Mild cognitive impairment

Mild cognitive impairment refers to the transitional period between normal cognition and dementia, but is not an extension of normal ageing. Subjects with mild cognitive impairment have subtle but measurable cognitive impairment that is not severe enough to interfere with independent living or fulfil diagnosis criteria of dementia.

Mild cognitive impairment is associated with an increased risk of future dementia, but dementia is not an inevitable outcome in mild cognitive impairment. A significant proportion of subjects with mild cognitive impairment either remain the same or even improve. Mild cognitive impairment has a reported prevalence of approximately 3% of the population over the age of 60 years, but the exact prevalence depends largely on the definition of mild cognitive impairment and the population examined. This review will cover the terminology, definition and diagnostic criteria of mild cognitive impairment. It will also cover the prevalence, subtypes and risk factors associated with conversion to dementia.

Terminology and background

Over the years a variety of terminologies have been used to describe cognitive changes that develop with ageing. Benign senescent forgetfulness was followed by age-associated memory impairment which was proposed in 1986 following a work group by the National Institute of Mental Health (Crook et al, 1986). More recently, the term age-associated cognitive decline was proposed by the International Psychogeriatric Association to describe multiple domain cognitive impairment that is presumed to develop with ageing (Levy, 1994). All these descriptions essentially refer to cognitive impairment as an extension of normal ageing. Mild cognitive impairment, however, is different as it is thought to represent a pathological condition with a considerable risk of future dementia.

Definition of mild cognitive impairment and diagnostic criteria

Mild cognitive impairment is characterized by chronic impairment of one or more cognitive skills, that does not represent a focal syndrome, and where the impairment is not severe enough to be regarded as dementia. Cognitive impairment that is not severe enough to meet criteria for dementia is common, and a number of diagnostic criteria have been proposed. The most widely accepted are those by proposed by Petersen and co-workers (1999), as outlined in *Table 1*. Here, subjects must have objective evidence of cognitive impairment outside what would be expected for their age and level of education. Affected individuals must also have subjective memory loss, without impairment of activities of daily living or fulfilling criteria for dementia.

Many experts in the field believe that the diagnosis of mild cognitive impairment can be made by most clinicians in much the same fashion as making the diagnosis of dementia or Alzheimer's disease. Neuropsychological testing can be very helpful in making the clinical judgment, but it must be emphasized that this is not a neuropsychological diagnosis. That is, there are no 'mild cognitive impairment tests' or cut-off scores that determine the diagnosis; it is a judgment call by the clinician in the same way as one would make the diagnosis of dementia or Alzheimer's disease. Some even argue that the diagnosis of mild cognitive impairment should be included as a diagnostic entity in the DSM-V (*Diagnostic and Statistical Manual* – version V) as it fulfils in many respects the inclusion criteria more adequately than many other conditions currently codified (Petersen and O'Brien, 2006).

Subtypes of mild cognitive impairment

The syndrome subtype may be recognized as early as the initial evaluation. This may include amnestic mild cognitive impairment, characterized by predominant impairment of the memory domain; or non-amnestic mild cognitive impairment, characterized by slight impairment of multiple cognitive domains (multiple-domain mild cognitive impairment); or may correspond to predominant impairment of a cognitive domain other than of memory (single-domain mild cognitive impairment). Examples of single domain non-amnestic mild cognitive impairment include subjects with impaired language function such as dysphasia, isolated apraxia or visuospatial dysfunction.

Table 1. Proposed criteria for mild cognitive impairment

Memory complaint
Normal in activities of daily living
Normal general cognitive function
Abnormal memory function for age
No dementia

From Petersen et al (1999)

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Most research so far has focused on the amnestic type of mild cognitive impairment because of the perceived high likelihood of this type to be a precursor of Alzheimer's disease.

Causes and pathology of mild cognitive impairment

The main interest in mild cognitive impairment is in the fact that it can represent the earliest sign of dementia and therefore allows earlier diagnosis and potentially treatment. However, significant cognitive impairment can also be caused by a variety of other conditions including stroke and other forms of cerebrovascular disease, head injury, depression, the effect of drugs and space-occupying lesions among others (*Table 2*). Very few studies have examined the pathology of mild cognitive impairment. Bennett et al (2005) reported that subjects with mild cognitive impairment who went on to have postmortem examination as part of the Religious Orders Study had an intermediate level of Alzheimer's disease pathology compared to subjects with normal cognition. Furthermore, subjects with mild cognitive impairment were significantly more likely to have cerebral infarction, but Lewy body pathology was only present in a minority of subjects. The same group also reported that Alzheimer's disease pathology can be found in the brains of subjects without dementia or mild cognitive impairment, but who had only a subtle deficit of episodic memory (Bennett et al, 2006). This means that by the time dementia patients start to be symptomatic, as in mild cognitive impairment patients, it is very likely that the brain pathology is already well underway.

Prevalence of mild cognitive impairment

Although the assumption is that mild cognitive impairment precedes dementia, especially Alzheimer's disease, other factors can have an effect on cognitive performance in older subjects including level of education, vascular risk factors, cerebrovascular disease, depression and other psychiatric disease, and the effect of drugs such as anticholinergic medication. A number of studies examined the prevalence of mild cognitive impairment, but these gave a huge variation in prevalence ranging from 1–36%. This considerable difference is related to the methodological differences, in particular the type of population examined, case identification method and, most importantly, diagnostic criteria of mild cognitive impairment.

Table 2. Causes of mild cognitive impairment

Neurodegenerative dementias	Alzheimer's disease
	Dementia with Lewy bodies
	Fronto-temporal dementia
Cerebrovascular disease	Cerebral infarctions
	Haemorrhage
Psychiatric illnesses	Severe depression
	Psychosis
Cerebral space-occupying lesions	
Chronic infections	Syphilis
	Human immunodeficiency virus (HIV)
Drug-induced	Anticholinergic medication
Metabolic	Poorly controlled diabetes
	Hypothyroidism
Head injury	

A number of studies have shown very clearly that the prevalence of mild cognitive impairment varies according to the definition and diagnosis criteria of mild cognitive impairment used. Fisk et al (2003) reported an mild cognitive impairment prevalence of 1% when the Petersen criteria (*Table 1*) were used, but this increased to 3% when the requirement for subjective memory complaint and intact activities of daily living was eliminated. In the Leipzig Longitudinal Study of the Aged (LEILA75+), applying different diagnostic criteria for mild cognitive impairment resulted in a marked variation of prevalence (Busse et al, 2003). The prevalence rate in this study was reported to be 3% when the Petersen criteria were used, but increased to 5% when the requirement for subjective memory loss was dropped. In the same study the prevalence of age-associated cognitive decline and of age-associated cognitive decline-modified was 8.8% and 19.7% respectively.

A study by Ritchie et al (2001), which related mild cognitive impairment to an isolated memory loss, reported a prevalence rate of only 3% in people aged 60 years and over, while Kivipelto et al (2001) included other areas of cognitive functions in the definition of mild cognitive impairment, and recorded a prevalence rate of 6% in people aged 65–79 years. Frisoni et al (2000) defined mild cognitive impairment as one standard deviation outside the mean of age- and education-specific norms on the mini mental state examination (MMSE), and reported a prevalence rate of 15% for their study sample, aged 75–95 years.

The prevalence of mild cognitive impairment also varies according to where the patients are recruited from, for example inpatient hospital setting, outpatient setting or the community, with prevalence being highest in the inpatient group and lowest in the community-based unselected group. In a sample of 794 non-demented patients in general hospitals aged 65–85 years, the prevalence of mild cognitive impairment was 36.1% (Bickel et al, 2006).

Natural history of mild cognitive impairment and future risk of conversion to dementia

There is an increased risk of dementia in subjects with mild cognitive impairment, but dementia is not inevitable. A significant proportion of subjects with mild cognitive impairment do not progress to dementia and even

return to normal cognition on follow up. Gabryelewicz et al (2007) reported that among 105 subjects with mild cognitive impairment eight showed cognitive improvement over a period of 3 years, while 23 developed dementia.

Overall, subjects with mild cognitive impairment develop dementia at a rate of approximately 10–15% per year compared to a rate of 1–2% per year in healthy age-matched controls (Petersen et al, 2001). Some investigators, however, believe that the risk of mild cognitive impairment subjects converting to dementia is at its highest in the first 18 months after the onset of cognitive impairment (Busse et al, 2006). A number of risk factors have been reported to be associated with an increased risk of future dementia and these include an amnestic, rather than non-amnestic type mild cognitive impairment (Aggarwal, et al, 2005b), age (Vesser et al, 2006), apolipoprotein E (APOE) genotype (Tschanz et al, 2006), medial temporal lobe atrophy on computed tomography or magnetic resonance imaging (Korf et al, 2004), functional brain imaging (Chetelat et al, 2003), and CSF levels of tau and beta amyloid (Maruyama et al, 2001; Buerger et al, 2002).

The Cache County Study is a community-based longitudinal study designed to investigate the prevalence and risk factors of dementia in Utah. In this study 46% of subjects with mild cognitive disorder converted to dementia after 3 years, compared to 3.3% of control subjects (Tschanz et al, 2006). The risk of conversion to Alzheimer's disease was particularly high in carriers of the APOE4 alleles.

The Rush Memory and Aging project is a longitudinal community-based clinico-pathological investigation with yearly clinical and neuropsychological evaluation of more than 800 subjects. Among the 221 subjects diagnosed with mild cognitive impairment and followed, 26% developed Alzheimer's disease over a mean of 2.5 years follow up, which is almost seven times the rate in subjects without mild cognitive impairment (Boyle et al, 2006). The study also reported that the subjects with mild cognitive impairment declined cognitively more rapidly each year, compared to normal subjects.

The Religious Order Study is a community-based clinico-pathological study of more than 2000 Catholic nuns, priests and brothers across the US. Enrolled subjects agreed to yearly detailed clinical and psychometric assessment as well as brain donation after death. The study has produced a wealth of information about normal and pathological ageing. The study reported a 30% risk of dementia in subjects with mild cognitive impairment over a period of 4.5 years (Bennett et al, 2002). The risk of mild cognitive impairment subjects converting to dementia was increased in those with early involvement of episodic memory (Aggarwal et al, 2005b), and carriers of APOE4 allele genotype (Aggarwal et al, 2005a). A 10-year memory clinic-based longitudinal study reported that approximately half the patients with mild cognitive impairment developed dementia, and that age strongly influenced the risk of dementia (Visser et al, 2006).

KEY POINTS

- Mild cognitive impairment is a transient condition between normal cognition and early dementia.
- Mild cognitive impairment affects approximately 3% of those above the age of 65 years.
- Dementia is not inevitable in mild cognitive impairment and approximately half of patients either remain the same or improve.
- Alzheimer's disease is the most likely dementia to emerge in mild cognitive impairment and those with amnestic-type mild cognitive impairment are particularly at risk.
- Mild cognitive impairment can result from factors other than neurodegenerative dementia such as cerebrovascular disease, drugs, depression and head injury.
- Certain factors increase the risk of mild cognitive impairment patients converting to dementia, including age, amnestic-type mild cognitive impairment, APOE4 genotype, and medial temporal lobe atrophy on computed tomography or magnetic resonance imaging.

Management of mild cognitive impairment and future directions

The value of early diagnosis of Alzheimer's disease and other dementias will assume a huge importance once neuroprotective therapies to slow down or arrest disease progression become available. Currently there are no neuroprotective treatments that can be offered, but therapies to improve cognitive function in Alzheimer's disease, namely anticholinesterase drugs, are available. The usefulness of anticholinesterase drugs in the context of mild cognitive impairment have been the subject of a number of studies with conflicting findings, but a Cochrane database review concluded that there is currently little evidence to support the use of these drugs in mild cognitive impairment (Birks and Flicker, 2006). If mild cognitive impairment can aid in early diagnosis of dementia this could allow patients to make plans for the future at a time when they are still able to make reasonable judgments.

Future studies are needed to further improve our understanding of mild cognitive impairment so that the entity can be more clearly defined and the outcome more accurately predicted. This will allow us to tell with more confidence which subjects are at greatest risk of developing dementia. **BJHM**

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