MANAGEMENT OF DEMENTIA

Second Edition

SERGE GAUTHIER
CLIVE BALLARD

informa
healthcare

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20150528

International Standard Book Number-13: 978-0-203-09188-3 (eBook - PDF)

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

Preface

The first edition of *Management of Dementia* has proven to be very useful to clinicians caring for persons with Alzheimer's disease and related disorders. Since 2001, there has been steady progress in this field, and all chapters have been updated with a clinical perspective based on the best available evidence.

The diagnostic criteria of Parkinson's disease dementia have been added to chapter 1. Behavioural disturbances cause a lot of distress to patients and caregivers, and continue to be a major management problem for clinicians, with considerable uncertainty as to the best overall approaches; we offer our advice in chapter 2 for the most troublesome behaviours, depression, psychosis and agitation, and in chapter 3 for sleep disturbances. Chapter 4 gives an update on the many genetic findings in Alzheimer's disease, Frontotemporal dementia and dementia with Lewy bodies. Chapter 5 on biological markers is complementary to chapter 1 on diagnosis. Chapters 6 and 7 on symptomatic and disease-modifying treatments discuss available drugs and potential preventive or stabilizing treatments. Chapter 8 offers advice for managing the difficult later stages of dementia in long-term care. Chapter 9 has been

updated to include new assessment scales. Chapter 10 is a perspective on the management of dementia in the near future using primary and secondary prevention and drug treatments selected for individual patients with specific causes of dementia, treatments possibly based on the individual's phenotypic and genetic features.

We think that the care of persons with dementia and their caregivers has improved greatly in the past two decades, and we hope that this book will help further. We are not far from offering evidence-based prevention advice for persons at risk.

Serge Gauthier
Clive Ballard

Contents

Diagnosis

1

Introduction

There has been a shift in the past few years to persons consulting their physician because they are concerned about their risk of developing Alzheimer's disease (AD) or have minimal complaints. This is in addition to persons being brought in by family or friends with the more traditional symptoms of cognitive decline interfering with daily life, thus with dementia at different stages of severity. The physician or other health professional caring for persons with cognitive complaints must therefore be ready for quite a range of issues pertaining to diagnosis and treatment.This chapter will summarize the current clinical approach to the diagnosis of dementia, with additional information about persons who have memory complaints but no dementia.

Doctor, I am worried about getting Alzheimer like my mother did'

More and more persons in their midlife are consulting their physicians because they are concerned about their risk of AD later in their life. If they have any symptoms, they are

minimal, such as losing tract of what they were looking for, delay in remembering someone's name. These persons perform well on screening tests such as the Mini Mental State Examination (MMSE; Folstein et al, 1975) supplemented by the Montreal Cognitive Assessment (MoCA; Nasreddine et al, 2005). Many will ask if there is 'a blood test' that can detect AD; there is currently no such test except for the rare families with early-onset, dominantly inherited AD (see chapter 4, 'Genetics'), although there is great interest in a blood marker for sporadic AD with adequate sensitivity and specificity (see chapter 5, 'Biomarkers').

These 'worried well' can be reassured that they do not have AD at this time, although they can have it later. We can estimate their risk relative to other individuals using variables derived from a population study and adding up into a 'midlife risk score' (Kivipelto et al, 2006), which identifies some excellent treatment targets for prevention (Panel 1.1).

Panel 1.1
*Treatment targets for the prevention of dementia among middle-aged people**

- *systolic BP < 140 mm Hg*
- *body-mass index < 30 kg/m^2*
- *total cholesterol < 6.5 mmol/L*
- *physical activity*

**Modified from Kivipelto et al, 2006.*

The advantage of looking systematically at such risk factors is that some can be modified by changes in lifestyle and interested persons can keep up to date with prevention strategies that include a Mediterranean diet (Scarmeas et al, 2006), building a social network (Bennett et al, 2006), leisure activities (Verghese et al, 2006), physical exercises (Larson et al, 2006), cognitive training (Willis et al, 2006) and one drink per day of alcohol or wine (Solfritti et al, 2007). Avoidance of certain risk factors in a prospective study in Japanese American middle-aged men was associated with a longer and healthier life (Willcox et al, 2006). It remains to be established if the prevalence of cognitive decline with age and dementia can be reduced using such population-based prevention strategy, which would be the most cost-effective way to reduce the burden of AD from a societal perspective (Brookmeyer et al, 2007). An illustration of a practical approach to prevention using a case study has been published by a workgroup of the Third Canadian Consensus Conference on the Diagnosis and Treatment Dementia (3CCCDTD; Patterson et al, 2008).

'Doctor, I am losing my memory'

Persons volunteering memory complaints and presenting themselves alone to their physicians rarely have dementia, but they are at risk of progressing towards one of the dementias

Panel 1.2
*Operational definition of mild cognitive impairment**

- *subjective memory complaints*
- *abnormal memory tests for age and level of education*
- *normal general cognitive performance*
- *normal activities of daily living*
- *not demented clinically*

**Petersen et al, 1999.*

(predominantly AD). The large group of persons with 'mild cognitive impairment' (MCI) has attracted a lot of interest in the past decade since an operational definition was proposed by Petersen et al in 1999 (Panel 1.2). The latest expert conference on this topic was held under the auspices of the International Psychogeriatric Association (Gauthier et al, 2006), and the primary care physician perspective was studied by workgroups of the 3CCCDTD (Chertkow et al, 2007; Massoud et al, 2007) followed by a representative case study (Chertkow et al, 2008).

The clinical workup of someone with MCI is similar to any person with a cognitive complaint. It is preferable to get additional information from an informant (spouse, child, friend, co-worker) since informant-reported memory problems correlate better with cognitive outcomes (Carr et al, 2000). In other words, although most persons with MCI come alone to the physician's office, an informant should be found in order to get the best information possible on function at home or at work. The MMSE and the MoCA are done routinely by physicians or other health professionals. In-depth neuropsychological testing may be required in some individuals with high social or familial responsibility, where earlier recognition of executive impairment may require delegation of such responsibility.

There is currently no specific treatment for MCI. Cholinesterase inhibitors have been studied against placebo in thousands of persons with MCI, with no demonstrable benefit overall. The advice for prevention, mentioned in the previous section, is highly relevant for persons with MCI. Many will be interested in research programs aiming at secondary prevention.

'Doctor, does my wife have dementia?'

Most patients with dementia, even in mild stage, are brought in the physician's office by a family member. A careful history is the key to the clinical diagnosis of dementia, bringing out the components of the 'dementia of the AD type' defined in 1994 by the American Psychiatric Association (Panel 1.3).

The history is supplemented by a physical examination searching for evidence of peripheral vascular disease (hypertension, irregular pulse, carotid bruits) and of systemic conditions that could interfere with cognition and/or functional autonomy (goitre associated

Panel 1.3
*Diagnostic criteria for dementia of the Alzheimer's type**

Multiple cognitive deficits
- *in memory*
- *one or more of language, praxis, gnosis, executive functioning*

Causing
- *significant impairment and decline in social or occupational functioning*
- *gradual onset and continuing cognitive decline*

Not due to
- *other central nervous system or substance-induced conditions*
- *deficits not exclusively during course of delirium and not better accounted for by depression or schizophrenia*

**Modified from American Psychiatric Association, 1994.*

with hypothyroidism, for example), and a neurological examination looking for asymmetry in motor strength, tone and reflexes, which would suggest a focal lesion (stroke or tumour). Ancillary tests vary among countries, Canada likely being the least invasive in terms of laboratory investigations (Feldman et al, 2008).

'Doctor, does she have Alzheimer or dementia?'

Once the clinical diagnosis of dementia has been made, a differential diagnosis takes place, using the best available information. The specific cause of dementia can often be positively identified from the pattern of symptoms as illustrated in Figure 1.1 for the typical patient with AD; the initial and transient change in mood is followed by a linear decline in cognitive and functional abilities, and then disruptive neuropsychiatric symptoms emerge followed by progressive rigidity, akinesia and gait instability.

The level of certainty for AD as a cause of dementia has been operationally defined by the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) in 1984: 'definite AD' requiring a brain biopsy or autopsy, 'probable AD' is similar to the APA criteria listed in Panel 1.3 and 'possible AD' indicates variations in the onset or course compared with typical AD, presence of a second brain disorder or systemic illness that is sufficient to cause dementia but that is not considered to be the cause of the dementia or a single gradually progressive deficit in the absence of other identifiable cause. (McKhann et al, 1984).

Each of the non-AD dementia has its own set of diagnostic criteria (Panels 1.4–1.7). Of particular clinical significance are the delirium-like fluctuating confusion and visual hallucinations in dementia with Lewy bodies (DLB) and dementia associated with Parkinson's disease (PDD), the early loss of

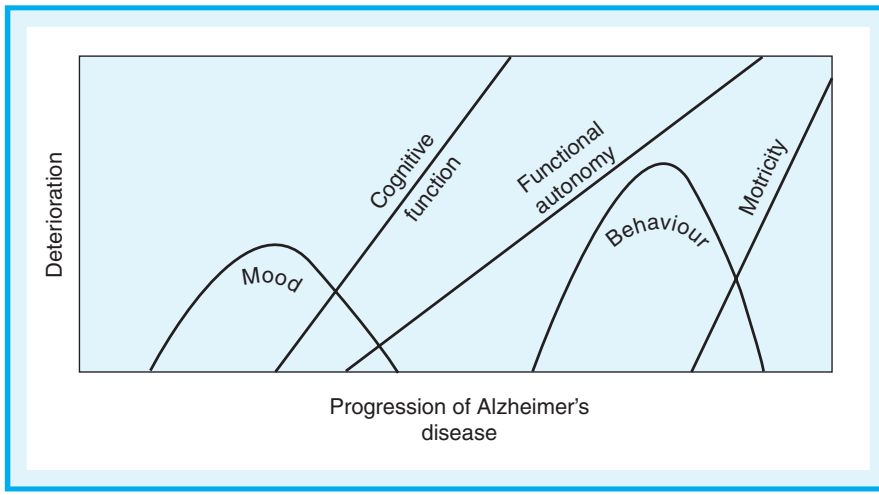

Figure 1.1
Pattern of symptoms over time in typical patients with Alzheimer's disease.

personal and social awareness combined with reduction in speech associated with fronto-temporal dementia and the stepwise deterioration with asymmetric neurological signs in vascular dementia.

The reality is that there is a lot of overlap between the different types of dementia: the majority of older patients with dementia have pathological features of AD, vascular disease and DLB/PDD (Schneider et al, 2007), with a marked overlap of Alzheimer and vascular changes almost inevitable over the age of 80 years (Lewis et al, 2006). This is important, as a lower burden of Alzheimer pathology is necessary to cause clinical dementia in the elderly in the presence of cerebrovascular disease (Snowdon et al, 1997) and the concurrent vascular changes add to the cognitive impairment (Esiri et al, 1999).

The diagnosis of AD may be possible before the stage of dementia. A proposal has been made to update the NINCDS-ADRDA criteria and allow for an earlier diagnosis, combining clinical evidence of a progressive decline in episodic memory and laboratory evidence of abnormalities compatible with AD, using neuroimaging, spinal fluid examination, genetic testing (Dubois et al, 2007). Although currently meant only for research, it is likely that these criteria will make possible the diagnosis of AD one or two years earlier than traditionally possible.

Panel 1.4
*Diagnostic criteria for DLB**

Progressive cognitive decline interfering with social or occupational functioning one (possible DLB) or two (probable DLB) of
- *fluctuating cognition with pronounced variations*
- *recurrent visual hallucinations*
- *spontaneous motor features of parkinsonism*

**Modified from McKeith et al, 2005.*

Panel 1.5
*Diagnostic criteria for PDD**

A dementia syndrome developing within the context of established Parkinson's disease, with
- *impairment in more than one cognitive domain*
- *decline from premorbid level*
- *deficits severe enough to impair daily life, independently of the impairment ascribable to motor or autonomic symptoms*

**Modified from Emre et al, 2007.*

Panel 1.6
*Diagnostic criteria for fronto-temporal dementia**

- *behavioural disturbances, including early loss of personal and social awareness*
- *affective symptoms, including emotional unconcern*
- *speech disorder, including reduction, stereotypy and perseveration*
- *physical signs, including primitive reflexes, incontinence, akinesia and rigidity*

**Modified from Lund Manchester Groups, 1994.*

Panel 1.7
*Diagnostic criteria for vascular dementia**

- *decline in intellectual function sufficient to interfere with activities of daily life and not due to the physical effects of stroke(s) alone*
- *evidence by history, physical and/or neuroimaging examination of stroke(s)*
- *temporal relationship between dementia and cerebrovascular disease*

**Modified from Chui et al, 1993, and Roman et al, 1994.*

Should the diagnosis of dementia be made early?

Clearly yes, to clarify uncertainty about the nature of symptoms ranging from apathy and social withdrawal to mistakes in handling tasks at home or at work. Concomitant disorders such as depression and hypothyroidism, as well as vascular risk factors such as systolic hypertension, hypercholesterolemia and diabetes mellitus, can also be treated. Early diagnosis gives better opportunity to plan for the future. Symptomatic drugs can be offered and hopefully soon disease-modifying treatments will be available.

A more difficult question is the very early (pre-dementia) diagnosis of AD, if possible through the revised NINCDS-ADRDA criteria (Dubois et al, 2007); there is a risk of catastrophic reaction in someone with full understanding of the impact of diagnosis. Possibly, an approach similar to the one used in genetic screening clinics can be used, e.g., pre-testing assessment of how the earlier diagnosis would help or hinder the subject (Chao et al, 2008).

Should we tell patients what is the cause of their symptoms?

Yes. Most people dislike the term 'dementia' because it has the connotation of mental illness, thus patients and carers will prefer a 'disease' label. Using a good news/bad news approach, people are often reassured by the knowledge that there is a medical cause for the symptoms, and that specific drugs can be tried to relieve them. The lack of known genetic risk for children of patients with DLB may offer some relief, but this is not the case for AD (see chapter 4). The relatively stable course of vascular dementia compared to AD (at least in the short term) may also offer some additional hope.

Is there a right time to give the diagnosis?

As clinicians, we may suspect that a patient is progressing towards a dementia such as AD long before the symptoms reach diagnostic threshold. For instance, a long, postoperative, delirium could antedate AD by a number of years. A decline on serial MMSE scores could precede symptoms (Small et al, 2000). The converse is also true where families detect changes in mood, personality and initiative that they have seen associated with dementia in older relatives. If in doubt about the presence of dementia, it is better to state that it is not present at this time, but that follow-up is required once a year with attention to risk factors such as systolic hypertension. This may be a good time to 'put the papers in order' such as will and advance directives, when people are fully competent to do so, and identify who is likely to be the most significant family member to act as a carer, should the need arise. Once the diagnosis of dementia is clear in the clinician's mind and documented in his chart, this carer should be notified without delay. If the patient is in an angry denial stage, it may be better to give him or her disclosure in a stepwise approach (Fisk et al, 2007). Once insight into the significance of dementia has been lost in intermediate to late stages, there should be no hesitation about keeping the patient informed in clear but truthful language.

Should we tell patients with mild cognitive impairment that they may progress to dementia?

Yes, with the reassuring news that most persons with mild cognitive impairment as

currently defined (Panel 1.2) do not progress to AD. Since up to 15% per year do progress to AD, interested patients can be referred to research sites running one of the many studies in this population.

Assessment of care needs

As a component of history taking towards the diagnosis of dementia, the clinician will have acquired knowledge of the functional abilities of the individual and of the resources available to cope with difficulties. For instance, someone may already be helping with finances and transportation. As part of a management strategy, additional information should be obtained on the person's life story, including work and leisure activities, as well as the quality of their social network, including family and close friends. Special attention will have to be paid to the carer, especially if older and frail, but also to a daughter or son caught between their responsibilities towards an elderly parent and their own children and spouse (the 'sandwich' effect). Family therapy or individual treatment for the distressed carer may be needed. Referral to a local Alzheimer society, whatever the cause of dementia, is an important step in the education of patients and carers (Brodaty and Berman, 2007). Referral to local community-based formal support services for help at home and access to support groups, day programs and respite care is another useful step, often underused by families (Katofsky, 2007).

Prognosis

The natural history of AD can be understood as a series of milestones that can be used in clinical trials as outcome, or in patients' and caregivers' education (Galasko et al, 1995; Panel 1.8).

There have been many attempts to predict which patients will do better or worse (Sarazin et al, 2007). A list derived from many publications for clinical features that predict a rapid decline is shown in Panel 1.9.

The clinician will have to schedule closer visits on follow-up of patients in the rapid-decline category, give advance warning of things to come, and facilitate planning for the carer, all the way to nursing-home placement. An example of how such cases may

Panel 1.8
*Milestones in progression of dementia**

- *conversion from mild cognitive impairment to dementia*
- *loss of instrumental activities of daily living (ADL)*
- *emergence of neuropsychiatric symptoms*
- *nursing home placement*
- *loss of self-care ADLs*
- *death*

**Modified from Galasko et al, 1995.*

Panel 1.9
Clinical features suggestive of rapid decline

- *aphasia, severe*
- *caregiver psychological morbidity*
- *concomitant vascular disease*
- *extra-pyramidal signs, early*
- *greater age*
- *myoclonus, early*
- *non-AD dementias*
- *psychosis, early*
- *unmarried men*

pan out follows. A woman practicing family medicine in her mid-fifties is brought to her physician by her husband because of mistakes at work over the past year. She has significant difficulties expressing herself in her second language and is reverting to her mother tongue, not well understood by the spouse. Myoclonus is visible in her limbs. The diagnosis of AD is made, confirmed by consultation with a specialist, and the spouse is warned of the poor prognosis. There was no improvement on a cholinesterase inhibitor, and she needed nursing-home placement 1 year later. The spouse had taken a year off work to care for her at home, and was able to go back to teaching. She died a year later from pneumonia.

Referral to specialist services

Although family practitioners have a central role in the diagnosis and management of dementia, they will face uncertainty in some patients with very early symptoms, atypical presentations of AD, or rare types of dementia. Some of the management issues need a team approach, both in the community and in institutions. Guidelines have been prepared to suggest when to refer to a specialist (Panel 1.10).

Panel 1.10
*Reasons to consider referral to a specialist**

- *continuing uncertainty about the diagnosis after initial assessment and follow-up*
- *request by family or patient for second opinion*
- *presence of significant not responsiveness to treatment*
- *intolerance or lack of response to disease-specific pharmacotherapy*
- *need for additional help for patient management or caregiver support*
- *need to involve other health professionals, voluntary agencies, or local service providers*
- *when genetic counselling is indicated*
- *when research studies into diagnosis or treatment are being performed*

**Patterson et al, 1999.*

Summary

- Family practitioners play a key role in the diagnosis and management of people with dementia and their carers.
- Practitioners have responsibility for disclosure of diagnosis, assessment of care needs, and prognosis.

- Carers and practitioners can and should call upon a number of resources in their community.

References

American Psychiatric Association (1994). *Diagnosis and statistical manual of mental disorders*, 4th edn. Washington DC: APA.

Bennett DA, Schneider JA, Tang Y, Arnold SE, Wilson RS (2006). The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. *Lancet Neurol* 5, 406–412.

Brodaty H, Berman K (2007). Caregiver support: support of families. In: Gauthier S, ed. *Clinical diagnosis and management of Alzheimer's disease,* 3rd edn. London, UK: Informa Healthcare, 279–298.

Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM (2007). Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement* 3, 186–191.

Carr DB, Gray S, Baty J, Morris JC (2000). The value of informant versus individual's complaints of memory impairment in early dementia. *Neurology* 55, 1724–1726.

Chao S, Roberts JS, Marteau TM, Silliman R, Cupples LA, Green RC (2008). Health behavior changes after genetic risk assessment for Alzheimer disease: the REVEAL study. *Alzheimer Dis Assoc Disord* 22, 94–97.

Chertkow H, Massoud F, Nasreddine Z, et al (2008). Diagnosis and treatment of dementia: 3. Mild cognitive impairment and cognitive impairment without dementia. *CMAJ* 178, 1273–1285.

Chertkow H, Nasreddine Z, Joanette Y et al (2007). Mild cognitive impairment and cognitive impairment, no dementia: part A, concept and diagnosis. *Alzheimers Dement* 3, 266–282.

Chui HC, Victoroff JI, Margolin D, et al (1993). Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centres. *Neurology* 42, 473–480.

Dubois B, Feldman HH, Jacova C, et al (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* 6, 734–746.

Emre M, Aarsland D, Brown R, et al (2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord* 12, 1689–1707.

Esiri MM, Nagy Z, Smith MZ, Barnetson L, Smith AD (1999). Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. *Lancet* 354, 919–920.

Feldman HH, Jacova C, Robillard A, et al (2008). Diagnosis and treatment of dementia: 2. Diagnosis. *CMAJ* 178, 825–836.

Fisk JD, Beattie BL, Donnelly M, Byszewski A, Molnar FJ (2007). Disclosure of the diagnosis of dementia. *Alzheimers Dement* 3, 404–410.

Folstein MF, Folstein SE, McHugh PR (1975). "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res* 12, 189–198.

Galasko D, Edland SD, Morris JC, Clark C, Mohs R, Koss E (1995). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part XI. Clinical milestones in patients with Alzheimer's disease followed over 3 years. *Neurology* 45, 1451–1455.

Gauthier S, Reisberg B, Zaudig M, et al (2006). Mild cognitive impairment. *Lancet* 367, 1262–1270.

Katofsky L (2007). Community-based formal support services. In: Gauthier S, ed. *Clinical diagnosis and management of Alzheimer's disease*. 3rd edn. London, UK: Informa Healthcare, 299–314.

Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J (2006). Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal,

population-based study. *Lancet Neurol* 5, 735–741.

Larson EB, Wang L, Bowen JD, et al (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann Intern Med* 144, 73–81.

Lewis H, Beher D, Cookson N, et al (2006). Quantification of Alzheimer pathology in ageing and dementia: age-related accumulation of amyloid-beta(42) peptide in vascular dementia. *NeuropatholAppl Neurobiol* 32, 103–118

Lund and Manchester Groups (1994). Clinical and neuropathological criteria for fronto-temporal dementia. *J Neurol Neurosurg Psychiatry* 57, 416–418.

McKhann G, Drachman D, Folstein M, et al (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.

McKeith IG, Dickson DW, Lowe J, et al.; for the Consortium on DLB (2005). Dementia with Lewy Bodies: Diagnosis and Management. Third Report of the DLB Consortium. *Neurology* 65, 1863–1872.

Massoud F, Bellevile S, Bergman H, et al (2007). Mild cognitive impairment and cognitive impairment, no dementia: part B, therapy. *Alzheimers Dement* 3, 283–291.

Nasreddine ZS, Phillips NA, Bédirian V, et al (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for Mild Cognitive Impairment. *J Am Geriatr Soc* 53, 695–699.

Patterson C, Feightner JW, Garcia A, et al (2008). Diagnosis and treatment of dementia. 1. Risk assessment and primary prevention of Alzheimer disease. *CMAJ* 178, 548–556.

Patterson C, Gauthier S, Bergman H, et al (1999). The recognition, assessment and management of dementing disorders: conclusions from the Canadian Consensus Conference on Dementia. *CMAJ* 160(suppl), S1–S20.

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kohmen E (1999). Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 56, 303–308.

Roman GC, Tatemichi TK, Erkinjuntii T, et al (1994). Vascular dementia: diagnostic criteria for research studies: report of the NINCDS-AIREN international workshop. *Neurology* 43, 250–260.

Sarazin M, Horme N, Dubois B (2007). Natural decline and prognostic factors. In: Gauthier S, ed. *Clinical diagnosis and management of Alzheimer's disease*. 3rd edn. London, UK: Informa Healthcare, 137–148.

Scarmeas N, Stern Y, Tabg MX, Mayeux R, Luchsinger JA (2006). Mediterranean diet and risk for Alzheimer's disease. *Ann Neurol* 59, 912–921.

Schneider JA, Arvanitakis Z, Bang W, Bennett DA (2007). Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* 69, 2197–2204.

Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR (1997). Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA.* 277, 813–817.

Solfritti V, D'Introno A, Colacicco AM, et al (2007). Alcohol consumption, mild cognitive impairment, and progression to dementia. *Neurology* 68, 1790–1799.

Verghese J, LeValley A, Derby C, et al (2006). Leisure activities and the risk of amnestic mild cognitive impairment in the elderly. *Neurology* 66, 821–827.

Willcox BJ, He Q, Chen R, et al (2006). Midlife risk factors and healthy survival in men. *JAMA* 296, 2343–2350.

Willis SL, Tennstedt SL, Marsiske M, et al (2006). Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA* 296, 2805–2814.