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Perspective

Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment

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Abstract Neuropsychiatric symptoms (NPSs) are common in dementia and in predementia syndromes such as mild cognitive impairment (MCI). NPSs in MCI confer a greater risk for conversion to dementia in comparison to MCI patients without NPS. NPS in older adults with normal cognition also confers a greater risk of cognitive decline in comparison to older adults without NPS. Mild behavioral impairment (MBI) has been proposed as a diagnostic construct aimed to identify patients with an increased risk of developing dementia, but who may or may not have cognitive symptoms. We propose criteria that include MCI in the MBI framework, in contrast to prior definitions of MBI. Although MBI and MCI can co-occur, we suggest that they are different and that both portend a higher risk of dementia. These MBI criteria extend the previous literature in this area and will serve as a template for validation of the MBI construct from epidemiologic, neurobiological, treatment, and prevention perspectives.

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1. Background

1.1. Neuropsychiatric symptoms of dementia, mild cognitive impairment, and normal cognition

Neuropsychiatric symptoms (NPSs) of dementia are common and of increasing interest to clinicians and researchers. NPSs are the noncognitive or behavioral and psychiatric symptoms of dementia and include disturbances of mood, perception, and behavior associated with neurodegenerative disease [1]. NPSs in dementia are associated with poorer outcomes including greater caregiver burden [2], greater functional impairment [3], higher rates of institutionalization [4], poorer quality of life [5], accelerated progression to severe dementia or death [6], and higher burden of neuropathologic markers of dementia [7]. Furthermore, NPSs are present in the prodromal or mild cognitive impairment (MCI) stages of dementia, with one study reporting them in 59% of subjects enrolled in a large MCI clinical trial; furthermore, these individuals with NPS had greater impairment on global, cognitive, and functional scores than those without NPS [8]. Large sample longitudinal studies provide further evidence that NPSs in MCI increase risk of dementia. In an analysis of National Alzheimer's Coordinating Center (NACC) data, the presence of NPS increased the incidence of dementia (hazard ratio [HR] = 1.37, 95% confidence interval [CI] = 1.17–1.84), with an estimated annual conversion rate of 25% for MCI comorbid with NPS [9]. Similarly, the population-based Cache County study identified NPS, even of mild severity, as a risk factor for conversion from cognitive impairment no dementia to all-cause dementia [10]. The 2011 National Institute on Aging–Alzheimer's Association (NIA-AA) consensus recommendations for diagnosis of all-cause dementia have included behavioral symptoms by modifying the core criteria to add "changes in personality, behavior, or comportment—symptoms include uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors" [11]. Inclusion as core criteria provided an emphasis on the importance of NPS in neurodegenerative disease.

Evidence suggests that even subtle NPS in cognitively normal adults can predict cognitive decline. Pietrzak et al. [12] described the predictive nature of "mild worry" symptoms for cognitive decline at 2-year follow-up in a group of 263 cognitively intact older adults. These "mild worry" symptoms did not meet threshold criteria for an anxiety disorder and yet were important predictors of cognitive decline in the domains of visual learning and memory compared with older adults with "minimal worry" at baseline. The population-based Mayo Clinic Study of Aging highlighted the importance of NPS in cognitively normal older adults (age ≥70 years). The presence at baseline of NPS such as agitation (HR = 3.06, 95% CI = 1.89–4.93), apathy (HR = 2.26, 95% CI = 1.49–3.41), anxiety (HR = 1.87, 95% CI = 1.28–2.73), irritability (HR = 1.84, 95% CI = 1.31–2.58), or depression (HR = 1.63, 95% CI = 1.23–2.16) increased the risk of developing MCI in comparison to participants without NPS at baseline [13]. In comparison, biomarker analysis from the Mayo Clinic Study of Aging estimated that hippocampal atrophy (by magnetic resonance imaging) increased the risk of incident MCI to a lesser degree than four of the five aforementioned NPS (HR = 1.8, 95% CI = 1.4–2.20) [14], affirming the clinical relevance of NPS in comparison to other well-established predictors of conversion from MCI to dementia. Data have continued to emerge in support of the notion of NPS manifesting in advance of cognitive impairment for neurodegenerative disease. Donovan et al. [15] studied 559 participants who were cognitively normal, had subjective cognitive concerns, or who had MCI, from the Massachusetts Alzheimer's Disease Research Center Longitudinal Cohort. Greater symptoms of depression, irritability, and agitation predicted more rapid progression to a worse diagnosis across all groups, including the cognitively normal. The authors state "these findings support a model of AD in which cognitive and neuropsychiatric alterations are measurable before the stage of MCI and offer potential to enhance early detection and intervention." Banks et al. [16] assessed 644 cognitively healthy older subjects from the ADCS Prevention Instrument Project. Over the 4-year follow-up, baseline symptoms of anxiety and depression (measured cross-sectionally with the NPI) predicted conversion to CDR ≥0.5. The authors state "early anxiety and depression may be the harbingers of future cognitive decline, and that patients exhibiting such symptoms, even in the absence of co-occurring cognitive symptoms, should be closely followed over time." Masters et al. [17] used NACC data from 2416 cognitively normal participants more than 50 years of age to describe the predictive nature of incident NPS on conversion from CDR = 0 to CDR >0. The authors found a significantly earlier presence of NPS in cognitively normal patients who subsequently developed a CDR >0. They described the initial phase of "noncognitive" AD as irritability, depression, and nighttime behavior changes, followed by anxiety, appetite changes, agitation, and apathy symptoms. These NPS