Neuropsychiatric Symptoms in the Prodromal Stages of Dementia

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Abstract and Introduction

Abstract

Purpose of Review. To critically discuss the neuropsychiatric symptoms in the prodromal stages of dementia in order to improve the early clinical diagnosis of cognitive and functional deterioration.

Recent Findings. Current criteria for cognitive syndrome, including Alzheimer's disease, comprise the neuropsychiatric symptoms in addition to cognitive and functional decline. Although there is growing evidence that neuropsychiatric symptoms may precede the prodromal stages of dementia, these manifestations have received less attention than traditional clinical hallmarks such as cognitive and functional deterioration. Depression, anxiety, apathy, irritability, agitation, sleep disorders, among other symptoms, have been hypothesized to represent a prodromal stage of dementia or, at least, they increase the risk for conversion from minor neurocognitive disorder to major neurocognitive disorder. Longitudinal investigations have provided increased evidence of progression to dementia in individuals with minor neurocognitive disorder when neuropsychiatric symptoms also were present.

Summary. Although neuropsychiatric symptoms are strongly associated with a higher risk of cognitive and functional deterioration, frequently the clinician does not acknowledge these conditions as increasing the risk of dementia. When the clinician accurately diagnoses neuropsychiatric symptoms in the prodromal stage of dementia, he could early establish appropriate treatment and, may be, delay the beginning of clinical and functional deterioration.

Introduction

Whereas progressive cognitive decline and functional disturbances have been established as typical clinical hallmarks of dementia, neuropsychiatric symptoms are currently considered an intrinsic condition associated with neurodegenerative processes.[1,2] However, these symptoms have been less emphasized in the preclinical stages of dementia.

An extensive review of population-based multicentric studies reported an overall last month prevalence of 31% of psychopathological features in cognitive impairment nondemented individuals (CINDs) and about 15.1% in cognitive normal individuals.[3]

The presence of psychopathological manifestations among nondemented elderly people was designated as mild behavioral impairment (MBI). Agitation, anxiety, apathy, depression, delusions, sleep disorders, loss of social skills, perseverant behaviors, loss of insight, dietary changes, impulsivity, irritability, among others, have been considered as evidences of persistent behavioral changes in MBI.

In addition to the neurobiological predictors of dementia, neuropsychiatric conditions may also represent the determinants of the disease progression. Thus, it becomes crucial to understand the prodromal behavioral stage of Alzheimer's disease and other dementias. As precocious intervention

seems to be more efficacious, this knowledge might contribute to the diagnosis, thus allowing a better response to pharmacological and nonpharmacological treatments.[4,5]

This review aims to discuss the neuropsychiatric symptoms in the prodromal stages of Alzheimer's disease and other dementias, the diagnosis accuracy of these symptoms and the outcome of these clinical manifestations in cognitive and functional deterioration.

Mild Behavioral Impairment as Prodromal Stages of Dementia

The operationalized criteria for MBI syndrome must include persistent behavioral changes occurring in late life (after 60s). Symptoms must persist for more than 6 months, even in the absence of cognitive or functional decline, and with the preservation of socio-occupational or daily living activities. These criteria obviously exclude the diagnosis of dementia. However, they confer increased risk of developing dementia even if significant cognitive symptoms are absent.

In order to validate the MBI construct, longitudinal studies may confirm the diagnostic criteria. To accurately diagnose the neuropsychiatric symptoms in nondemented individuals, the clinician needs to understand the psychopathological manifestations from the onset of symptoms up to the present time, the circumstances in which they emerge as well as the impact on patient's cognition or daily functionality are required.

Neuropsychiatric Symptoms: Toward Improvement of the Accuracy in Identifying the Prodromal Stages of Dementia

Longitudinal investigations have provided evidence concerning the risk of progression to dementia in nondemented individuals with cognitive decline, for instance, in patients with mild cognitive impairment (MCI) because of Alzheimer's disease.[5] The comprehensive assessment of cognitive processes including executive functions and episodic memory in nondemented individuals prior to clinical decline onset is crucial. This identification permits the recognition of individuals at risk of dementia and allows appropriate intervention to be proposed when recommendable.[6] Furthermore, improved accuracy of diagnosis at the prodromal stage of dementia may facilitate early detection of patients presenting any potential treatment response.[4,5]

In addition to the mild cognitive alterations, patients with MCI may present subtle decline on instrumental activities. This phenomenon can reflect a clinicopathological continuum, MCI-Alzheimer's disease, when it encompasses either amnestic decline or executive dysfunction[7] and biomarker alterations such as disorders firstly of amyloid-β followed by disorders of tau protein.[1,8] On the basis of the notion that functional decline represents a core domain to separate MCI from the prodromal stages of dementia, nowadays, a challengeable issue concerns the recognition of patients before the decline of instrumental activities.[7] During the last decade, biomarkers have provided growing support to understand the pathophysiological process of Alzheimer's disease.[8] In spite of this, behavioral markers could be considered as potential clinical markers for early recognition of the disease.[1] Distinct MCI types such as amnestic (single or multiple domains) and nonamnestic (single or multiple domains), as well as subsequent types of dementia such as Alzheimer's disease, frontotemporal, Lewy, and others, at least in part depend on the underlying neuropsychiatric subsyndromes, including depression, apathy, disinhibition, irritability, and sleep disorders.[5,9]

A challengeable issue comprises the achievement of longitudinal studies with older individuals, combining Alzheimer's disease biomarker patterns to detect mild cognitive and functional impairments, and early neuropsychiatric symptoms, this combination being more accurate than each one alone. This proposition assumes that Alzheimer's disease dementia is preceded by a long asymptomatic prodromal phase, characterized by progressive pathophysiological process, in which

cognitive and behavioral changes could be present and increase the risk of conversion to definite clinical deterioration.[1]

There are several strategies targeting the measurement of neuropsychiatric symptoms in dementia. In general, scores have been based on reports provided by the caregiver or family member. A new approach is the Neuropsychiatric Inventory-Clinician Rating Scale (NPI-C), which is a comprehensive and versatile scale that permits a consistent assessment of neuropsychiatric symptoms in dementia, even at early stages.[9,10] This scale includes, simultaneously, the description of patient's symptoms from the knowledgeable informant, patient observation directly by the clinician, information from patient records, and the clinician's interpretation for each symptom based on the overall data accessed. The clinician's judgment reduces emotional and cognitive interferences, which frequently occur given that the caregiver or knowledgeable informant may suffer emotional burden, such as depression, anxiety and sleep disorders, as well as present cognitive impairment; because of these occurrences, they may hypervalue or hypovalue the patient's symptoms[9–11] By including simultaneously a comprehensive view and eligible domains, as well as the clinician's judgment, this scale represents an advantageous tool to investigate neuropsychiatric symptoms in the prodromal stages of dementia.

As widely established, reduced Aβ42 and elevated total tau and phosphorylated tau levels in cerebral spinal fluid as well as high amyloid uptake in molecular imaging[12] and temporoparietal abnormalities in either functional[13,14] or structural brain imaging[15] are valuable biomarkers of Alzheimer's disease. Incorporation of biomarkers of amyloid disorder and neuronal injury to improve the diagnostic accuracy of Alzheimer's disease at prodromal stage has been lately proposed.[5] As widely established, reduced Aβ42 and elevated total tau and phosphorylated tau levels in cerebrospinal fluid (CSF), as well as molecular and structural neuroimaging changes in temporoparietal regions, are important biomarkers of Alzheimer's disease neuropathology. Incorporation of biomarkers of amyloid disorder and neuronal injury to improve the diagnostic accuracy of Alzheimer's disease at prodromal stage has been lately proposed.[5] During the last decade, the risk of progression to Alzheimer's disease dementia in MCI patients who present structural abnormalities or CSF disorders such as reduced Aβ42 and elevated tau protein has been broadly discussed.[1,5] Some groups have proposed an integrative approach, which should include neurochemical and neuroimaging biomarkers, cognitive and functional decline, as well as neuropsychiatric symptoms, requiring these components to be managed together in Alzheimer's disease even at prodromal stage.[1,5,6,15–17]

However, the impact of neuropsychiatric symptoms on the risk of dementia has received less attention. Whether these clinical syndromes, mainly when associated with specific neurobiological correlates, depict a prodromal stage of dementia nowadays represents a challenge to be explored.

Evidence from the neurochemical and neuroimaging abnormalities in patients with neuropsychiatric symptoms strengthens the hypothesis that they could represent a prodromal stage of dementia, particularly Alzheimer's disease. Neurobiological correlates have been associated with depression in patients with Alzheimer's disease before dementia onset. Hence, structural brain abnormalities were detected in patients with late-onset major depression, prominently in the orbitofrontal, mediofrontal, parietal regions adjacent to the temporal cortex, as well as in the mesial temporal areas, such as hippocampus, amygdala, and parahippocampal area. In patients with late-onset depression, gray matter loss was detected predominantly in the right lateral temporal cortex and parietal cortex, particularly in sensorimotor areas, when compared with individuals without depression.[18]

However, a recent study did not find the association of depression severity with Alzheimer's disease CSF biomarkers in either Alzheimer's disease patients or in nondemented individuals.[19] Conversely, another investigation with neuropathologically confirmed diagnosis of Alzheimer's

disease based on postmortem histopathological analysis verified more pronounced amyloid plaques and neurofibrillary tangles in the hippocampus from patients with history of major depression when compared with those without history of this condition.[20] This controversy suggests the interference of a complex interaction of factors associated with the cause of depression in nondemented elderly, probably including neurobiological components. Despite the existing controversies, a recent review found significantly reduced β-amyloid peptide and high Aβ40/Aβ42 ratio in depressed patients, suggesting an increased risk for developing Alzheimer's disease.[21] Taking these aspects together, the neuropathological mechanisms underlying the association between a history of major depression and brain atrophy, especially reduced hippocampal volume, remain to be clarified.

Another interesting point concerns the association of late-life major depression with reduced brain-derived neurotrophic factor (BDNF)[22] and disruption of neurotrophic regulatory mechanisms, particularly reduced nerve growth factor (NGF).[23] Depressed patients tend to present hippocampal atrophy and episodic memory decline, suggesting a crucial interaction between this condition and the neuropathological process of Alzheimer's disease.[20,24] Conversely, an autopsy investigation of patients with lifetime depression without dementia reported subcortical and hippocampal neuronal loss, but not Alzheimer's disease.[25] To date, there are some controversies regarding the magnitude of the impact of depression on the neuropathological process of Alzheimer's disease. If late-onset major depression reflects a prodromal stage of neurodegenerative disorders, including Alzheimer's disease, it is an important avenue to be explored further.

Furthermore, in amnestic MCI, patients with apathy may present fractional anisotropy in several structures, suggesting that these changes contribute to the disruption of emotional approaches and cognitive performance in motivation processes.[26,27]

Neuropsychiatric Symptoms in Mild Cognitive Impairment and Risk of Dementia

Whether cognitive impairment or neuropsychiatric symptoms *per se* are useful predictors of progression to dementia remains unclear.[1,3] However, the combination of clinical changes, including neuropsychiatric symptoms, with neuroimaging and neurochemical biomarkers could more powerfully predict faster conversion to Alzheimer's disease.[1,28,29]

In this scenario, there is growing evidence that neuropsychiatric syndromes increase the risk of dementia such as Alzheimer's disease or frontotemporal dementia, among others. Probably, a specific type of dementia at least in part could represent the outcome of both neuropathological processes and neuropsychiatric features prior to the clinical manifestations. For instance, clinical features of frontotemporal dementia or Alzheimer's disease could be preceded by changes in specific neurobiological mechanisms and behavioral changes years before the beginning of cognitive and functional decline.

Late-onset depression may constitute a prodromal stage of Alzheimer's disease or increase the risk of developing MCI in cognitively preserved individuals.[30] Vascular risks also could contribute to cognitive deterioration.[31] A recently published study with MCI patients submitted to neuropsychological, neuropsychiatric, and neuroimaging assessments at baseline and during a 2-year follow-up period reported that depression was associated with significant atrophy in the frontal, parietal, and temporal white matter regions, structures usually affected in Alzheimer's disease.[32] The authors observed increased cognitive deficits in depressed patients with high rates of progression to Alzheimer's disease and that depression in MCI could be related to the underlying neuropathological features of prodromal stages of Alzheimer's disease.

Whether target treatment for MBI using nonpharmacological strategies or psychopharmacological intervention may delay the conversion to dementia remains to be demonstrated with the longitudinal

studies. The clinician should begin specific treatment depending on the frequency and severity of symptoms, as well as their impact on functionality. Validated scales enable researchers and clinicians to follow up the effectiveness of psychopharmacological or nonpharmacological interventions on the neuropsychiatric symptoms.[10,33] Treatment of neuropsychiatric symptoms may intervene on the neural pathways, reducing the risk of progressing to MCI and subsequent dementia.

Selective serotonin reuptake and dual serotonergic–noradrenergic reuptake drugs improved working memory, attention and executive functions in patients with major depressive functions.[34] Potential neurobiological changes induced by antidepressants may be related to the modulation of BDNF. Some studies suggested that this neurotrophin plays a critical role in the pathophysiology of late-onset depression.[22,35] In addition, antidepressants might protect neuronal activity and contribute to neurogenesis in the hippocampus, which has been implicated in cognitive impairment in depressed patients.[35] Conversely, visuospatial ability, information-processing speed, and delayed memory still remained impaired despite the remission of depressive symptoms after antidepressant therapy.[36]

A strategy to be considered concerns the combination between antidepressants and anticholinesterase inhibitors to treat depressed patients with CIND. In a pilot study, elderly patients with depression and CIND were treated for a period of 8 months with antidepressants and donepezil with a short-term improvement in verbal memory when compared with antidepressants and placebo.[37] The authors suggest that this drug combination may confer a potential benefit in decreasing the conversion rates from neuropsychiatric clinical diagnosis to dementia.

Nonpharmacological interventions as problem-solving therapy was effective in reducing the depressive symptoms and increasing the executive functions in a considerable cohort of elderly patients with major depression, this intervention being an additional strategy in an older population likely to be resistant to antidepressants.[38] Integrated approaches to improving cognitive decline and depression symptoms combining antidepressants, cholinesterase inhibitors, psychosocial interventions, appropriate diet, and healthy lifestyle, including aerobic exercises, could bring favorable outcomes, particularly for memory and cognitive frontal processes.[39]

An intriguing aspect concerns the concept of 'cognitive reserve' and its relationship with neuropsychiatric symptoms in the prodromal stages of dementia. This theoretical construct proposes that individuals may recruit more efficiently preserved networks to cope with or to compensate brain disorder.[40] In addition to being associated with cerebral functioning, this reserve encompasses intellectual abilities, which are progressively accumulated through individual experiences, educational life, and complex psychosocial processes. In this context, neuronal resilience targets to cope with the clinical deterioration determined by neuropathological mechanisms, providing support for cognitive, functional, and behavioral performance. Whether cognitive reserve protects against the deflagration or aggravation of neuropsychiatric syndromes in the prodromal stages of dementia remains to be explained.

Comments

As neuropsychiatric symptoms are strongly associated with higher risk of cognitive decline, an important question refers to the lack of awareness regarding the occurrence of behavioral changes in patients with MCI. Many patients do not recognize either their own cognitive symptoms or their behavioral changes. Likewise, family members tend to ignore these changes.[10,33] In addition, unsurprisingly, clinicians do not acknowledge mild behavioral symptoms in individuals with MCI as an increasing risk of progression to dementia. Understanding these occurrences before the onset of clinical deterioration could further improve the available nonpharmacological strategies and pharmacological interventions aimed at delaying the progression to dementia. In this context,

presumably self-complaint of memory decline or subtle behavioral changes combined with Alzheimer's disease biomarkers could be useful predictors of progression from the prodromal disease stage to dementia state.[1]

Available sensitive measures are required to recognize very quickly the neuropsychiatric symptoms and subtle cognitive or functional decline in order to early diagnose the clinical manifestations of Alzheimer's disease or other dementias. Thus, additional efforts are desirable to combine sensitive clinical assessments with other neurobiological markers such as CSF abnormalities of Aβ peptide and tau protein, as well as neuroimaging evidence of synaptic dysfunction in neural interconnections associated with Alzheimer's disease. Furthermore, clinical and neurobiological sensitive measures applied to prodromal manifestations of Alzheimer's disease should be helpful in controlling the response to potential interventions designed to change the disease course even at early stages.

Whether treatment of these symptoms could prevent or delay the progression from the cognitively normal condition to MCI and, later, to subsequent dementia remains an intriguing challenge.

Conclusion

Neuropsychiatric symptoms have been associated with increased risk of cognitive decline and, subsequently, of conversion to dementia. Longitudinal studies combining the biomarker patterns from Alzheimer's disease or other neurodegenerative processes, as well as the occurrence of mild cognitive or functional impairments and early neuropsychiatric symptoms, represent a more accurate strategy for diagnosis than each one alone. Early acknowledgement and treatment of these symptoms, even in the prodromal stages of dementia, may contribute to avoid or delay the clinical deterioration.

Key Points

- Patients presenting mild cognitive impairment with neuropsychiatric symptoms have an increased risk to progress to dementia.
- The impact of neuropsychiatric symptoms on the risk of dementia has received less attention than the cognitive changes.
- The combination of clinical changes, including neuropsychiatric symptoms, with neuroimaging and neurochemical biomarkers could more powerfully predict faster conversion to Alzheimer’s disease.
- Whether treatment of neuropsychiatric symptoms could prevent or delay the progression from the cognitively normal condition to mild cognitive impairment and, later, to subsequent dementia remains an intriguing challenge.

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