The Neural and Cellular Bases of Cognitive Aging and Neurodegeneration in MS

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Perspective

So far, we have addressed cognitive changes associated with aging and dementia in PwMS. On the molecular and cellular levels, multiple mechanisms have been proposed to contribute to cognitive decline in PwMS. Some reports have shown that aging may reduce the ability of older MS patients' brains to recover from inflammatory attacks, because of reduced neuroplasticity due to impaired synaptic functions (e.g., inflammatory synaptopathy) affecting long-term potentiation and depression, which are strongly associated with mechanisms of learning and memory. In addition, neuronal senescence has been discussed as a possible mechanism driving the progression of neurodegeneration in PwMS by promoting sustained and chronic inflammation, alteration of glial function with failure of remyelination and cellular recovery, and impairment of the blood-brain barrier's integrity. A recent publication has identified the toxic accumulation of the synaptic protein Bassoon in neurons as a potential driver of neurodegeneration (i.e., proteinopathy) in MS, although this is yet to be replicated in other human studies. A detailed discussion of these and other mechanisms is beyond the scope of this review and can be found elsewhere. Here, we seek to discuss current evidence derived from research using biomarkers including the CSF and structural magnetic resonance imaging (MRI), as well as their implications for cognitive aging and neurodegeneration in older PwMS. Studies using CSF analysis have assessed the potential utility of some biomarkers to detect cognitive decline and/or neurodegeneration in PwMS. A recent meta-analysis of 64 articles including >4000 study individuals revealed that markers of axonal damage (including neurofilament light chain (NFL) and total tau) and glial activation (including Glial Fibrillary Acid Protein (GFAP) and s100B) were higher in PwMS, as well as in patients with the clinically isolated syndrome, compared to control patients. GFAP levels were higher in progressive MS compared relapsing–remitting MS, while all other markers did not differ between MS subtypes. Of note, no difference was found between the relapse and remission stages of MS in these markers except for NFL, although information was limited regarding how close in time CSF was sampled relative to the clinical event among the studies included in this meta-analysis. Even though the meta-analysis did not assess the association of these markers with cognitive performance, some studies have shown that CSF total tau is associated with disability and cognitive impairment. In addition to markers of neurodegeneration, inflammatory markers have been also examined and found to correlate with cognitive impairment in MS. How aging and other age-related neurodegenerative processes may play a role in shifting neurodegenerative or inflammatory profiles in the CSF is less clear, and has only been examined by a few. Imaging studies offer a valuable approach to examining in vivo how changes in gray and white matter may contribute to cognitive decline in older PwMS. Particularly, reduced volume in the thalamus and other subcortical gray matter structures based on MRI has been associated with both aging and neurodegenerative processes in MS. Hasan et al. (2011) identified thalamic volume loss in a large cohort of PwMS (n=109, age range 20.8 years–68.5 years) as a marker for disability compared to HC subjects, after adjusting for natural aging and whole-brain lesion volume. The thalamic atrophy occurred independently from lesions in this area, suggesting a neurodegenerative process as the underlying pathophysiology. Jakimovski et al. (2020) examined a group of 112 older PwMS (mean age 60.3 years) and found that PwMS had reduced deep gray matter and the lowest thalamic volume compared to patients with Parkinson's disease, AD, and aMCI. Interestingly, no difference in whole-brain volume loss was noted between patients with MS and other patient groups. To further characterize and distinguish MS-related from age-related regional volumetric changes, a longitudinal study included 520 patients with relapsing–remitting MS and 130 HC subjects. The authors found that the rate of global atrophy increased by 0.11% per decade from age 30 to 60 years in normal aging, while it decreased by 0.09% per decade in MS. Thalamic atrophy followed a similar pattern, increasing by 0.16% per decade from age 30 years to 60 years in normal aging, while it decreased by 0.18% per decade in MS. Normal aging and MS-specific atrophy in the putamen and caudate did not vary by age. Notably, these subregions were not pre-selected but instead ranked as the top 5 regions (among all 83 regions) using a data-driven approach. These results suggest that age-related thalamic changes may be more prominent than MS-specific changes in older PwMS. Although thalamic atrophy has been associated with cognitive performance and is predictive of cognitive decline in younger PwMS, how these dynamic volumetric changes in the thalamus and other brain regions may contribute to either the degree or the pattern of cognitive decline in older PwMS remains to be investigated. The bulk of studies to date have concluded that white matter lesion burden evident on clinical MRI shows little correlation with the degree of cognitive impairment, compared to damage in gray matter and disruption in normal-appearing white matter. More advanced MRI techniques have demonstrated decreased white matter integrity in MS in the corpus callosum, hippocampal and thalamic tracts, and other major white matter tracts. Neuropathological studies support these in vivo imaging findings, demonstrating thalamic and hippocampal demyelination in MS. Compared to research focused on gray matter volume, it is less clear how age may interact with MSrelated white matter lesions/changes and contribute to cognitive changes in older PwMS. Vascular risk factors are associated with brain atrophy and white matter disease in MS. Drivers of cerebrovascular injury are more prevalent in PwMS, and the prevalence of these conditions further increases with age. Thus, studies seeking to analyze CSF and imaging biomarkers will need to consider both age and vascular diseases to better disentangle their impact on the neural basis of cognitive decline and neurodegeneration in older PwMS. These findings suggest that cognitive decline in older PwMS is multifactorial, with both neuroinflammatory and neurodegenerative processes as important contributing factors. Studies using in vivo biomarkers (i.e., CSF markers for neurodegeneration and neuroinflammation; imaging markers for gray and white matter changes and other neurodegenerative processes) have the promise to elucidate the underlying pathophysiology as well as identify an active window for more targeted intervention and disease monitoring.

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