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EDITORIAL

Time to target brain atrophy and neurodegeneration in multiple sclerosis

Hora de focar na atrofia cerebral e na neurodegeneração em esclerose múltipla

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease affecting the central nervous system (CNS) characterized by a relapsing-remitting course in the majority of the patients. In the last two decades, an increasing number of approved drugs for MS showed efficacy on clinical relapses and magnetic resonance imaging (MRI) lesions related to inflammatory activity in the CNS. Although, MS treatments have limited effect in the progressive disease course[1], which is probably not just related to the damage caused by accumulation of disease relapses over time[2]. Axonal loss can be already observed in the early stages of the disease[3], suggesting that neurodegenerative mechanisms may play a role in the long-term disability. Brain atrophy measured by MRI scans may be a non-invasive tool to quantify neuronal and axonal loss.[4] Interestingly, the loss of cerebral volume can be already seen on patients with the first clinical event and radiologically isolated syndrome cases highly suggestive of MS[5]. Brain atrophy also correlates with cognitive decline and disability progression[3] and might predict conversion from clinically isolated syndrome to definite MS[6].

In this issue of *Arquivos de Neuropsiquiatria*, Rojas et al.[7] review the impact of brain atrophy in the clinical practice. The neuroimaging techniques that have been proposed to measure brain atrophy include automated and semi-automated methods (transversal and longitudinal) with a certain level of reproducibility. Amongst several MRI techniques used to estimate brain volume loss, there are several available cross-sectional and longitudinal methods (e.g. brain parenchymal fraction - BPF, structural image evaluation using normalization of *atrophy* - SIENA, Freesurfer, voxel-based morphometry and Brain Boundary Shift Integral). The BPF and SIENA were the most frequently used.[3] However, these methods could yield some technical difficulties when applied in daily practice. Some years ago, Figueira et al.[8] proposed the corpus callosum index, a morphometric parameter that correlates with BPF and could potentially distinguish relapsing-remitting and progressive forms of MS. However, given the possible confounding factors that could cause loss of brain volume, like pseudoatrophy phenomenon, concomitant diseases that might also lead to brain atrophy (e.g. cardiovascular risk factors, stroke) and the lack of standard parameters that take into account other factors commonly seen in the clinical practice[3], the reproducibility of the proposed methods and their application should be validated in large MS populations. Nevertheless, it might be only a question of time and allocation of resources to translate some of this research into the clinical practice.

Rojas et al.[7] also discuss about the disability progression and cognitive impairment associated with global or segmental brain volume loss. The global gray matter volume loss correlates with the progression of motor disability and both gray and white matter losses are associated with cognitive impairment[3]. Moreover, Steenwijk et al.[9] recently found that brain atrophy in MS occurs in a non-random manner and described different anatomical patterns associated with cognitive dysfunction. Physical dysfunction as measured with Expanded Disability Status Scale (EDSS) score correlated with changes in the cortical thickness of the bilateral sensorimotor cortex and bilateral insula, while cognition correlated with cortical atrophy of the bilateral posterior cingulate cortex and bilateral temporal pole. In another study, Damasceno et al.[10] evaluated functional tests, cognition and brain atrophy in 42 relapsing-remitting MS patients receiving treatments who achieved no evidence of disease activity (NEDA)[9] status,

defined as a composite outcome measure that includes absence of clinical relapses, no progression in the EDSS and the lack of new or enlarging T2 and gadolinium-enhancing MRI lesions. In the group of MS patients remaining with NEDA status after 2 years of follow-up, there was a slower atrophy rate of the subcortical gray matter volume, but 58.3% of them had deterioration in ≥2 cognitive domains. Taken together, these studies suggest that the progressive clinical and cognitive worsening are associated to neurodegenerative processes that may occur more aggressively in specific areas of the brain and they cannot be totally explained by the presence of actual inflammatory activity in the CNS. Therefore, it is expected that current MS treatments that mainly control the inflammatory process may have a limited therapeutic impact on these outcomes.

In the near future, we expect a 'new drug development era' in MS, tackling the current lack of treatment options to undoubtedly control specific neurodegenerative processes seen in MS. The development of advanced neuroimaging techniques to measure brain atrophy allows us now to incorporate MRI parameters beyond inflammation and blood-brain barrier disruption commonly used by neurologists. The evidence of progression on clinical disability scores and/or cognitive tests associated with brain atrophy and other potential biomarkers may be used as endpoints in clinical trials. If a single drug cannot control effectively both inflammation and neurodegeneration, a combination therapy with currently approved drugs for MS and pro-remyelinating inducers[11] or other restorative therapies might be an alternative to reduce the cognitive dysfunction and long-term disability.

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