. They also seem to be due, in large part, to the definitions and inclusion criteria that were used in different studies (Ganguli et al., 2004).

Several predictive features of conversion are beginning to emerge, like ApoE4 (Petersen et al., 1995), atrophy of the hippocampal formation (Jack et al., 1999), Pittsburgh compound B (PiB) (Klunk et al., 2004), and cerebrospinal fluid biomarkers including tau, phosphotau epitopes, and the 42 aminoacid form of B amyloid

(Hansson, Zetterberg, Buchhave, Minthon, & Warkentin, 2006).

Most of the amnesic MCI patients who died appeared to have been transitional between the neuro-pathological changes found in aging and those characteristic of very early AD (Petersen et al., 2006).

Treatment

The increased awareness of MCI has triggered the development of therapies to prevent AD, but the first wave of clinical trials aimed at symptomatic drug treatment for amnesic MCI over a period of 6 months to 3 years have largely been unsuccessful (Gauthier et al., 2006). The status of MCI as a therapeutic target for regulatory approval is unclear (Rockwood et al., 2007).

Several clinical trials with cholinesterase inhibitors have been undertaken on MCI, albeit with variable results (Petersen, 2007). The Memory Impairment Study with donepezil, vitamin E, and placebo showed that the donepezil group had a reduced risk of developing AD for the first 12 months but not at 36 months. A prolonged response persists at 24 months in the ApoE4 carrier subgroup (Petersen et al., 2005). Galantamine (Gold, Dodge, Shen, & De Kosky, 2003) and rivastigmine studies in MCI were negative (Feldman, Ferris, Winblad, Sfikas, Mancione, & He, 2007).

There is increasing evidence that suggests the role of environment and lifestyle as protective factors for the development of Alzheimer's disease from MCI. These protective factors include premorbid IQ, education level, leisure activities, and social activities in aging people (Serrano et al., 2007).

Encouraging results have been reported from studies that use cognitive training in MCI (Belleville, 2008). The success of cognitive training seems to be dependent upon the level of severity across the range of normal aging to dementia. These findings in individuals with mild cognitive impairment need to be confirmed in randomized controlled trials (Gauthier et al., 2006).

Believe it or not?

Gradual decline in cognitive abilities is characteristic in longitudinal studies of elderly people. Because of intrinsic (e.g. native intelligence) and extrinsic (e.g. education) factors, there is inter-individual variability in intellectual function that increases with age, so what may constitute impairment for one person may be normal for another. We must consider this variability in normal people when we assess potential MCI. The notion that incipient dementia is common among elderly people is

supported by neuropathological studies that reveal evidence of Alzheimer's disease years before clinical symptoms present themselves (Morris et al., 2001). Significant memory impairment without dementia, often denoted as MCI, in elderly people may be a transition phase between the normal aging process and AD (Petersen et al., 1999). Some papers argue that MCI cannot be a diagnostic entity because the increased predisposition for AD may be because 20% of those with MCI already have AD (Morris, 2006).

The construct of MCI has been challenged both by those whose studies suggest that MCI is, in fact, early or incipient AD (Morris et al., 2001; Petersen et al., 1999) and by those who find that MCI is an unstable condition with poor predictive validity for AD (Ritchie et al., 2001; Whitehouse, 2007). Some forms of MCI, like the amnesic type, are more likely to progress to AD, whereas other MCI subtypes progress to other type of non-Alzheimer dementia. Whitehouse (2007) argues that this alleged empirical and conceptual progress was simply an acknowledgement of the logical necessity that every progressive dementia must have an early phase that is characterized by milder symptoms than those that would impair activities of daily living. MCI was originally described as pre-AD syndrome (Petersen et al., 1999) but recently has been used to refer to a pre-dementia (e.g. AD, vascular dementia, fronto-temporal dementia) stage or to normal aging (Petersen, 2004, 2007). Despite many consensus conferences, experts cannot agree on critical aspects of the label MCI, particularly on its clinical utility (Whitehouse, 2007). After a major attempt at consensus published in the *Lancet* (Gauthier et al., 2006), an e-mail survey revealed that only 57% of the workshop participants believed that the term MCI should be used clinically (Whitehouse & Brodaty, 2006). There is a fragility of the broad MCI concept when one attempts to operationalize it strictly in test performance.

One of the proposed advantages of MCI has been its potential usefulness for clinical trials directed at delaying the time to onset AD, but with only small variations in the inclusion criteria for MCI, four trials (MIS, InDDEX, Gal-Int 11 and Rofecoxib) have had very wide-ranging annual rates of progression to AD dementia (Dubois et al., 2007).

In this light, MCI cannot be seen as pre-Alzheimer construct; rather, it is cognitive impairment with preserved activities in daily living. We need better identification of prodromal AD. Current definitions of MCI are quite diverse. They put forth a variety of prognoses and pathologies, which leads to some confusion in the literature (De Carli, 2003).

Reisberg and Gauthier (2008), for instance, propose 'subjective cognitive impairment' (SCI) as a pre-MCI stage of subsequently manifested

Alzheimer's disease. Current studies indicate that SCI is a common condition in older persons, but the precursor relation of SCI to MCI has not been well studied epidemiologically (Reisberg & Gauthier, 2008). Dubois (2000) proposed 'prodromal AD', as a more useful term than MCI. The memory deficit represents the central core of AD and is observable very early in the course of the disease. This deficit may precede the occurrence of dementia (Dubois, 2000). It is possible to identify prodromal AD on the basis of patients' memory deficit. In the longitudinal study of Sarazin et al. (2007), the amnesic syndrome of the medial temporal type, as indicated by the Free and Cued Selective Reminding Test, is able to distinguish patients of Alzheimer's disease at an early stage from mild cognitive impairment non-converters.

Another methodological problem is the performance on memory test 1.5 SD below the mean. This condition constrains the diagnosis to late and severe memory impairment and therefore can't be used to detect early pre-symptomatic cognitive (memory) impairment when declining performance is still in the normal range. Rigorous use of neuropsychological tests provides a more reliable, early diagnosis and is useful for clinical trials. MCI may be diagnosed earlier in memory centres that have greater access to neuropsychological evaluation than found in general practice (Laurent & Anterion, 2002).

New neuropsychological approaches, both qualitative and quantitative, distinctive cerebrospinal fluid biomarkers, and molecular neuro-imaging are now available. We need to further refine our definition of AD. Dubois et al. (2007) developed newly revised research criteria for the diagnosis of Alzheimer's disease. Dementia is not a disease, it is only a syndrome with a lot of etiologies (AD, FTD, etc.), and we need to reliably identify the diseases at their earliest stages. We need to make AD diagnosis before the DSM-IV criteria for dementia are met.

Future research will make clear the value of diagnosis of AD in the early pre-dementia stage. This diagnosis will depend on a combination of neuropsychology, structural and functional neuroimaging, and biomarkers.

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References

- Allegri, R. F., Butman, J., Arizaga, R. L., Machnicki, G., Serrano, C., Taragano, F. E. et al., (2007). Economic impact of dementia in developing countries: An evaluation of costs of Alzheimer-type dementia in Argentina. *International Psychogeriatrics*, 19, 705–718.
- Allegri, R. F., Drake, M., Harris, P., Serrano, C. M., & Taragano, F. E. (2005). Intrusions in verbal learning in mild cognitive impairment: Prodromal Alzheimer's disease? *Neurology*, 65, 165.
- Allegri, R. F., Sarasola, D., Serrano, C. M., Taragano, F. E., Arizaga, R. L., Butman, J. L. et al., (2006). Neuropsychiatric symptoms as a predictor of caregiver burden in Alzheimer's disease. *Neuropsychiatric Disease and Treatment*, 2, 105–110.
- APA (1994). *Diagnostic and Statistical Manual of Mental Disorders*. DSM-IV. Washington, DC: American Psychiatric Association.
- Artero, S., Petersen, R., Touchon, J., & Ritchie, K. (2006). Revised criteria for mild cognitive impairment: Validation within a longitudinal population study. *Dementia and Geriatric Cognitive Disorders*, 22, 465–470.
- Belleville, S. (2008). Cognitive training for persons with mild cognitive impairment. *International Psychogeriatrics*, 20, 57–66.
- Blackford, R. C., & La Rue, A. (1989). Criteria for diagnosis AAMI: Proposed improvement from the field. *Developmental Neuropsychology*, 5, 295–306.
- Brookmeyer, R., Gray, S., & Kawas, C. (1998). Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *American Journal of Public Health*, 88, 1337–1342.
- Buschke, H. (1984). Cued recall in amnesia. *Journal of Clinical Neuropsychology*, 6, 433–440.
- Buschke, H., Sliwiski, M. J., Kuslansky, G., & Lipton, R. B. (1997). Diagnosis of early dementia by the Double Memory Test: Encoding specificity improves diagnostic sensitivity and specificity. *Neurology*, 48, 989–992.
- Crook, T., Bartus, R. T., Ferris, S. H., Whitehouse, P., Cohen, G. D., & Gershon, S. (1986). Age associated memory impairment: Proposed diagnostic criteria and measures of clinical change. Report of a National Institute of Mental Health work group. *Developmental Neuropsychology*, 2, 261–276.
- De Carli, Ch. (2003). Mild cognitive impairment: Prevalence, prognosis, aetiology and treatment. *Lancet Neurology*, 2, 15–21.
- De Kosky, S. T. & Chertkow, H. M. (2001). Just forgetfulness or onset of Alzheimer's disease? 53rd annual Meeting, American Academy of Neurology, Philadelphia, PA.
- Dubois, B. (2000). Prodromal Alzheimer's disease: A more useful concept than mild cognitive impairment? *Current Opinion in Neurology*, 18, 367–369.
- Dubois, B., & Albert, M. L. (2004). Amnesic MCI or prodromal Alzheimer's disease? *Lancet Neurology*, 3, 246–248.
- Dubois, B., Feldman, H., Jacova, C., DeKosky, S., Barberger-Gateau, P., Cummings, J. L. et al., (2007). Research criteria for the diagnosis of Alzheimer's disease: Revising the NINCDS-ADRDA criteria. *Lancet Neurology*, 6, 734–746.
- Feldman, H. H., Ferris, S., Winblad, B., Sfikas, N., Mancione, L., & He, Y. (2007). Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the In DDEX study. *Lancet Neurology*, 6, 501–512.
- Flicker, C., Ferris, S. H., & Reisberg, B. (1993). A two year longitudinal study of cognitive function in normal aging and Alzheimer's disease. *Journal of Geriatric Psychiatry and Neurology*, 6, 84–96.
- Flicker, C., Ferris, S. H., & Reisberg, B. (1991). Mild cognitive impairment in the elderly: Predictors of dementia. *Neurology*, 41, 1006–1009.

- Ganguli, M. (2006). Mild cognitive impairment and the 7 uses of epidemiology. *Alzheimer Disease and Associate Disorders*, 20, S52–57.
- Ganguli, M., Dodge, H. H., Shen, C., & De Kosky, S. T. (2004). Mild cognitive impairment, amnesic type: An epidemiological study. *Neurology*, 63, 115–121.
- Gauthier, S., Reisberg, B., Zaudig, M., Peretsen, R., Ritchie, K., Broich, K., et al., (2006). International Psychogeriatric Association Expert Conference on mild cognitive impairment. Mild Cognitive Impairment. *Lancet*, 367, 1262–1270.
- Gold, M., Wang, D., & Truyen, L. (2003). Galantamine for the treatment of mild cognitive impairment: Two double blind, placebo-controlled studies. *International Psychogeriatrics*, 15, 259.
- Graham, J. E., Rockwood, K., Beattie, B. L., Eastwood, R., Gauthier, S., Tuokko, H. et al., (1997). Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet*, 349, 1793–1796.
- Grober, E., & Buschke, H. (1987). Genuine memory deficits in dementia. *Developmental Neuropsychology*, 3, 13–36.
- Grober, E., Buschke, H., Crystal, H., Bang, S., & Dresner, R. (1988). Screening for dementia by memory testing. *Neurology*, 38, 900–903.
- Hansson, O., Zetterberg, H., Buchhave, P., Minthon, L., & Warkentin, S. (2006). Association between CSF biomarkers and incipient Alzheimer's disease in patients with MCI: A follow-up study. *Lancet Neurology*, 5, 228–234.
- Harris, P., Drake, M., & Allegri, R. F. (2001). Deterioro cognitivo leve: En búsqueda de la pre-demencia. *Acta Psiquiátrica y Psicológica de América Latina*, 47, 11–20.
- Helmer, C., Pasquier, F., & Dartigues, J. F. (2006). Epidemiology of Alzheimer disease and related disorders. *Medecine Sciences (Paris)*, 22, 288–296.
- Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for staging of dementia. *British Journal of Psychiatry*, 140, 566–572.
- Jack Jr, C. R., Petersen, R. C., Xu, Y. C., O'Brien, P. C., Smith, G. E., Ivnik, R. J. et al., (1999). Prediction of AD with MRI based hippocampal volume in mild cognitive impairment. *Neurology*, 52, 1397–1403.
- Jelic, V., Kipivelto, M., & Winblad, B. (2006). Clinical trials in mild cognitive impairment: Lessons for the future. *Journal of Neurology Neurosurgery and Psychiatry*, 77, 429–438.
- Klunk, W. E., Engler, H., Nordberg, A., Bacskai, B. J., Wang, Y., Price, J. C. et al., (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Annals of Neurology*, 55, 306–319.
- Kral, A. V. (1962). Senescent forgetfulness: Benign and malignant. *Canadian Medical Association Journal*, 86, 257–260.
- Kral, A. V. (1978). Benign senescent forgetfulness. In R. Katzman, R. D. Terry & K. L. Bick (Eds.), *Alzheimer's disease: Senile dementia and related disorders* (Aging, Vol. 7; pp. 47–51). New York: Raven Press.
- Larrieu, S., Letenneur, L., Orgogozo, J., Fabrigoule, C., Amieva, H., Le Carret, N. et al., (2002). Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. *Neurology*, 59, 1594–1599.
- Laurent, B., & Anterion, C. T. (2002). Incertitudes et limites du MCI: Apport de la neuropsychologie. *Revue Neurologique (Paris)*, 158, 5S11–5S20.
- Levy, R. (1994). Ageing-associated decline. *Psychogeriatrics*, 6, 63–68.
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology*, 34, 939–944.
- Morris, J. C. (2006). Mild cognitive impairment is early stage Alzheimer disease – Time to revise diagnostic criteria. *Archives of Neurology*, 63, 15–16.
- Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H. et al., (2001). Mild cognitive impairment represents early stage Alzheimer's disease. *Archives of Neurology*, 58, 397–405.
- Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, 256, 183–194.
- Petersen, R. C. (2007). Mild cognitive impairment: Current research and clinical implications. *Seminars in Neurology*, 27, 22–31.
- Petersen, R. C. (2000). Mild cognitive impairment or questionable dementia. *Archives of Neurology*, 57, 643–644.
- Petersen, R. C., & Morris, J. C. (2005). Mild cognitive impairment as a clinical entity and treatment target. *Archives of Neurology*, 62, 1160–1163.
- Petersen, R. C., Parisi, J. E., Dickson, D. W., Johnson, K. A., Knopman, D. S., Boeve, B. F. et al., (2006). Neuropathology of amnesic mild cognitive impairment. *Archives of Neurology*, 63, 665–672.
- Petersen, R. C., Smith, G. E., Ivnik, R. J., Tangalos, E. G., Schaïd, D. J., Thibodeau, S. N. et al., (1995). Apolipoprotein E status as a predictor of development of Alzheimer's disease in memory impaired individuals. *Journal of the American Medical Association*, 273, 1274–1278.
- Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kolmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. *Archives of Neurology*, 56, 303–308.
- Petersen, R. C., Thomas, R. G., Grundman, M., Bennett, D., Doody, R., Ferris, S., & the Alzheimer's Disease Cooperative Study Group, (2005). Vitamin E and donepezil for the treatment of mild cognitive impairment. *New England Journal of Medicine*, 352, 2378–2388.
- Portet, F., Ousset, P. J., Visser, P. J., Frisoni, G. B., Nobili, F., & Scheltens, P. (2006). Mild cognitive impairment in medical practice: A critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's disease. *Journal of Neurology Neurosurgery and Psychiatry*, 77, 714–718.
- Rabins, P. V., Lyketsos, C. G., & Steele, C. (1999). *Practical dementia care*. New York: Oxford University Press.
- Reisberg, B., Ferris, S. H., de Leon, M. J., & Crook, T. (1982). The Global Deterioration Scale for assessment of primary degenerative dementia. *American Journal of Psychiatry*, 139, 1136–1139.
- Reisberg, B., Ferris, S. H., Kluger, A., Franssen, E., Wegiel, J., & de Leon, M. J. (2008). Mild cognitive impairment (MCI): A historical perspective. *International Psychogeriatrics*, 20, 18–31.
- Reisberg, B., & Gauthier, S. (2008). Current evidence for subjective cognitive impairment (SCI) as the pre-mild cognitive impairment (MCI) stage of subsequently manifest Alzheimer's disease. *International Psychogeriatrics*, 20, 1–16.
- Ritchie, K., Artero, S., & Touchon, J. (2001). Classification criteria for mild cognitive impairment: A population-based validation study. *Neurology*, 56, 37–42.
- Rockwood, K., Chertkow, H., & Feldman, H. H. (2007). Is mild cognitive impairment a valid target of therapy? *Canadian Journal of Neurological Sciences*, 34, S90–S96.
- Sarazin, M., Berr, C., De Rotrou, J., Fabrigoule, C., Pasquier, F., Legrain, S. et al., (2007). Amnesic syndrome of the medial

- temporal type identifies prodromal AD: A longitudinal study. *Neurology*, 69, 1859–1867.
- Serrano, C. M., Allegri, R. F., Caramelli, P., Taragano, F., & Camera, L. (2007). Deterioro cognitivo leve. Encuesta sobre actitudes de médicos especialistas y generalistas. *Medicina (BsAs)*, 67, 19–25.
- Whitehouse, P. J., & Brodaty, H. (2006). Mild cognitive impairment. *Lancet*, 367, 1979.
- Whitehouse, P. J. (2007). Mild cognitive impairment – A confused concept? *Nature*, 3, 62–63.
- Winblad, B., Palmer, K., Kipivlto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O. et al., (2004). Mild cognitive impairment: Beyond controversies, towards a consensus-report of the international Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine*, 256, 240–246.