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GUEST EDITORIAL

Mild cognitive impairment (MCI) twenty years on

Evolution of the concept

Cognitive decline has commonly been considered an inevitable result of brain aging and has been of clinical interest principally because of related difficulties with everyday functioning. Since the 1990s the "normality" of age-related cognitive decline has been called into question, being commonly attributed to a number of underlying disorders. Numerous concepts have been proposed which link subclinical cognitive change to pathological states (mild cognitive disorder, mild neurocognitive disorder, mild cognitive impairment). Of these, mild cognitive impairment (MCI) has become the most popular, driven on the one hand by industrial interests seeking to extend new dementia treatments for a more prevalent subclinical syndrome, and on the other by researchers attempting to identify at-risk populations. MCI has been both criticized for "medicalizing" behavior still within normal limits (Stephan *et al.*, 2008; Moreira *et al.*, 2008) and welcomed in that it suggests cognitive decline with aging may not be inevitable, but rather due to abnormalities which could ultimately be treated. Recently, in both Europe (DuBois *et al.*, 2007) and the USA (Albert *et al.*, 2011), panels of experts have scrutinized the concept of MCI and more broadly the pre-dementia stages of neurodegenerative diseases and offered new research diagnostic criteria. These proposed criteria have highlighted the (potential) value of biomarkers in assisting diagnosis, although some have considered the elevation of biomarkers to this level of importance in diagnosing disease before dementia develops to be premature given both the extent and quality of diagnostic biomarker data currently available (McShane *et al.*, 2011a; 2011b).

First proposed by Flicker *et al.* (1991), MCI was above all a pragmatic concept emerging from the observations of neurologists and psychiatrists that older persons presenting with cognitive complaints mostly went on to develop dementia. Petersen *et al.* (1997) then proposed diagnostic criteria for MCI for research purposes: complaints of defective memory, abnormal memory functioning for age on testing, with normal general cognitive functioning and conserved ability to perform activities of daily living. MCI was initially considered to be a prodrome of dementia; however, "dementia" and "Alzheimer's disease" (AD) were, and still often are, used interchangeably. The application of the concept to general practice and general population samples has subsequently shown cumulative conversion rates to any type of dementia – even after long-term follow-up – to be only around 30%, with high rates of reversion to normal, and many subjects classified as non-MCI subsequently developing dementia (Ritchie *et al.*, 2001; Moreira *et al.*, 2008; Mitchell and Shiri-Feshki, 2009). This calls into question the status of MCI as a dementia prodrome. Subsequently, the concept has rather confusingly come to represent not only early AD, but early forms of all dementias, and even cognitive impairment due to any cause.

If the overall concept of a state mid-way between normal cognitive functioning and dementia was applauded for its therapeutic potential, from the outset it has been beleaguered by the failure of its operational criteria. The following are the main problems:

Which cognitive domains are implicated?

MCI initially referred to memory deficits only; however, while clinically it has been observed that an isolated memory disorder may exist, it is rare, and the conclusion of isolated memory impairment has more often been the result of inadequate testing of other areas of cognition (Petersen *et al.*, 1999; Richards *et al.*, 1999). The cognitive tests used to assess MCI are unlikely to be able to detect this degree of specificity; so-called memory tests, for example, also involve attentional and verbal processing skills. Different tests are observed to give different results, with the common conclusion being that the measures are inadequate, rather than that the concept is too vague to operationalize.

What is impairment?

Although referring to decline, MCI is assessed at one point in time, with the level of functioning being considered to be "beyond that expected for both age and education level" (Petersen *et al.*, 1997). However, "beyond" has been set with little empirical justification at 1.5–2 standard deviations below highly variable comparison groups, even though the cognitive tests used tend to produce highly skewed distributions so that standard deviations are inappropriate. An

alternative approach has been to define impairment as early-stage dementia by reference to dementia scale scores (Zaudig 1992; Kluger *et al.,* 1997) thus conceptually permitting the syndrome to drift between a non-specific form of poor memory performance and early dementia.

Absence of functional loss as a diagnostic criterion

MCI is defined as a cognitive impairment identified by testing in the absence of functional impairment, which, given that psychometric tests are themselves essentially behavioral tasks, is incoherent. Numerous studies have now shown difficulties in everyday functioning to be a feature of MCI, and associated furthermore with MCI biomarkers (Ritchie *et al.*, 2001; 2010; Touchon and Ritchie, 1999; Aretouli and Brandt, 2010; Okonkwo *et al.*, 2010a; 2010b).

Is MCI a prodrome of all dementias?

Validation studies of MCI make reference to the risk of developing Alzheimer's dementia only, Alzheimer's and vascular dementia, or all dementias, while population studies often refer to cognitive decline due to all causes (see the review by Mariani *et al.,* 2007) leading to high variability across studies in prevalence estimates and associated risk factors. Retrospective validation of the concept has been impossible in the absence of a clear definition of the dementias for which MCI is a prodrome.

The Chicago consensus conference of 2001 (Petersen *et al.,* 2001), which aimed to address some of these issues, concluded that MCI is not normal aging, and is a disorder likely to progress to Alzheimer's dementia or another form of dementia or improve. MCI subtypes (amnestic, non-amnestic, multiple and single cognitive domains) were also proposed. While widening the cognitive spectrum, no solution was proposed, however, to the problems of standardization of measurement, definition of impairment or specification of control groups. While the question of functional loss was raised (both clinical and population studies having observed it to be an early feature of prodromal dementia; Aretouli and Brandt, 2010), the definition of MCI maintained the notion that it did not significantly compromise everyday activity. The notion that MCI could also improve has added to the confusion as to which clinical end-points MCI is referring.

Current status

Despite inadequacies and ambiguities in the operational criteria, which has given rise to considerable variability in prevalence estimates (1%–29%; Ritchie, 2004), research on MCI has flourished with 11,659 publications being reported by PubMed at the time of writing. The main focus in recent years has been on establishing the prognostic value of MCI, and extending cognitive criteria to include other prodromal indicators. Research into the proposed MCI subtypes has shown two broad subtypes to be useful: amnestic MCI and non-amnestic MCI (in which memory is less impaired than other cognitive functions). Amnestic MCI is most closely associated with Alzheimer's dementia, whereas non-amnestic MCI is more heterogeneous in its associations which include vascular dementia, frontotemporal dementia and dementia with Lewy bodies (Mariani *et al.*, 2007). While standardized cognitive measures are still lacking that differentiate these subtypes, the distinction appears to have prognostic utility. Incidence studies show a narrower range of estimates in non-amnestic MCI (28–36.3 per 1000 person years) than for amnestic MCI (9.9–40.6 per 1000 person years) suggesting that there may be greater agreement in the definition of the former (Luck *et al.*, 2010).

Prospective studies of the evolution of MCI across time have generally brought increased scientific rigor to the definition of cognitive decline, as well as extending criteria to non-cognitive features ranging from genotypes to radiological findings and cerebrospinal fluid (CSF) biomarkers. As cognitive tests alone have rarely been able to achieve better than 70% sensitivity and specificity (Modrego, 2006) in identifying MCI subjects developing dementia, the addition of supplementary indicators – notably ApoE genotype, neuropsychiatric symptoms, history of stroke and diabetes, increasing difficulty with activities of everyday living, hippocampal or enterorhinal atrophy on MRI – significantly raise predictive values, further suggesting that risk factors for MCI conversion may be gender specific, with vascular risk factors being more predictive for men and neuropsychiatric symptoms for women (Modrego, 2006; Artero *et al.*, 2008; Ritchie *et al.,* 2010). More recently, CSF biomarkers have been examined as potential criteria for MCI, notably, low levels of $A\beta_{42}$, and/ or high tau protein and an epitope of tau protein (P231). Work has been initiated by the Cochrane Collaboration to provide clear estimates of the diagnostic accuracy of these (and other) tests for neurodegenerative disease in people with early cognitive impairment (Mason *et al.,* 2010). This

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scrutiny of the evidence base will provide valuable information for testing currently proposed MCI criteria and influence future attempts at modifying these when necessary.

The main clinical justification for the development of the concept has been the possibility of early-stage drug trials for AD; however, despite numerous trials to date targeting various mechanisms of action (acetylcholinesterase inhibitors, antioxidants, anti-inflammatories and nootropics), neither symptomatic nor disease progression trials in MCI have demonstrated either symptom reduction or delays in longer-term disease progression (Jelic *et al.*, 2006; Farlow, 2009). Consequently we do not know whether there is lack of efficacy or simply inadequacies in MCI case identification, with the tantalizing possibility that the treatments may have been effective in a more homogenous subgroup. Insensitive cognitive measures or too slow disease progression to capture change using clinical markers may have also led to the negative study results to date.

The future of MCI

While MCI does not meet the necessary validation criteria for a formal nosological entity (Ritchie *et al.*, 2001), and it has often been suggested that the concept be abandoned, it has, however, been widely adopted by clinicians and has led to considerable useful research on the prodromal features of dementia. It has also become an attractive target for both symptomatic and disease progression therapies. While it does not constitute a valid diagnostic entity, it is a useful label to describe persons who may benefit from early drug intervention for AD. While MCI publications continue to proliferate, it is interesting to note the very large number of articles which terminate with "better criteria are clearly required". If MCI is to acquire credibility as an early target for drug development, then a number of issues must be addressed.

- A universal definition of MCI is required which is distinct from operational criteria for case-identification for research. Given that the majority of research has taken AD as the clinical end-point of MCI, and it is the underlying AD pathology which is currently the target of early intervention, it would greatly clarify conceptual issues to simply define MCI as pre-clinical AD, characterized by cognitive complaints with functional consequences which cannot be attributed to other disease states, accompanied by changes identified by imaging and proteomic techniques.
- Unambiguous case-identification criteria are needed to permit cohort comparisons and drug trials. As the principal aim will be clinical intervention including risk modification strategies, high specificity is essential in terms of both ethical considerations and for demonstration of drug effects. Multi-site studies currently suggest these criteria should be subjective cognitive complaints (the subject reports cognitive loss and is also worried about it) with the presence of an ApoE $\varepsilon 4$ allele, a high Tau :Aβ_{42} ratio in CSF and increases in ventricular volume (Mattisson *et al.*, 2009; Visser *et al.*, 2009; Petersen, 2009) being the current front runners for biomarker support for the diagnosis.
- Standardized measurement of change across time is required which should include the designation of cross-culturally applicable cognitive measures. The problem here is less which cognitive tests should be used, but rather the associated metric problem of defining dysfunction. This is likely to be best clarified by international use of a small number of standardized tests, permitting the construction of a large psychometric database which may indicate rates of change across time. Associated measures of activity loss (taking into account both very high and very low levels of premorbid functioning), changes in neuropsychiatric symptoms (Aretouli and Brandt, 2010), volumetric changes on MRI and possibly Aβ deposition in the brain (though cost and availability currently limits the use of this as a test) all currently appear to constitute valid measures of change.

However, even if these problems were satisfactorily resolved the question remains as to whether cognition should remain the central feature of what is essentially pre-clinical AD. No matter how the cognitive deficit is described, the concept has poor predictive validity for dementia (Matthews *et al.*, 2008). Performance results are eagerly awaited for the new MCI criteria recently proposed by the National Institute on Aging workgroup led by Marilyn Albert and incorporating putative biomarkers (Albert *et al.*, 2011) as convincing evidence indicates that neuropathology and neuronal loss are observable a decade before its manifestation as cognitive decline (Morris and Price, 2001). We may in time thus have to admit that many elderly persons are likely to have AD without dementia for many years, which might nonetheless be treatable. With better definition of the disease state, there is also the intriguing possibility that a proportion of individuals may have a very slowly progressing form of AD that will never manifest as dementia. Tying definitions of pre-clinical AD to cognition may thus hamper the development of more specific neuropathologically-based criteria and prevent trials of therapeutic intervention procedures at pre-dementia stages when they may arguably be more effective. This would, however, require the development of economically viable

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screening methods to detect these pre-clinical cases in the absence of a cognitive complaint.

Over the past 20 years we have been using, both in clinical and research settings, definitions of dementia and MCI based exclusively on a clinical phenotype. From this we have attempted to define an underlying pathology and etiology in the genesis of the symptom profiles. As imaging modalities have improved and we understand more about the expression of neuropathology through CSF and plasma markers, we are presented with the opportunity to pause, and move towards more specific criteria for pre-manifest dementias of various types. MCI needs to mature further and in the future will be expected to adopt coincident biological and non-cognitive clinical symptoms as part of case definition which should lead to more specific and meaningful nomenclature. This priority given to biomarkers is reflected in the new proposals (DuBois *et al.,* 2007; Albert *et al.*, 2011), though the true accuracy of such tests is not yet known and may be less than we all desperately hope.

Summary

MCI has been a useful concept in psychiatry, geriatric medicine and neurology in describing cognitive complaints occurring midway between normal cognitive functioning and dementia. However, it lacks an unambiguous and operational definition and there remains uncertainty as to whether it refers to cognitive difficulties due to any cause or constitutes a prodrome of AD. Moreover we might question whether by focusing on cognitive complaints we are overlooking even earlier signs of neuropathology. In the light of these uncertainties, the clinician should presently keep the concept of MCI at arm's length in diagnostic practice while researchers continue to explore its core features and predictive value.

Conflict of interest

None.

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