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Mild Neurocognitive Disorder: A Model for Accelerated Biological Aging?

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In the general population there is a continuum of cognitive functioning with aging, from high performance, normally intact, to severe impairment. During the last two decades, there has been growing interest in efforts to diagnose neurocognitive disorders as early as possible, driven by the recognition of a long pre-dementia stage, improvements in early diagnosis, and increasing emphasis on early interventions to prevent or delay dementia (1). This has led to development of various sets of criteria for Mild Cognitive Impairment (MCI). Among the most familiar MCI criteria are the Peterson Criteria (2), which emphasized the presence of subjective memory complaints and subnormal objective memory performance, in the context of unimpaired/intact everyday functioning. Here the focus was on early detection of subclinical Alzheimer's Disease (AD). However, only a proportion of patients with MCI progress to AD. Another problem with most criteria for MCI is that abnormal or subnormal objective performance on individual neuropsychological tests is, in fact, the normative/modal state for most people. Very high base-rates of abnormal performance on one or two neuropsychological tests among healthy older adults have been reported by a number of investigators (3). Thus, isolated statistical deviation from the normative mean is an insufficient basis to assume significant brain-based impairment implied in a diagnosis of MCI and thereby expose those individuals to a stigmatizing label and in some cases, unhelpful pharmacological and other interventions.

In part motivated by these concerns, the neurocognitive disorder sections of the DSM-5 were developed to meet a more stringent standard for what in DSM-5 is called Mild Neurocognitive Disorder (MNCD). The DSM-5 criteria were arrived at by consensus among selected experts (including one of us – DVJ - and Ronald Peterson, who had previously developed the Peterson criteria), and were based on a clinical approach to diagnosis. They require a decline in one or more cognitive domains, usually modest in severity, but objective demonstration of cognitive deficits is essential. The DSM-5 concept of MNCD also focuses on functional impairment, stating that, while “the cognitive deficits do not interfere with

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capacity for independence in everyday activities” (unlike those in dementia), greater effort, compensatory strategies, or accommodation may be required to maintain independence. Thus, the DSM-5 criteria allow for subclinical functional impairment, whereas the Peterson criteria do not. It is stressed, however, that MNCD too is not always a precursor of major neurocognitive disorder or dementia, and there may be either continued cognitive decline or the impairment may be static, and may even improve.

The study by Santabarbara, et al. (4, this issue) represents a useful step in addressing longer-term implications of MCI and MNCD. A representative community sample of 4,803 individuals aged 55 years or older was followed for a median of 11.1 years, and up to 17 years, as part of the longitudinal Zaragoza Dementia and Depression study, in Zaragoza, Spain. Using standardized assessment instruments, research psychiatrists retrospectively diagnosed MCI using the Peterson criteria (P-MCI) and MNCD (per DSM-5), following operationalized criteria. These authors had previously reported that the prevalence of MCI diagnosed using DSM-5 criteria (MNCD) was approximately half that using Petersen’s criteria for MCI (P-MCI), and the conversion rate to AD with DSM-5-MNCD was substantially higher than with P-MCI, together suggesting that the DSM-5 criteria are more specific to actual pre-clinical AD. In the present study, these investigators examined mortality risk of P-MCI and DSM-5-based MNCD. Over half (53.6%) of the participants died during the follow-up. In comparison with non-cases, the mortality rate ratio was 2.3 times in MNCD and 1.2 times in P-MCI individuals. The association of mortality with MNCD (but not P-MCI) remained significant even after adjusting for age, gender, and education.

Overall, the data by Santabarbara, et al. (4) show that the DSM-5-based MNCD, which requires some, albeit mild, compromise in functional independence, is associated with elevated mortality risk. This finding, coupled with the higher conversion rate to AD that these authors previously demonstrated with the DSM-5 criteria for MNCD, indicates that the latter may indicate a more definitive (and more advanced) cognitive impairment than P-MCI.

One issue not addressed in this study is whether the individuals who died had AD at the time of their deaths. If they did, it would indicate that MNCD increases the risk of mortality only when it is followed by AD. The causes of death were not specified in their report. Knowing the causes of mortality in the patients is critically important. Generally individuals live for 8–10 years after a diagnosis of AD. They may remain otherwise healthy for several years. In later stages of dementia, their overall health declines rather rapidly, leading to death.

On the other hand, if MNCD patients who did not convert to AD also had a significantly higher mortality rate (– i.e., they did not have dementia at the time of their death), it would suggest that MNCD itself is a risk factor for early mortality. MNCD may then serve as a model for accelerated aging as it would seem to be associated with significantly increased mortality relative to non-cases. Other neuropsychiatric conditions such as schizophrenia (5), bipolar disorder (6), and post-traumatic stress disorder (7), and are reported to be associated with accelerated biological aging and early mortality. As the search for causes of accelerated aging in these other conditions continues, one of the keys may be comparison with a more

well-established condition of accelerated aging such as a neurocognitive disorder. Understanding the mechanisms underlying accelerated biological aging may pave the way to discovering interventions that would slow the rate of aging in people with serious mental illnesses and neurocognitive disorders. To reverse paraphrase the famous quote by President Kennedy, our job is not merely to add life to the years but also years to the life of people with neuropsychiatric disorders.

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