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Neuropsychiatric Symptoms in Mild Cognitive Impairment as Risk Factors for Progression to Dementia

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Dementia is a public health problem with increase prevalence and relationship with aging population. Life expectancy has been increasing exponentially worldwide. While it represents a goal of medical advances, rapid changes in population demographics have also brought new challenges. Many health conditions are more prevalent in the older population. Cognitive problems, in particular dementia, have a high prevalence in older people. Alzheimer's disease (AD) is the most frequent dementia in older people (over 65). AD has an estimated prevalence of 5.3 million patients in the U.S.A. alone (33 million worldwide), and it is expected to increase to 11 to 16 million by the year 2050 (and over 115 million worldwide) [1,2]. There is substantial clinical evidence about that the neuropathological features of AD begins years before of functional decline in patients; therefore, the identification of prodromal AD states will be crucial for future interventions diseases [3,4].

Mild cognitive impairment (MCI) refers to an intermediate stage between normal cognitive aging and dementia. Clinically, MCI can be defined as cognitive impairment in one or more domains, usually memory or, a slight alteration in all cognitive abilities higher to expected for age and education, but not enough to interfere with social and occupational functioning as required for a dementia syndrome [5]. The amnestic type, characterized by memory impairment, is the most common, but other subtypes such as single non-memory and multiple domain, also are prevalent. The concept of MCI was first described by Peterson in 90´s, who described it as a continuum between normal aging and dementia [6]. The American Academy of Neurology defined MCI as those patients with memory problems preferably corroborated by an informant, but with a normal global cognitive functioning and intact activities of daily living [7]. The diagnostic criteria have been expanded to include individuals with intact memory but significant impairment in other cognitive functions.

Recently, it has become aware of the importance of neuropsychiatric symptoms (NPS) in dementia, given its high prevalence over the course of dementia and its association with caregiver burden and early institutionalization [8]. NPS are present in a large number of patients with dementia, and they are common features of all types of dementia, regardless of etiology. In recent years, various studies have shown that patients diagnosed with MCI have a higher rate of NPS than subjects without cognitive impairment [1,4]. The presence of NPS in dementia patients is associated with high caregiver burden, poor prognosis, and higher rates of institutionalization and drug therapy; all of which contributes to an increased clinical, social and economic impact in people with dementia and MCI [9]. These are important reasons that NPS should be recognized and treated as soon as possible in the course of neurodegenerative process. More prevalent NPS can include agitation, anxiety, irritability, illusion and delusions, apathy, depression, disinhibition, aberrant motor and obsessive-compulsive behaviors, and sleep disorders, among others. These manifestations can be present at any stage of dementia and MCI. We can use different general scales and focused scales to determine the presence, intensity or frequency of NPS in patients with MCI and dementia. General scales are used in multidimensional examinations [10], and include the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), the Neurobehavioral Rating Scale, the Behavioral Rating Scale for Dementia, and the Neuropsychiatric Inventory (NPI). The NPI is the most widely used scale to measure NPS associated with cognitive disorders [11]. NPI is a fully structured interview, which contains data from an informant, usually the patient's caregiver. This scale provides data of frequency, intensity and impact on the caregiver of these symptoms.

It is recognized that persons with MCI have an elevated risk of developing dementia [6,12]. It has been investigated about clinical factors that are associated with cognitive deterioration in MCI. Evidence has shown that neuropsychological profile (intensity and type of cognitive impairment), neuroimaging data

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(medial temporal lobe atrophy), cerebrospinal fluid biomarkers (total tau, phosphorylated tau, βamyloid 1-42) and a combination of cognitive, genetic (ApoE) and neuroimaging measures can predict conversion to dementia [13-16].

NPS also appears to influence the risk of conversion from MCI to demencia [17]. Several NPS have been suggested to be associated with an increased risk of deterioration, including depression [18], anxiety [19] and apathy. Depression is the most studied symptom in MCI and dementia. The prevalence of depressive symptoms may be as high as 45% [18,20]. However, there are conflicting results in the literature and inconsistent results have been reported [21]. Apathy (lack of motivation and decreased emotional engagement) is a prevalent behavioral manifestation in MCI patients. Several studies have found that near of one-third of patients with a diagnosis of MCI suffers apathy [22]. The presence of apathy symptoms increases the risk of developing dementia. Palmer et al reported that a diagnosis of apathy in amnestic-MCI patients represented a 7-fold increased risk of developing AD [23]. There is also medical evidence supporting the influence of other NPS as anxiety, irritability, agitation or psychotic symptoms in conversion from MCI to dementia [8].

We have recently presented preliminary results of a study that evaluates various NPS and the risk of conversion to dementia in a cohort of patients with MCI [24]. Our cohort consisted of 175 patients with MCI (53.7% male; mean age 74.9 years ± 8.7 SD) who were followed for an average 25.8 months (SD ±17.5). During follow-up 46 patients (26.3%) of the initial sample showed a conversion to dementia. Univariate analysis showed that significantly influenced the conversion to dementia a multi-domain-amnestic MCI ($p<0.001$), disinhibition ($p<0.001$) and psychotic symptoms ($p=0.001$) but not the rest NPS or depression. A model with survival curves (COX) including these factors, sex and age found relevant multi-domain amnestic MCI with OR 4.06 ($p<0.001$; 95% CI 1.97 to 8.38), psychotic symptoms with OR 4.80 ($p=0.04$; 95%CI 1.06 to 21.63) and disinhibition with OR 19.24 ($p<0.001$; 95% CI 4.04 to 91.74). In our sample, disinhibition was the most relevant NPS to predicting conversion to dementia.

Conclusion

There is increasing evidence that presence of NPS in MCI patients is an indicator of increased risk of progression to dementia. Patients with MCI who have a high number of NPS or great intensity may be more likely to progress to dementia, than those with fewer or less severe NPS. Although it seems that all NPS can influence to increase the risk of conversion, there is controversy regarding the presence of depression. On the other hand, apathy, psychotic symptoms and disinhibition are NPS that seem to have a high predictive power. Data previously provided support that evaluation of NPS is important for predicting the prognosis of MCI. Clinicians should conduct a detailed clinical evaluation of these symptoms in the management of all patients with MCI.

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