Journal of the Neurological Sciences 369 (2016) 57–62

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review article

Does mild cognitive impairment always lead to dementia? A review

Seema Y. Pandya Ph.D. [a,b,*], Matthew A. Clem M.Ed. [a], Lynette M. Silva Ph.D. [a], Fu L. Woon Ph.D. [a,c]

[a] Department of Psychiatry, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, United States
[b] Department of Clinical Health and Psychology, University of Florida, 1600 SW Archer Road, Gainesville, FL 32610, United States
[c] Seton Brain & Spine Institute Neurology, University of Texas at Austin-Dell Medical School, 1501 Red River Street, Austin, TX 78712, United States

ARTICLE INFO

Article history:
Received 23 August 2015
Received in revised form 24 July 2016
Accepted 25 July 2016
Available online 26 July 2016

Keywords:
Mild cognitive impairment
Alzheimer's disease
Dementia
Reversion
Stability
Neuropsychology

ABSTRACT

Mild cognitive impairment (MCI) has often been studied in its association with dementia, yet higher rates of reversion to normal cognition than progression to dementia suggest that MCI does not necessarily lead to dementia. Compared to the numerous studies on MCI progression, relatively few have examined reversion. This paper highlights the current literature on characteristics and predictive factors of MCI reversion, along with an overview of studies on MCI patients who remain diagnostically stable (i.e., MCI stability). Of the available studies, predictors of reversion have been noted in areas of cognitive/global functioning, demographic/genetic/biomarker data, and personality/lifestyle factors. However, there is a need for increased study of MCI reversion, considering that patients in this group can fluctuate between different trajectories of MCI (e.g., normal cognition back to MCI or even progression to dementia) within a given follow-up time period. Further examination of reversion via a longitudinal, multifactorial approach would better inform clinicians regarding the likelihood of reversion amongst MCI patients and subsequently modify treatment methods accordingly. Furthermore, researchers would have greater power in detecting treatment effects in their clinical intervention studies of early dementia by improving selection criteria to exclude MCI participants who are more likely to revert and remain cognitively normal than progress to a dementia.

Contents

1. Introduction . . . 57
2. MCI reversion incidence/prevalence rates . . . 58
3. Predictors of MCI reversion to normal cognitive function . . . 58
4. MCI stability prevalence/incident rates . . . 59
5. Predictors of MCI stability . . . 59
6. MCI trajectories: beyond MCI stability and MCI reversion . . . 60
7. MCI trajectories: implications . . . 60
8. Conclusions . . . 60
Acknowledgments . . . 60
References . . . 60

1. Introduction

Mild cognitive impairment (MCI) refers to a transitional state between "normal aging" and dementia [10,29]. MCI has been receiving much attention in research for its associated risk for dementia, particularly Alzheimer's disease (AD) [4–7,9,12,14–16,24,30,37,40,42,44,47]. A meta-analysis of 41 MCI studies, using Mayo Clinic criteria [32,34], identified the annual progression rate to dementia from MCI as 10% in clinical settings (8% of the entire sample progressed to AD) and 5% in community settings (7% of the entire sample progressed to AD) [26], suggesting that the annual MCI progression rate is low (5–10%). More importantly, these data clearly suggest that a large proportion of MCI patients do not progress to dementia and may revert to normal

* Corresponding author at: 1600 SW Archer Road, Room G042-2, Gainesville, FL 32611, United States.
E-mail addresses: seemapandyaphd@gmail.com (S.Y. Pandya), Matthew.Clem@UTSouthwestern.edu (M.A. Clem), Lynette.Silva@UTSouthwestern.edu (L.M. Silva), Martin.Woon@UTSouthwestern.edu (F.L. Woon).

http://dx.doi.org/10.1016/j.jns.2016.07.055
0022-510X/

cognition. Surprisingly, few studies have examined the characteristics of MCI patients who follow this trajectory, and the available studies constitute only a small fraction of those on progression to dementia from MCI. Further, no review to date has fully integrated the findings of predictors of MCI reversion. Thus, the main purpose of this article is to examine the characteristics and/or predictive factors of MCI reversion. Additionally, we review the few but intriguing studies that evaluate the characteristics and/or predictors of patients with MCI who remain diagnostically stable over time. Articles for this review were selected from databases of Medline, Web of Science, Scopus, Embase, PsycINFO, and PubMed, using keywords "dementia," "Alzheimer's disease," "mild cognitive impairment," "pre-MCI," "reversion," "normal cognition," "aging," "course of illness," and "recovery."

2. MCI reversion incidence/prevalence rates

To date, several studies have estimated the incidence rate of MCI reversion. We will focus on findings of incidence/prevalence rates of MCI reversion from community-based, rather than clinic/referral-based, studies to minimize subject selection bias and a spuriously high MCI prevalence rate often inherent in the latter. It is also important to consider that incidence rate of MCI reversion can vary depending on the MCI criteria used in the study. For example, the MCI criteria from the Mayo Clinic (revised) [29], International Working Group (IWG) [46], National Institute on Aging-Alzheimer's Association (NIA-AA) [1], Alzheimer's Disease Neuroimaging Initiative (ADNI) [31], and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; Mild Neurocognitive Disorder, MNCD) [2], share the following basic definitions of MCI: 1) self-and/or informant reported cognitive decline; 2) impairment in at least one cognitive domain; 3) no diagnosis of dementia; and 4) relatively preserved daily functioning. These basic definitions (i.e., criteria) of MCI are further described in Tables 1 and 2, along with its four subtypes of amnestic single/multiple domain and nonamnestic single/multiple domain. Notably, sources of MCI criteria differ slightly in the elements of those definitions, including types of cognitive assessments and respective cut-off scores used to determine impairment. Not all of the MCI criteria referenced above specify the measures used to assess cognitive function, let alone provide standardized cut-off levels. Specifically, only the DSM-5 provides a general cut-off level of 1.0 to 2.0 standard deviations below the mean for cognitive performance in various domains of functioning to characterize impaired cognition. Such differences between these criteria can subsequently affect the incident MCI reversion rate.

Overall, available studies have noted that the incidence rate of MCI reversion in various global regions (e.g., France, the United States, Italy, Australia, and Korea) ranged from 30% to 50% (versus 4% to 40% MCI progression rate) with two- to five-year follow-up [3,18,25,35,36,38]. Also, another study followed community-dwelling adults up to 10 years and noted a reversion rate of up to 55% for those diagnosed with amnestic MCI subtype at baseline [11]. Further, the annual reversion rate from MCI to normal cognition was substantially higher (20%) than the annual progression rate from MCI to dementia (6%) in a study spanning between 1992 and 2009 [13]. Similarly, prevalent and incident MCI reversion cases were higher (175 per 1000 person-years) than MCI progression cases (71.3 per 1000 person-years) [36].

The findings across the aforementioned studies suggested that a larger proportion of MCI individuals reverted to normal cognition, despite heterogeneous methodology (e.g., varying definitions/classifications of MCI used, types of cohort studies, duration of follow-up, cognitive measures/impairment cut-off scores, demographic characteristics, and geographical regions). Also, the incidence/prevalence rates of reversion were consistently higher than those of progression, raising the question as to whether clinicians and researchers should view MCI as a "benign" entity, a comparatively high-risk condition for incident dementia ("malign"), or both. Additionally, some researchers may be biased when assigning the category of reversion depending on whether they were blinded from the patient's previous diagnosis of MCI. Thus, if they were not blinded, then they may be less inclined to assign the category of reversion to the patient. Further study to assess these questions can have important implications for MCI patients (and their families), treatment (e.g., randomized clinical trials), research, and/or social policies.

Table 1
Mild cognitive impairment diagnostic criteria.

- Cognitive complaint by subject or informant
- Notable decline in cognition
- Cognitive deficits not normal for subject's age
- Normal or near-normal functional activities
- Cognitive and functional difficulties not severe enough to yield diagnosis of dementia

Petersen and Morris [33].

Table 2
Mild cognitive impairment subtypes.

	Impairment observed in the following cognitive domains:
Amnestic single domain	Memory only
Amnestic multiple domain	Memory plus ≥1 of the following: • Language • Attention • Executive function • Visuospatial function • Processing speed
Nonamnestic single domain	One of the following: • Language, • Attention, • Executive function, • Visuospatial function, or • Processing speed
Nonamnestic multiple domain	>1 non-memory domains

Petersen and Morris [33].

3. Predictors of MCI reversion to normal cognitive function

Despite the relatively high rates of MCI reversion, significantly fewer studies have characterized MCI patients who follow this trajectory compared to studies of MCI progression. The first comprehensive MCI reversion study [22], using data from the National Alzheimer's Coordinating Center and revised MCI criteria by Petersen and Morris [33], found higher Mini Mental State Exam (MMSE) scores, lower Clinical Dementia Rating-Sum of Boxes (CDR-SOB) and Functional Assessment Questionnaire (FAQ) scores, absence of APOE ε4 allele, and nonamnestic single-domain subtype at baseline visit to be predictive of reversion compared to "non-reverters" (defined as those who continued to have a diagnosis of MCI or progressed to a dementia) at one-year follow-up. Additionally, younger individuals with neither self-reported nor clinician-reported decline in the memory domain at baseline showed an increased likelihood of reversion. Notably, the study did not specify the non-memory domain(s) in which these individuals had self-reported or clinician-reported (or even informant-reported) complaints. It should also be noted that reverters and those meeting criteria for *Impaired/Not MCI*