Grumpy Old Men (and Women): Mere Hassle or Meaningful Clinical Evidence?

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The discovery of a prodromal or transitional state between normal aging and dementia has generated a great deal of interest. Mild cognitive impairment (MCI) describes cognitive impairment in older individuals that is not of sufficient severity for a diagnosis of dementia. Individuals with MCI have impairments in memory or other cognitive functions that are usually noticeable to those around them. While their performance on memory and cognitive tests is below what is expected for age and education, functional abilities are generally preserved.[1,2]

It is useful to characterize MCI further for both practical and theoretical purposes. Not everyone progresses to greater impairment, and not all who do progress go toward the same condition. This distinction is important and may have implications regarding critical nuances in studying and interpreting these transitional states and possible future treatment interventions.

Various MCI descriptive subtypes have been identified and fall mainly into 2 categories: amnestic MCI, in which the patient demonstrates deficits specifically related to progressive or static memory problems, and non-amnestic MCI, in which there are multiple cognitive deficits not including those related to memory.[3]

The term *neuropsychiatric symptoms* (NPS) describes behavioral or mood disturbances such as agitation, delusions, hallucinations, depression, and apathy. These are commonly found among patients with dementia and compound the patients' disability as well as the burden experienced by their caregivers.[4] Neuropsychiatric symptoms have not been part of the defining diagnostic criteria of MCI, and their characterization and importance in the presentation of MCI and potential conversion to dementia are just being established. Several studies have shown that NPS are common and highly morbid in patients with MCI and are associated with greater impairment in global, cognitive, and functional measures.[4–7] Subjects progressing to dementia have a higher prevalence of psychopathology than subjects who remain stable or improve, and thus, NPS appear to be a predictor of progression to dementia alongside other established factors such as APOE-ε4 carrier status, features of memory function, and MRI volumetric measurements of hippocampal formation.[8] This finding raises questions as to the pathophysiology of NPS, which are likely consequences of damage to the brain from underlying brain disease.

As discussed in a recent review article by Apostolova and Cummings,[9] the utility of NPS in the diagnosis, prognosis, and epidemiologic study of MCI should become clearer with large prospective longitudinal studies. In this month's Focus on Alzheimer's Disease and Related Disorders section, Taragano and colleagues[10] describe such a study. Over the course of 5 years, they followed and carefully evaluated a group of 358 patients who had been referred to an outpatient specialty clinic in Buenos Aires, Argentina, and were monitored for conversion to dementia. The patients were classified into 2 diagnostic categories: MCI and *mild behavioral impairment* (MBI), a term proposed by the authors to describe a syndrome emergent later in life in which persistent neuropsychiatric symptoms and behavioral changes are present in the absence of patient- or caregiver-reported cognitive deficits, impairment with activities of daily living, and dementia.

Two thirds of their subjects met criteria for MCI and one third met criteria for MBI. After further examination, 35.5% of the MCI group was found to demonstrate NPS, and 49.6% of the MBI group was found to have cognitive deficits, even though initially such symptoms were not reported present. Thus, 4 subgroups emerged: MCI without NPS, MBI without cognitive deficits, MCI + NPS, and MBI + cognitive deficits.

The 4 subgroups followed 3 different trajectories. MCI without NPS converted mainly to Alzheimer's disease, but at a slow rate, while MBI without cognitive symptoms converted mainly to frontotemporal lobe dementia and had a much shorter time to any dementia onset. Neuropsychiatric symptoms were consistently and robustly associated with faster time to dementia conversion across groups. The MCI + NPS patients had a 4-fold increase in

Received January 20, 2009; accepted January 20, 2009. From the Alzheimer's Disease Care, Research and Education Program and the Memory Disorders Clinic, University of Rochester School of Medicine, Rochester, N.Y.

The authors report no financial or other affiliation relevant to the subject of this article.

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risk of conversion to dementia over the observation period as compared to MCI only. The MCI + NPS and MBI + cognitive symptoms patients had very similar conversion risks in terms of timing and type of dementia and can be seen as a single group.

Although the study is not without its limitations, overall, the results suggest that the MBI construct is valid. MCI and MBI seem sufficiently different to be considered as 2 different groups; however, the operational criteria for MBI need refining in order to exclude the MBI + cognitive symptoms subgroup, requiring both informant and clinician input. The novel finding in this study is the impact of NPS even in the absence of cognitive symptoms as evidenced by the fate of the MBI-only group; this finding highlights the importance of emergence of NPS in later life.

Many patients develop NPS as the first indicator of impending dementia before the occurrence of cognitive symptoms, and comorbidity is the rule rather than the exception. Behavioral assessment at the time of the initial clinical evaluation and at follow-up visits may be as informative regarding prognosis as cognitive assessment. We do not know whether treatment intervention is helpful in the short or long run, but recent findings highlight that there is no easy solution to pharmacotherapy of neuropsychiatric symptoms in dementia, and it is unlikely that the situation is different in prodromal states. Finding thoughtful, more effective, and better tolerated interventions for NPS is a major challenge for investigators and clinicians and must become an urgent priority. Targeting the underlying pathophysiology is the future goal that may dictate our patients' welfare.

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