Mild cognitive impairment

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Mild cognitive impairment is a syndrome defined as cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life. Prevalence in population-based epidemiological studies ranges from 3% to 19% in adults older than 65 years. Some people with mild cognitive impairment seem to remain stable or return to normal over time, but more than half progress to dementia within 5 years. Mild cognitive impairment can thus be regarded as a risk state for dementia, and its identification could lead to secondary prevention by controlling risk factors such as systolic hypertension. The amnestic subtype of mild cognitive impairment has a high risk of progression to Alzheimer's disease, and it could constitute a prodromal stage of this disorder. Other definitions and subtypes of mild cognitive impairment need to be studied as potential prodromes of Alzheimer's disease and other types of dementia.

Mild cognitive impairment is a syndrome defined as cognitive decline greater than that expected for an individual's age and education level but that does not interfere notably with activities of daily life. It is, thus, distinct from dementia, in which cognitive deficits are more severe and widespread and have a substantial effect on daily function. However, mild cognitive impairment with memory complaints and deficits (amnestic mild cognitive impairment) is consistently shown to have a high risk of progression to dementia, particularly of the Alzheimer type. This text summarises the content of an Expert Conference convened by the International Psychogeriatric Association in Bethesda, MD, USA, Jan 21–23, 2005, with the objective of clarifying the diagnosis and management of mild cognitive impairment.

Background and conceptual development

Many attempts have been made to define the clinical entity of declining cognitive abilities associated with ageing. In the early part of the 19th century, Prichard[1] identified the earliest stage of dementia as impairment of recent memories with intact remote memories. More than a century later, Kral[2] espoused a contrasting viewpoint, with his description of benign senescent forgetfulness, in which fairly unimportant data and parts of an experience are not recalled and in which the forgotten data seem to belong to the remote past rather than the recent past.

In 1982, two clinical staging systems were published, which continue to be used today by clinicians to assess the boundaries of ageing and dementia. These are the clinical dementia rating (CDR)[3] and the global deterioration scale for ageing and dementia (GDS).[4] The CDR distinguishes a stage of questionable dementia (CDR 0·5) from people termed healthy (CDR 0) and those with mild dementia (CDR 1). Individuals at CDR 0·5 have mild consistent forgetfulness and doubtful or mild impairment in independent function at the usual level in job, shopping, business and financial affairs, and volunteer and social groups.

Definitions of dementia were published in 1980 by the American Psychiatric Association[5] and in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA),[6] which remain today as benchmarks for clinicians. The American Psychiatric Association's primary degenerative dementia definition notes that the diagnosis should be restricted "to cases in which there is clear evidence of progressive and significant deterioration of intellectual and social or occupational functioning".[5] The definition by McKhann and colleagues[6] also notes that a diagnosis of probable Alzheimer's disease should include deficits in two or more areas of cognition, with progressive worsening of memory and other cognitive functions. Diagnosis is lent support by impaired activities of daily life. Hence, from these definitions, the CDR 0·5 stage of questionable dementia includes mild dementia and mild cognitive impairment, but allows for such affected individuals to have measurable deficits in several areas of cognition without meeting criteria for dementia.

The term mild cognitive impairment was first used in association with stage 3 of the GDS.[4,7] This scale identifies seven clinical stages, of which four range from normality to mild dementia. Stage 1 individuals are free of both subjective and objective clinical deficits. Those at stage 2

Search strategy and selection criteria

This Seminar is based on discussions that took place during an Expert Conference sponsored by the International Psychogeriatric Association. Presenters were asked to review published work relevant to their assigned topics and to summarise the available evidence, areas of agreement, areas of uncertainty, and research priorities. This was not a consensus conference, but rather an opportunity to review available data and offer an expert opinion on where mild cognitive impairment stands as a clinical entity. The current text includes references up to Dec 19, 2005.

have subjective deficits only, such as self-perceived difficulties remembering names. Perhaps the best current terminology for this disorder is subjective cognitive impairment. People at GDS stage 3 have subtle deficits in cognition and may have some impairment in executive functioning that affects complex occupational and social activities. GDS stage 4 individuals have clear deficits in cognition and functioning with reduced performance in instrumental activities of daily life, such as preparing meals and managing personal financial affairs. People at GDS stage 4 fulfil criteria for mild dementia. According to Reisberg,[4] the GDS 3 description of mild cognitive impairment accords with that subsequently formulated by an international working group[8] and describes a severity range of cognitive and functional impairment largely in keeping with other subsequent definitions described below.

Petersen[9] says it is important to note that the GDS and the CDR are severity rating scales and not diagnostic instruments. Some investigators have equated GDS 3 or CDR 0·5 to mild cognitive impairment, but Petersen believes that this practice might not always be correct, stating that: "as severity scales, these stages may correspond to mild cognitive impairment or may describe individuals with very mild dementia." As such, Petersen believes that the rating scales are not synonymous with the syndrome of mild cognitive impairment. Reisberg and associates disagree with respect to the GDS 3 stage, which they believe to be fully consistent with, for example, the definition of mild cognitive impairment posed in the opening statement of this report.

As noted above, the CDR 0·5 stage of questionable dementia is a broad category that encompasses mild dementia and mild cognitive impairment. Reisberg points out that the global staging definition of mild cognitive impairment has advantages of inclusivity, whereas other definitions of the disorder are frequently more restrictive—eg, from an epidemiological standpoint. For example, the amnestic subtype of mild cognitive impairment described below and in the panel requires memory complaints.[9] Many individuals with mild cognitive impairment deny they have the disorder and do not report symptoms, although they nevertheless show signs of cognitive impairment consistent with the disorder that are evident to clinicians or informants. The GDS 3 definition of mild cognitive impairment—unlike the preceding GDS 2 stage of subjective cognitive impairment and the amnestic subtype of mild cognitive impairment—does not require memory complaints; only signs of the disorder are required for GDS stage 3 assignment. Hence the GDS stage 3 definition of mild cognitive impairment is more encompassing of individuals with these clinical signs than, for example, the amnestic category.

Panel: **Amnestic subtype of mild cognitive impairment[9]**

- Memory complaint, preferably corroborated by an informant
- Memory impairment relative to age-matched and education-matched healthy people
- Typical general cognitive function
- Largely intact activities of daily living
- Not clinically demented

The model of cognitive impairment no dementia (CIND) includes all individuals falling in between healthy and demented states, and has been used in population-based epidemiological studies such as the Canadian Study of Health and Aging[10] and the Indianapolis Study of Health and Aging.[11] As originally derived by the investigators of the Canadian study, this model encompasses many disorders, from circumscribed memory impairment to chronic alcohol and drug use, psychiatric illness, mental retardation, and vascular pathologies. CIND represents cognitive impairment that may or may not progress to dementia. Another perspective on this model, described by Petersen[12] and Winblad and colleagues,[8] is that although previous criteria for mild cognitive impairment were specific to isolated deficits in memory, developments have extended them so that the definition of mild cognitive impairment now includes a broad range of cognitive deficits and clinical subtypes with many potential causes. In other words, mild cognitive impairment and CIND could previously be distinguished by the fact that mild cognitive impairment referred to isolated memory deficits—now called amnestic mild cognitive impairment—whereas CIND included global cognitive impairment and deficits in several cognitive domains. Currently, attempts are being made[12] to broaden the definition of mild cognitive impairment to include non-memory deficits and impairment in several cognitive domains, with causal mechanisms including degenerative, vascular, and psychiatric factors.

Findings of longitudinal population studies, which have been undertaken using various definitions of mild cognitive impairment adapted to epidemiological research, have shown a prevalence in the general elderly population between 3% and 19%, with an incidence of 8–58 per 1000 per year, and a risk of developing dementia of 11–33% over 2 years.[13] Conversely, findings of population-based studies have shown that up to 44% of patients with mild cognitive impairment at their first visit were estimated to return to normal a year later.[13,14] These epidemiological studies underline the fact that there are many factors affecting cognition performance in elderly populations apart from neurodegenerative disorders, including education, vascular risk factors, psychiatric status, genetic background, hormonal changes, and use of anticholinergic drugs, and that these factors can account for why many cases of mild cognitive impairment are reversible.

Patients referred to memory clinics and other specialised centres are unlike the general population in that they are

seeking services for a perceived memory disorder. At these centres, they are diagnosed after detailed, systematic, clinical and neuropsychological assessments. In these clinical research settings, individuals with mild cognitive impairment have been shown to progress to dementia (generally Alzheimer's disease) at a rate of 18% per year.[15] Similarly, those diagnosed with amnestic mild cognitive impairment with the research criteria defined by Petersen and colleagues (panel),[9] who also fulfil exclusion criteria for various medical, psychiatric, and neurological disorders, have a high rate of progression to dementia, particularly Alzheimer's disease.

In a 3-year multicentre randomised clinical trial, a 16% per year rate of progression to Alzheimer's disease was noted with the definition of amnestic mild cognitive impairment.[16] This rate accords with findings of previous studies in which similar inclusion and exclusion criteria were used.[17] Findings of another study, in which the same definition of amnestic mild cognitive impairment was used for patients referred on the basis of history of progressive memory changes, showed a progression rate to Alzheimer's disease of 41% after 1 year and 64% after 2 years.[18] Thus, application of the same amnestic criteria can lead to different progression rates despite baseline similarity in cognitive performance. This finding suggests a need to broaden clinical criteria for amnestic mild cognitive impairment (and probably mild cognitive impairment at large) to include history and duration of symptom progression and more explicit acknowledgment of the exclusion criteria applied in various studies.

The category of mild neurocognitive disorder in the diagnostic and statistical manual, 4th edition, is similar, but not identical, to the syndrome of mild cognitive impairment. Research criteria for mild neurocognitive disorder include the presence of two or more disturbances, including impairment in memory, executive function, attention or speed of processing, perceptual-motor abilities, and language. Two cognitive domains must show decline and cause impairment in social, occupational, or another area of function. Objective evidence has to be present of a neurological or general medical disorder that is judged to be caused by the cognitive disturbance.

In summary, patients defined by the terms CDR 0·5, GDS stage 3, CIND, and mild cognitive impairment represent a large segment of the population older than age 65 years. The prognosis in terms of progression to dementia is more heterogeneous in population studies than in the setting of specialised clinics and is driven by the nosological and exclusionary criteria being used in either setting.

Pathophysiology

Much clinical evidence exists for the detrimental effects of anticholinergic drugs on cognition.[19] A central cholinergic deficit is thought to be present in amnestic mild cognitive impairment, related to loss of neurons in the nucleus basalis of Meynert,[20] although findings of a post-mortem study showed upregulation of choline acetyltransferase activity in the frontal cortex and hippocampus.[21] This upregulation could be a compensatory mechanism, which is suggested by recruitment of memory and attentional networks, shown by functional magnetic resonance imaging.[22]

The role of cerebrovascular disease in mild cognitive impairment is probably under-represented, particularly in population studies in which brain imaging has not been undertaken.[23] Findings of the Religious Order Study[24] indicated that cerebrovascular involvement in mild cognitive impairment is intermediate between that seen in ageing and early Alzheimer's disease. Both cerebrovascular disease and neurodegenerative features were shown to contribute to mild cognitive impairment. The importance of white-matter lesions and small lacunar infarcts is becoming increasingly apparent in vascular cognitive impairment.[25] In view of the fact that cerebrovascular disease is frequent in elderly individuals, and that treatment of cerebrovascular risk factors constitutes one of the most important prevention strategies for Alzheimer's disease and vascular dementia, more research is needed on vascular mild cognitive impairment or vascular CIND. These disorders need to be defined operationally, as was done for mild cognitive impairment associated with subcortical cerebrovascular disease.[26]

The role of amyloid deposition and neurofibrillary tangle formation in mild cognitive impairment has not yet been studied extensively. Pathological findings of neurofibrillary tangles in the mesial temporal structures do correlate with mild cognitive impairment.[27,28] Compared with people with dementia and those without cognitive impairment, individuals with mild cognitive impairment have intermediate amounts of Alzheimer's disease pathological findings identified by silver stain,[24] with amyloid deposition and tau-positive tangles[29] in the mesial temporal lobes.

Mutations in apolipoprotein E alleles clearly raise the risk of progression from amnestic mild cognitive impairment to Alzheimer's disease.[16,30,31] This mutation alters cholesterol transport and synaptic plasticity.[32] Other gene mutations are likely to be identified, which will be of relevance to the progression of mild cognitive impairment towards dementia.

In summary, a combination of causal factors are interacting in patients with mild cognitive impairment, including cholinergic dysfunction, white-matter lesions and cerebral infarctions, extracellular amyloid deposition, and intracellular neurofibrillary tangle formation. Apolipoprotein E4 allele status can increase the risk of progression from mild cognitive impairment to Alzheimer's disease.

Diagnosis

In terms of research diagnostic criteria, there is uncertainty about whether a lumping-together approach to mild cognitive impairment[33] is preferable to a splitting

approach, with various categories of the disorder.[34] Prospective cohort studies are underway to establish whether amnestic and non-amnestic subtypes of mild cognitive impairment (figure)[35] have different prognoses for progression to dementia and which type of dementia they predict[35] and their effect on survival times.[36] It is possible that all progressive dementias have their own predementia states.[37]

The operational definition of amnestic mild cognitive impairment proposed by Petersen (panel)[9] has been used repeatedly in randomised controlled trials, with some variations on the test for delayed recall and cutoff scores to distinguish people with mild cognitive impairment from healthy individuals (table).[16,17,38,39] These apparently minor differences in entry criteria for the level of memory impairment are associated with different rates of progression to Alzheimer's disease, ranging from 5% to 16% per year. Other factors affect the rate of progression, such as the number of people carrying the apolipoprotein E4 allele. It should be noted that these trials applied inclusion and exclusion criteria similar to those proposed by McKhann and colleagues[6] for Alzheimer's disease, with the important exception of the presence of dementia and the size of the cognitive and functional decline.

An international working group on mild cognitive impairment formulated specific recommendations for criteria, including: (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; and (3) activities of daily life are preserved and complex instrumental functions are either intact or minimally impaired.[8] These criteria serve to expand the construct of mild cognitive impairment to involve cognitive domains other than memory and make it a prodrome to multiple types of dementia.

Standard neuropsychological tests have established that poor performance on delayed recall and executive function tests indicate a high risk of progression to dementia,[7,40,41] particularly delayed recall, since this measure was a highly accurate predictor of progression to Alzheimer's disease in longitudinal studies of 2–10 years' duration in clinical samples[42,43] and large epidemiological samples.[44] There is a need for sensitive but user-friendly cognitive tests for clinicians, such as the Montreal cognitive assessment.[45] This test is a useful complement to the mini-mental state examination,[46] which is within the normal range in most patients with mild cognitive impairment. Informant rating scales significantly improve the accuracy of the mini-mental state examination in predicting progression to Alzheimer's disease.[47]

Although cognitive symptoms and tests have been the core features of mild cognitive impairment up to now, there is increasing awareness of a behavioural component, which includes anxiety, depression, irritability, and apathy.[48,49] The presence of behavioural and psychological signs, including depression, predicts a high likelihood of progression to dementia.[50] A semi-structured interview to psychiatric symptoms and use of standardised scales such as the neuropsychiatric inventory[51] have shown an important contribution of behavioural changes to mild cognitive impairment in a clinical trial setting.[39] Depressive symptoms can contribute to mild cognitive impairment and have been shown to modify positive predictive value, specificity, and sensitivity in randomised controlled trials.[52] It is likely that future formulations of the broader definition of mild cognitive impairment will include non-cognitive symptoms that might be important in the prodrome of disorders such as frontotemporal dementia and Lewy body dementia.

Difficulties remain in defining the boundaries between normal ageing and mild cognitive impairment, and between mild cognitive impairment and mild dementia.[53] Many of these distinctions depend on the degree of functional impairment. Findings of epidemiological studies have shown that subtle difficulties in the performance of everyday activities (eg, complex hobbies, finance handling) are common in individuals with mild

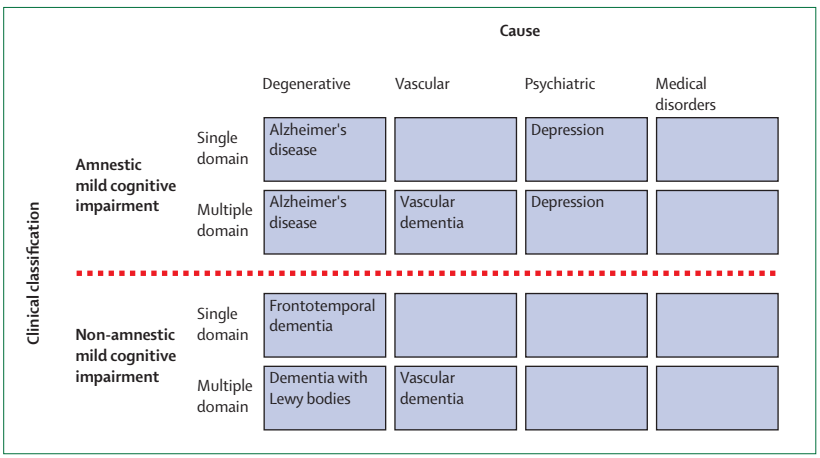

Figure: **Outline of the syndrome of mild cognitive impairment**
Figure shows mild cognitive impairment with predominantly amnestic versus non-amnestic neuropsychological features, potential prodrome to neurodegenerative disorders such as Alzheimer's disease, frontotemporal dementia, Lewy body disease, or caused by vascular cognitive impairment, psychiatric disorders such as depression, or as a prodrome to other medical disorders, including metabolic and nutritional deficiencies, upper airway obstruction, and head trauma. Figure adapted from reference 35.

The **Montreal cognitive assessment** is available at http://www.mocatest.org

	Criteria for impaired performance on delayed recall score
Memory Impairment Study[16,17]	Delayed recall of one paragraph from logical memory II subtest of the Weschler scale-revised, adjusted for age and education (score of 8 or less for 16 years or more of education)
GAL-INT-11 and 18[38]	Delayed recall score of 10 or less on the NYU paragraph recall test
InDDEx Study[39]	Delayed recall score of 9 or less on the NYU paragraph recall test

Table: **Operational diagnostic criteria for amnestic mild cognitive impairment in three large randomised clinical trials**

cognitive impairment 2 years before a diagnosis of dementia,[42] whereas overt difficulties in certain abilities (use of the telephone, finances, transportation, drugs) signal the onset of dementia.[54] The lack of awareness of such impairments in people with mild cognitive impairment has been postulated to be predictive of progression to dementia.[55] Individuals with memory complaints and informants should be asked about performance on hobbies, executive level tasks, and instrumental activities of daily life.[56,57] Mild cognitive impairment is also accompanied by other changes, such as balance and coordination.[58] A structured assessment of functional capacities will become increasingly important in determining the point at which people with mild cognitive impairment progress to dementia. Analysis of data from randomised controlled trials such as the Memory Impairment Study[59] could help in this respect.

Neuroimaging and electrophysiological tests for the workup of mild cognitive impairment could be the same as those used in early dementia. Several methods are sensitive for mild cognitive impairment, including brain imaging with MRI,[60,61] positron emission tomography,[62,63] and quantitative electroencephalography.[64–66] Medial temporal lobe atrophy on magnetic resonance imaging and hypometabolism on fluorodeoxyglucose-positron emission tomography have been recorded in people with mild cognitive impairment compared with cognitively normal individuals,[62,67] and presence of these signs has a high predictive value for progression to dementia.[68,69]

Biomarkers in cerebrospinal fluid under study include total tau, phosphotau epitopes, and the 42 aminoacid form of β amyloid.[70,71] Specific phosphotau epitopes have met criteria for an ideal biological marker candidate, with properties for both classification and early diagnosis.[71–73] Evidence suggests that phosphotau 231 and isoprostane can increase the diagnostic accuracy of conventional cognitive and magnetic resonance assessments in people with mild cognitive impairment.[71] Many of these biomarkers have been selected by the National Institute on Aging biological markers working group[74] as feasible core biomarkers suitable for multicentre longitudinal studies of Alzheimer's disease with special consideration given to mild cognitive impairment. A large study from the Alzheimer's Disease Neuroimaging Initiative has just begun investigating the role of imaging measures and biomarkers in predicting progression to dementia in individuals with mild cognitive impairment.

In summary, research diagnostic criteria are being validated for the different subtypes of mild cognitive impairment, with emphasis on amnestic mild cognitive impairment. Until such validation is available from prospective cohort studies, a pragmatic approach to mild cognitive impairment has been proposed by Gauthier and Touchon[75] to distinguish subtypes in clinical practice, based on the most prominent feature at a given time, from amnestic to dysphoric, vascular, or associated with other medical disorders. It might be time to consider revisions of the international classification of mental and behavioural disorders and of the diagnostic and statistical manual of mental disorders, to include specific diagnostic criteria for mild cognitive impairment or its different subtypes. Furthermore, an update to the NINCDS/ADRDA criteria for Alzheimer's disease[6] should be considered, to include a prodromal or very early stage of Alzheimer's disease that would correspond to amnestic mild cognitive impairment, as defined in the clinical trials described in the next section.

Management

The first wave of clinical trials aimed at symptomatic drug treatment for amnestic mild cognitive impairment over 6 months to 3 years have been largely unsuccessful.[76] Results from the Memory Impairment Study[16] showed no significant differences in the probability of progression from amnestic mild cognitive impairment to Alzheimer's disease in patients allocated vitamin E or donepezil, compared with placebo, during the 3 years of treatment, although significant differences were recorded favouring the donepezil group on various measures during the first 12 months of the study including delay of diagnosis of Alzheimer's disease.[16] Furthermore, there was a prolonged response to donepezil over 24 months in the apolipoprotein E4 carrier subgroup. Potential reasons for the apparent lack of sustained benefit of the cholinesterase inhibitors might be the compensatory upregulation of central cholinergic activity, lack of sensitivity of the cognitive outcomes (ceiling effects), and heterogeneity of patients. If there is benefit from these inhibitors, it seems to be limited and transient.[77] Conversely, randomised controlled trials of cholinesterase inhibitors and other pharmacological drugs are worth pursuing in mild cognitive impairment, possibly targeting populations at high risk of progression to dementia, since there are indications that postponement between mild cognitive impairment and manifest dementia could result in short-term economic benefits of US$5300 per patient per year[78] and advantages for individuals with mild cognitive impairment and their families. It should be noted that resource use and costs attributable to the disorder during the mild cognitive impairment phase are low, and possibilities to detect intervention effects on direct costs are also low during this phase. However, many people with mild cognitive impairment retire from their occupations and other productive activities as the disorder progresses, and economic models should take into consideration productivity losses. Additionally, from clinical experience, it is known that depressive symptoms are common in people with mild cognitive impairment. However, the extent to which these symptoms cause resource use in terms of informal care is not known.

Encouraging results have been reported from uncontrolled studies using cognitive training.[79,80] Large

effect sizes have been noted within the range for healthy elderly people[81] and better than that for patients with Alzheimer's disease.[82] The success of cognitive training seems to be dependent on the level of severity across the range of normal ageing to dementia. These findings in individuals with mild cognitive impairment need to be confirmed in randomised controlled trials.

The management of patients with mild cognitive impairment is currently non-specific: control of vascular risk factors; treatment of concomitant disorders such as depression and hypothyroidism; and phasing out anticholinergic drugs. Many people with mild cognitive impairment are very aware of their difficulties and seek information about the nature of their disorder and their outlook. They are also interested in coping strategies, particularly if they are in demanding occupational settings. Since these patients are at higher risk of dementia and death than usual, they need sensitive counselling about such risks and the current lack of certainty in predicting prognosis. It would not be appropriate to falsely reassure them that they are healthy, since they should have the opportunity to make future plans while fully competent to do so, including advance directives for power of attorney in case of incapacity. A caregiver burden has already been identified for spouses of people with mild cognitive impairment, for which selective preventive interventions to keep psychological wellbeing to a maximum should be considered.[83]

Currently, there is debate about whether the term mild cognitive impairment should be used at all in clinical practice, in view of the heterogeneity of progression to dementia and the possibility of reverting back to normal. Caution should thus be exercised in using this term. Some researchers are attempting to broaden the discussion about mild cognitive impairment to the political, philosophical, and economic implications of anti-ageing drugs.[84] Systematic screening for mild cognitive impairment in asymptomatic elderly people is not recommended because of insufficient data about its usefulness. On the other hand, spontaneous memory complaints from people older than 50 years, particularly if corroborated by an informant, should lead to a medical assessment as per standard clinical practice for individuals suspected of early dementia. Mild cognitive impairment is regarded as a medical diagnosis by some clinicians, as suggested in the American Academy of Neurology practice parameter statement that "patients with a mild cognitive impairment should be recognized and monitored for a cognitive and functional decline due to their increased risk for subsequent dementia",[85] a state of risk considered by other authors, possibly amenable to prevention. However, in view of the variation in specificity with respect to the outcome of amnestic mild cognitive impairment, one must be cautious in presenting a diagnosis such as incipient Alzheimer's disease prematurely.

Prevention

Although no specific disease-modifying treatment has yet been shown to be effective for any of the degenerative dementias, control of risk factors might prove useful. The best evidence available so far is in the control of isolated systolic hypertension.[23] The idea of interventional epidemiology proposed by Ritchie[13] for mild cognitive impairment will probably lead to international randomised controlled trials linking the consortia of investigators interested in the causes and treatment of mild cognitive impairment and dementia (European Alzheimer's disease consortium, Alzheimer's disease cooperative study in the USA, and consortium of Canadian centres for clinical cognitive research).

Clinical continuum of cognitive decline

The advent of current understanding of mild cognitive impairment and the clear findings that the disorder is a frequent precursor of overt dementia raises the question of the antecedents of mild cognitive impairment. Is mild cognitive impairment in general, and the impairment that precedes Alzheimer's disease in particular, one step in a process that has additional clinical antecedents? Support for this view can be extrapolated from findings of neuropathological studies, which show that Alzheimer's disease-related neuropathological findings, including neurofibrillary changes, seem to occur decades before the overt appearance of dementia.[86]

It has been recognised for many years that many healthy older people have subjective complaints of cognitive decline. As noted earlier in this Seminar, the GDS staging procedure differentiates individuals with such symptoms, but who are otherwise free of clinical signs from healthy older people who are free of complaints of impairment. In 1986, a US National Institute of Mental Health workgroup proposed an entity—age-associated memory impairment—to characterise healthy individuals at least 50 years of age with subjective complaints of memory loss and performance on a recent memory test at least 1 SD below the mean established for young adults.[87] A similar entity with somewhat modified specific psychometric and other criteria has been proposed by Levy.[88]

The prognostic relevance of subjective cognitive complaints in older people, without reference to psychometric test data, has been investigated in several studies, most of which have noted relations between subjective complaints and future cognitive decline.[89–92] For example, Reisberg and associates[93] are finding a five-fold greater likelihood of decline to mild cognitive impairment or dementia, over a 7-year mean follow-up interval, in people with subjective complaints compared with similarly aged individuals who are free of subjective complaints of impairment. Wolf and co-workers[94] reported a significant difference in urinary cortisol concentrations between older individuals with and without subjective complaints, perhaps, in part, a marker of concerns of older people about these self-perceived

deficits, since cortisol concentrations are a well-known marker of stress.

As an entity that precedes mild cognitive impairment, studies are presently noting that about 7–8% of otherwise healthy older people with subjective cognitive impairment progress to mild cognitive impairment or overt dementia every year.[93,95] Hence, findings of several longitudinal studies lend support to the belief that mild cognitive impairment, with subtle but manifest clinical signs, is a stage in a clinical process that might be subjectively evident many years earlier. Although, current estimates need to be examined in much greater detail in future studies, it has been suggested that the subjective cognitive impairment stage before mild cognitive impairment could last for about 15 years.[96] Hence, the appearance of mild cognitive impairment seems to be on a clinical continuum that is preceded by subjective cognitive impairment.

Conclusions

The syndrome of mild cognitive impairment as a transition state between normal ageing and dementia has increased awareness that memory complaints in elderly people, particularly when accompanied by subtle cognitive performance difficulties, should be assessed in a systematic way by clinicians. Prospective cohort studies with clinicopathological correlations will help to clarify whether some of the subtypes of mild cognitive impairment are prodromal stages of specific dementias, paving the way for early therapeutic interventions.

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Conflict of interest statement

None of the participants listed works for a pharmacological company as an employee. No drug has been approved for the indication of mild cognitive impairment. H Brodaty is a consultant or speaker for, or has received investigator support from, Eisai, Janssen, Lundbeck, Novartis, Pfizer, Sanofi, and Servier. M de Leon is a consultant to GE Health Care and has received educational grants from Janssen and Forest. H Feldman has received grants from Eisai, Glaxo, Jenssen, Lilly, and Pfizer, and has acted as a consultant or speaker for AstraZeneca, Axonynx, Eisai, Forest, GlaxoSmithKline, Janssen, Lundbeck, Myriad, Novartis, Pfizer, Targacept, Sanofi, and Servier. S Gauthier is a consultant or speaker for GlaxoSmithKline, Hoffman-LaRoche, Janssen, Lundbeck, Merz, Neurochem, Novartis, Pfizer, Sanofi, and Servier. B Reisberg has received grants from Forest, Novartis, and Janssen, and has been a consultant or speaker for Ajinomoto, Amersham, Aventis, Bristol Meyers, Squibb, Glaxo, Janssen, Lundbeck, and Merz. R C Petersen has acted as a consultant for Elan Pharmaceuticals and GE Global Research. P Scheltens has been a consultant or speaker for Eisai, Janssen, Merck, Novartis, and Servier. M C Tierney has received a research grant from Shire Biochem. P J Whitehouse has been a consultant or speaker for AstraZeneca, Bristol Myers Squibb, Cerebrio/Avenir, Forest, Janssen, Sanofi, Takeda, and Pfizer. B Winblad has been a consultant for advisory boards with Janssen, Merz, Lundbeck, Novartis, Pfizer, Sanofi, and Servier. M Zaudig has acted as a consultant to Pfizer.

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