Mild Cognitive Impairment: A Clinical Approach

Dr. David LK Dai
MBBS, FRCP, FHKAM (Medicine)
Consultant Geriatrician, Department of Medicine and Therapeutics, Prince of Wales Hospital, Hong Kong

The Clinical Problem

Increasing numbers of elders from 70 years and above will be brought to see the doctor for memory or cognitive impairment of a mild nature for 1-2 years. The clinical questions are "Is my patient suffering from dementia in the earliest stage?"; How do I investigate the patient?"; "Shall I start treatment?"; and "How shall I explain to the patient and the family members who have brought the patient to me?".

The Concept of Mild Cognitive Impairment (MCI)

The concept of MCI is a useful concept which represents a stage of deteriorating cognition overlapping the boundaries between normal memory and dementia. MCI indicates the pre-dementia stage in an affected person. However, the concept is difficult to apply clinically, because cognitive impairment is common in elders and can remain stable or improve with time. Most studies of MCI have included subjects according to the clinical criteria of Petersen of 2001, (i) memory complaint preferably corroborated by an informant, (ii) objective memory impairment for age and education, (iii) preserved general cognition, (iv) preserved activities of daily living, and (v) clinically not meeting the criteria of dementia. Using MMSE in a person with substantial education, the score is 24 or above. These studies show a progression rate of 10-15% into dementia usually referring to Alzheimer's disease (AD). Higher conversion rates are seen in clinically selected samples.

Heterogeneity in the Concept of Mild Cognitive Impairment

Mild cognitive impairment in an older person has been recognised under different descriptions, as benign senescent forgetfulness (Kral, 1962), age-associated memory impairment, AAMI (Crook et al, 1986), age-associated cognitive decline, AACD (levy, 1994), cognitive impairment, no dementia, CIND (Graham et al, 1997) and mild cognitive impairment, MCI. How much the criteria will also include normal persons depend on the specificity of the cognitive function being studied and its reference norm. For example, AAMI will include many normal persons because the memory impairment is compared with young samples; AACD is more specific for indicating the predementia stage because reference is drawn to peer norms, but also includes substantial normal patients because other cognitive domains than memory are included. CIND carries a similar problem of inclusion of impairment in more than one cognitive domain. Petersen narrows down the concept to memory impairment compared to 1.5 standard deviation below peer norms in psychometric tests and coined the term MCI to indicate the predementia stage of Alzheimer's disease where memory (amnestic) is affected in the early stage.

Refinement of Definition to Increase Clinical Relevance

Since emergence, the MCI concept has been criticised to be uncertain, ambiguous, poorly conceptualised and labelling a normal person with a detrimental disease. The latter carries significant emotional, ethical and legal consequences. Gauthier has additionally pointed out the variable prevalence (3-16.8%) and poor efficacy of cholinesterase inhibitors in the treatment of the condition as a clinical predementia state. Petersen argued on the other hand that heterogeneity prompted refinement of the entity and characterisation of the prodromal stage of different types of dementia. The concept also offered an opportunity to treat reversible factors of cognitive impairment, and to provide counselling. MCI indicates advancing the diagnostic threshold to the earlier stage of impairment of dementing illnesses. Hence, Petersen has clarified MCI to focus on a significant change in performance in the person ideally corroborated by an informant, to take into consideration educational factors and other non-memory cognitive domains such as language, executive function and visuo-spatial ability. Petersen considers clinical judgment from the history to remain the mainstay of diagnosis and to recognise the clinical significance of mild cognitive impairment in the person but being still more "normal" than dementia.

Impairment in Non-cognitive and Multiple Domains

While prodromal AD starts with predominantly memory impairment, progression to disease will involve semantic and attentional cognitive domains and subsequently generalised decline. The prodromal stage of non-AD can involve a non-amnestic domain and transition to disease will affect other cognitive domains. Figures 1 and 2 summarise the approach to MCI according to the presentation of impairment in single, multiple and different domains. Overall, the conversion...
rates differ markedly in different subtypes of MCI indicating the varying underlying aetiopathologies. Multiple domains involvement at inception denotes conversion of 30% in 2 years, and a single non-amnestic domain confers a rate of only 4%; non-amnestic multiple domains increases the likelihood of non-AD. Previous stroke and impairment in instrumental activities of daily living increases the risk of progression to dementia in an Italian cohort of CIND and MCI.10

Narrowing Down the Ambiguities with Biomarkers

Clinical history can at best define a group of persons with significant decline in cognitive function in varying domains in the past 1-2 years and will put the client in the high risk category in developing a dementing illness. However the patient and family members expect a more definite diagnosis of possible disease. The accuracy of diagnosis of prodromal disease can be enriched with biomarkers. A full array of such markers are available, but the applicability is constrained by accessibility and cost such as advanced neuroimaging and detailed neuropsychology, invasive nature of the test such as CSF analysis, and overlap of abnormal test results with normal.11

MR volumetry of hippocampal atrophy predicts disease.12 A higher ventricular/brain ratio (VBR) increases progression indicating underlying vascular burden. Different rates of decline in individuals is also related to underlying brain reserve eg education raises brain reserve and MCI may already indicate significant neuropathological burden and may pursue a more rapid decline. A higher VBR in persons with low brain reserve may progress to dementia without an obvious MCI stage. 13

MRSpectroscopy also provides an affordable option in demonstrating metabolic changes in different dementing illnesses. N-acetyl Aspartate (NAA) and myo-inositol (ml) patterns vary in different diseases. A reduction in NAA combined with hippocampal volume can be a surrogate marker of AD progression; ml is raised in AD and FTD in the predementia stage.14

CBF SPECT is useful in characterising non-AD in the prodromal stage. Fig 3 demonstrates hypoperfusion in the left fronto-temporal region in a 57 year old housewife presenting with speech impairment. The CDR (clinical dementia rating) score was 0.5 indicating normal daily functioning compatible with the MCI stage of FTD. She developed sudden emergence of artistic ability which has been reported in about 15% of FTD patients; 15 Fig 4 demonstrates perfusion defects in the right occipital lobe in a 68 year old gentleman with subtle cognitive decline for 2 years; MMSE registered at 26/30 with secondary education. In a delirious episode from urinary retention and infection, the patient developed visual hallucinations and vividly described ants crawling on the hospital walls. Family members reported that the patient had screamed out in his sleep compatible with REM behavioural disorder. CDR on recovery was 0.5 compatible with the MCI stage of DLB.

FDG (Flurodeoxyglucose) PET can provide characteristic perfusion patterns in aiding diagnosis. Direct imaging of amyloid burden with PIB (Pittsburg Compound B) using PET offers a promising tool in characterising amyloid burden in different AD stages and different patterns in non AD.16 A study of small numbers of different diseases showed increased PIB uptake in AD with elevated cortical binding and lesser in DLB; 60% of 9 MCI subjects showed AD pattern but the rest showed normal uptake. In 27 healthy subjects, 22% also showed increased cortical uptake. Increased binding is also seen in APOE €4 carriers. Uptake is absent in the 6 FTD patients.17 A more recent study showed that both FDG and PIB showed high diagnostic accuracy of 94% in differentiating established AD from normal. In classifying MCI, FDG was superior to PIB. Combining the two techniques increases the accuracy of both in classifying MCI.18

CSF tau and amyloid A 42 have been studied as a biomarker. The latter can differentiate AD from non-demented elders with sensitivity and specificity of 90%. MCI shares a similar CSF pattern but with lower sensitivity. The concern is the application of a rather invasive procedure to a person in a still clinically “normal” state. At the moment, CSF markers remain a research tool.

The trend however is to consider MCI as a pathological predementia clinical state and accurate diagnosis needs to be enriched with biomarkers. We await further evidence for the approach to be practised in the clinical setting.

The Importance of Diagnosis of Incipient Dementia

Increased awareness to the true incipient stage of dementia by a clinician will avoid premature diagnosis of dementia and misdiagnosis such as depression. At the same time, false reassurance of normal ageing should also be avoided. An opportunity is provided for comprehensive evaluation of underlying illnesses and medical diseases. Final rapid decline into AD is associated with comorbid medical conditions and optimisation may delay the rapid progression into clinical disease.19 It is important to recognise cardiovascular risks in MCI. HbA1c > 7 increases risk of AD four fold.20 White matter disease is associated with MCI.21 The risk of MCI conversion to dementia is associated with atrial fibrillation and low folate.22 Continued follow up and monitoring of deterioration in the several ensuing years can capture the onset of definite dementing illness and initiation of specific treatment. The incipient stage also offers lead time in characterising possible non AD with advanced neuroimaging and anticipating the behavioural symptoms of the illness, “Mild Behavioral Impairment”. MCI being the subclinical prorome of an underlying severe neurodegenerative diseases, the risk factors for development of MCI and subsequent progression to dementia will necessarily be the same as that for the underlying dementing illness.

Management of MCI

Cholinesterase inhibitors (CHEI) are established treatment agents for AD, DLB and vascular dementia (VaD). A double blind RCT examined the efficacy of donepezil, vitamin E and placebo in preventing
conversion to disease. Donepezil lowered the conversion rate in the first 12 months, the rate of conversion at 3 years remained the same as placebo yielding conversion rate of 16% per year. Vitamin E had no effect as expected. Understanding that MCIa represents the incipient stage of a dementing illness at which stage neuropathological burden has already accumulated to a substantial degree, only a disease modifying regime can have significant effect in reversing or stabilising the disease. CHEI in the treatment of mild and moderate AD has only a symptomatic stabilising effect. A meta-analysis of CHEIs in MCI concluded a modest positive treatment effect with a weighted reduction of risk of progression of 24%, but more than 40% of subjects remained stable during long term follow up; and 97/100 with MCI might have been unnecessarily treated. Moreover, adverse events were encountered in a high proportion of subjects. Upregulation of choline acetyl transferase (ChAT) in the frontal cortex and hippocampus can be an important neurobiochemical mechanism in preventing the clinical transition of MCIa to AD, and too early application of CHEI may dampen down the compensatory pathway. Hence, clinical and physiological data do not seem to recommend CHEI in MCI in the absence of reliable predictors of good response and the relatively small efficacy, but high adverse event rates.

However, the author sees some indications in specific treatment of MCIa in certain group of subjects; these include a rapid decline in cognition on close follow up, significant subjective impairment in a well educated person whose neuropsychological deficits and advanced imaging such as MRS or PET shows deficits compatible with AD pattern; in such a subject, the onset of cognitive decline already indicates significant neuropathological burden and advancement of treatment to the prodromal stage can be considered on an individual basis. Improvement in cognitive function may mean maintenance of independent living and quality of life in the early stage of disease. The real breakthrough in the treatment for MCIa will be disease modifying agents, yet to appear, which should theoretically be applied to the earliest stage of disease.

**Screening for MCI in the Community: NO; for Early Established Dementia: YES**

Screening with simple clinical tools in the general community is not recommended. Such a population will necessarily include a large number of healthy persons with age related impairments. Advanced neuroimaging, detailed neuropsychological evaluation and close clinical follow up and medical treatment should be available to support the persons being identified. It should be noted that once a person is diagnosed with MCI in the clinical sense, legal competence is at stake in matters relating to financial decisions, driving and insurance. The validity of a will made at this stage may also be contested.

However, screening for early clinical dementia is recommended particularly to elder persons above 75 years. They should be comprehensively evaluated with blood tests and simple neuroimaging such as CT brain. At the same time, the clinician should be aware of the incipient but not yet demented MCI stage when the patient is considered more "normal" than demented. Such patients should be monitored for further progression in the ensuing 1-2 years.

**Conclusion**

Mild Cognitive Impairment is a clinical condition indicating the predementia stage in an affected person. Biomarkers such as advanced neuroimaging can enrich and improve the diagnostic accuracy in the subclinical stage. Diagnosis carries important ethical and legal implications. Screening for MCI in the non clinical sense in the general population is not recommended. However, screening for established early dementia in persons over 75 years old is recommended in the clinical setting; and in the process, the clinician should be aware of the preclinical state of the dementing illness, when the person is still more "normal" than dementia. It is in this context that MCI becomes clinically relevant and further evaluation and close monitoring are provided. Specific drug treatment is considered on an individual basis and counselling is to be given. The question now is not what effective treatment is available; but how to accurately diagnose a preclinical disease and when to start specific treatment.
References

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