

The Prognosis of Mild Cognitive Impairment - Is it Better than Expected?



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There is much misinformation about the natural history of people with subjective memory complaints (SMC) who do or do not have objective evidence of cognitive decline. The combination of the two, where insufficient to meet criteria for dementia, is essentially mild cognitive impairment or MCI (Table 1).¹ From these criteria it is evident that MCI is not a diagnosis based on specific cognitive tests, neuroimaging or neuropathology but is a descriptive syndrome of convenience likely to represent many possible underlying causes. Yet MCI is still important and common, more common than dementia itself. For example in a primary care sample of 3,327 individuals aged 75+ the prevalence of MCI was 15.4% to 25.2% depending on definition used.²

The main role of MCI has been its ability to predict later dementia as it has been assumed (perhaps wrongly) that most with MCI are not functionally impaired. Many authors have suggested that MCI is an inescapable intermediate stage between normal ageing and dementia.³ This is because numerous short term studies have generated a view that the annual conversion rate (ACR) averages 10 to 15%⁴ and logically if this rate held true in a linear fashion then within 10 years of diagnosis all surviving MCI sufferers would have developed dementia (cumulative conversion rate CCR = 100%). However, most very large studies dispute this. In The Three Cities community study, which followed 2882 individuals with MCI for four years only, 6.6% progressed to dementia.⁵ In a 10 year community study Ganguli and colleagues found a low ACR of only 2.75%.⁶ Even in the multicentre memory clinic-based Descripa study the CCR was only 29.7% after three years.⁷ What might explain this discrepancy in risk? It is most likely due to sampling effects. Thus where individuals with definite memory

complaints (and other risk factors) seek help from specialist centres there is indeed a typical 10% ACR, according to a recent meta-analysis (95% CI 6.3% to 13.4%).⁸ However, if data are limited to the longest studies lasting at least 5 years (including six long term clinical studies in hospital settings and nine community studies), the mean ACR to dementia is 4.2% (95% CI 3.9% to 4.6%) and the CCR 31.4%. Risk is appreciably lower outside of hospital settings and for those not spontaneously reporting SMC. Remarkably, the ACR also diminishes according to the length of follow-up suggesting a bias in shorter studies from recruitment of individuals at highest risk.⁹

For the clinician the take home message is that MCI has low sensitivity but high specificity which means a modest positive predictive value for predicting dementia especially when the prevalence is low but conversely high negative predictive value. For example, in the large and clinically representative Cache County study, sensitivity (Se) was 34% and specificity (Sp) 98% for prediction of later decline (Table 2).¹⁰ In the previously mentioned meta-analysis of 41 studies, the predictive power of MCI averaged 32.3% for those with Mayo clinic defined MCI (that is MCI with SMC) and 24.1% for those with non-Mayo criteria.⁸ To increase accuracy additional risk factors must be measured. For example in several countries CSF is routinely sampled and CSF phosphorylated tau appears to be a promising biomarker. In a new meta-analysis soon to be reported, p-tau was able to separate MCI from healthy individuals with a Se of 79.6% and Sp of 83.9% (PPV 85.9%, NPV 76.9%).¹¹ Of even more interest, p-tau was reasonably successful in predicting progression to dementia in MCI (separating progressive from stable MCI) with a Se of 81.1%, a Sp 65.3%, a PPV 63.0% and a NPV of 83.0% and thus showing

Table 1: Consensus Criteria for MCI from Portet et al 2006

A. Moderate cognitive deficits, short of dementia
B. Self-reported and/or informant reported cognitive complaints
C. Impairment on objective / clinical cognitive tests
D. Preserved basic activities of daily living and minimal impairment in complex instrumental functions

Table 2. Predictive Accuracy of MCI from Cache County

Cache County Results	Dementia	Non-Dementia	Predictive Value
MCI	55	65	PPV 45.8%
Healthy Elderly	104	3042	NPV 96.7%
	Se 34%	Sp 97.9%	

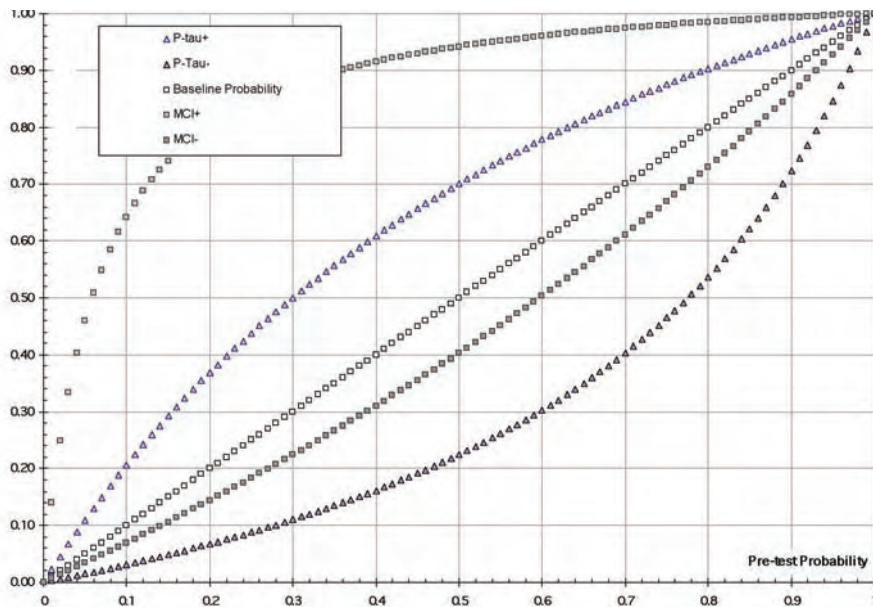


Figure 1. Bayesian Pre-Post Test Probabilities of Dementia; MCI Status vs P-tau Status.

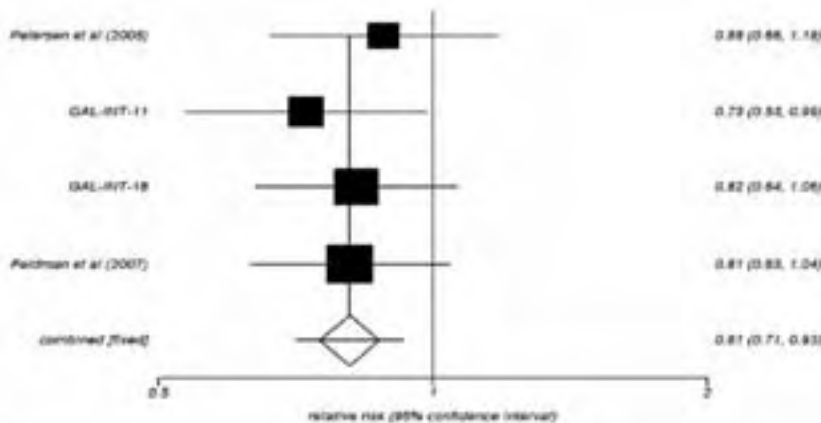


Figure 2. Relative risk of Progression of MCI, Acetylcholinesterase inhibitors vs Placebo.

reasonable value as a screening (or “rule-out”) test. The predictive abilities of MCI alone vs P-tau alone for predicting dementia are plotted in Figure 1. Unfortunately no single risk factor appears sufficient for wholly accurate prediction and a complex panel (such as age + neuropsychological status + function + ApoE + MRI + CSF p-tau + vascular risk) may be required akin to the predictors in cardiovascular settings.

From the patient’s perspective the take home message is that MCI is not an inescapable condition that is always a prodrome of dementia. In the large AD Anti-inflammatory Prevention Trial of 2528 individuals who developed incident dementia over 3 years, only 63% had a prodromal phase of MCI or a related condition.¹² Non-degenerative, potentially treatable causes of cognitive decline are found in 10-30% of people with MCI.¹³ Equally importantly, many people do not deteriorate. Wolf and colleagues (1998) demonstrated that over 3 years 20% of MCI sufferers had recovered and an additional 60% neither improved nor deteriorated.¹⁴ Later

Ganguli et al (2004) also found that, of those with MCI at baseline, 55% no longer met criteria for either MCI or dementia after 6 years of follow-up,⁶ and similarly in the Three Cities Study over four years 56.5% of those with MCI remained stable and 37% actually improved.⁵

Finally, let’s address the question of whether treatment alters the progression of the condition. Most research has been conducted on the acetylcholinesterase inhibitors but new data is emerging on non-pharmacological strategies. The first meta-analysis of three published and five unpublished trials (three on donepezil, two on rivastigmine, and three on galantamine) did not find significant differences compared with placebo groups although analysis was incomplete.¹⁵ Our own re-analysis of the four largest studies involving 1701 individuals (one donepezil, one rivastigmine, and two galantamine) does indeed show a reduced risk of progression in the short term (RR 0.81; 95% CI 0.71-0.93) for those taking an acetylcholinesterase inhibitor which is statistically significant (Figure 2) but really requires fur-

ther confirmation from much longer trials which are of course expensive to complete.

In conclusion, only recently has sufficient data accrued to say with confidence that MCI is not a uniform prodromal condition but rather a collection of disorders united by a propensity towards modest memory (and to a lesser extent non-memory) cognitive difficulties. Surprisingly, most individuals with MCI do not develop dementia within the first 10 years although a caveat is that no studies have yet to exceed that period. A substantial minority remain stable for some years and a significant proportion actually improve which means we may need to moderate what we tell individuals and families with MCI and related conditions. ♦

REFERENCES

1. Portet F, Ousset PJ, Visser PJ, Frisoni GB, Nobili F, Scheltens P, Vellas B, Touchon J. *Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure.* Journal Of Neurology Neurosurgery And Psychiatry 2006;77(6):714-18.
2. Luck T, Riedel-Heller SG, Hanna Kadszkievicz et al. *Mild Cognitive Impairment in General Practice: Age-Specific Prevalence and Correlate Results from the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe).* Dement Geriatr Cogn Disord 2007;24:307-16.
3. Petersen RC, Doody R, Kurz A, et al. *Current concepts in mild cognitive impairment.* Arch Neurol 2001;58:1985-92.
4. Bruscoli M, Lovestone S. Is MCI really just early dementia? A systematic review of conversion studies. *International Psychogeriatrics* 2004;16(2):129-40.
5. Artero S, Ancelin M-L, Portet F, et al. *Risk profiles for mild cognitive impairments and progression to dementia are gender specific.* J Neurol Neurosurg Psychiatry. 2008;79(9):979-84.
6. Ganguli M, Dodge HH, Shen V, DeKosky ST. *Mild cognitive impairment, amnesic type An epidemiologic study.* Neurology 2004;63:115-21.
7. Visser PJ, Verhey FRJ et al. *Development of Screening Guidelines and Clinical Criteria for Predementia Alzheimer’s Disease.* The DESCRIPA Study. *Neuroepidemiology* 2008;30:254-65.
8. Mitchell AJ, Shiri-Feshki M. *Rate of progression of mild cognitive impairment to dementia – meta-analysis of 41 robust inception cohort studies.* Acta Psychiatr Scand 2009;119(4):252-65.
9. A J Mitchell, M Shiri-Feshki. *Temporal trends in the long term risk of progression of mild cognitive impairment: a pooled analysis.* Journal of Neurology, Neurosurgery, and Psychiatry 2008;79:1386-91.
10. Tszchanz JT, Welsh-Bohmer KA, Lyketsos CG et al. *Conversion to dementia from mild cognitive disorder: The Cache County Study.* Neurology 2006;67:229-34.
11. Mitchell AJ. *CSF Phosphorylated Tau in the Diagnosis and Prognosis of Mild Cognitive Impairment and Alzheimer’s Disease – A Meta-analysis of 51 Studies.* JNNP Online first May 2009.
12. Breitner JCS for the ADAPT Research Group. *Onset of Alzheimer’s dementia occurs commonly without prior cognitive impairment.* Results from ADAPT. Chicago 02-01-02 2008.
13. Jicha GA, Abner E, Schmitt FA et al. *Clinical features of mild cognitive impairment differ in the research and tertiary clinic settings.* Dementia and Geriatric Cognitive Disorders 2008;26(2):187-92.
14. Wolf H, Grunwald M, Ecke GM, et al. *The prognosis of mild cognitive impairment in the elderly.* J Neural Transm Suppl 1998;54: 31-50.
15. Roberto Raschetti R, Albanese E, Vanacore N, Maggini M. *Cholinesterase Inhibitors in Mild Cognitive Impairment: A Systematic Review of Randomised Trials.* PLOS medicine November 2007;4(11):e338.