Neurodegeneration in multiple sclerosis is a process separate from inflammation: Yes

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Multiple sclerosis (MS) is historically described as an immune-mediated inflammatory disease of the central nervous system (CNS) characterized by focal areas of demyelination in the white matter (WM). However, advances from neuropathological and imaging studies have highlighted early and sustained neurodegenerative mechanisms, including neuronal and neuritic (axon and dendrites) injury, correlating best with long-term clinical disability. It is still debated whether these two components, inflammation and neurodegeneration, are primary or secondary processes and how they interplay over the disease course. Despite evidence that loss of myelin in acute inflammatory WM lesions can locally induce axonal degeneration, several reports emphasize that neuronal and axonal loss also occurs outside areas of inflammation, suggesting, at least partly, independent processes.

What is the evidence that neurodegeneration and inflammation are distinct processes in MS?

Long-term natural history studies in MS have established that a proportion of patients have a progressive course marked by continuous worsening of neurological disability, either from disease onset or after a relapsing–remitting (RR) phase, with a median delay of 15 years between RR disease onset and secondary progression.1 Available disease-modifying therapies mainly aim to modulate or suppress the abnormal immune response occurring within the CNS, thus decreasing the relapse rate. However, no treatment, including the most recent immunosuppressive molecules with an increased influence on relapses, has shown efficacy in decreasing long-term disability and there is still no approved drug to treat MS patients with a progressive course.

Based on these observations, it was speculated that neurodegeneration gradually becomes prominent and independent of acute inflammation. Neuropathological studies confirmed that axonal degeneration and neuronal loss represent the hallmark of progressive MS, correlating only mildly with focal WM lesion volume.2 Interestingly, diffuse axonal pathology in normal-appearing WM together with massive cortical demyelination was observed in cases with only few WM plaques. Cortical lesions in particular are characterized not only by oligodendroglial injury, but also transected neurites and apoptotic neurons, and the absence of massive inflammatory infiltrate in most cases.3 A gradient of neuronal loss expanding from the pial surface throughout the cortical width was described both within and outside cortical lesions, not exclusively located close to foci of meningeal inflammation.4 The thalamus, a central hub for neuronal connections and networks, is another structure particularly vulnerable to MS-related neurodegeneration, within areas of demyelination predominating near the ventricle, as well as in the normal-appearing thalamus.5 It is important to notice that diffuse inflammation with microglial activation is much milder in the thalamus relative to the WM. Hippocampal demyelination is also extensive in MS, despite very marginal inflammatory activity.6

Neurodegeneration is not the exclusive hallmark of late-stage MS but was also described at early stages, affecting all gray matter (GM) compartments including the cortex7 and the thalamus.8 To overcome the limited availability of brain tissue from early MS patients, imaging tools to assess in vivo neurodegeneration have been developed and represent an exciting and promising research field to get insight into the mechanisms of disease progression. A recent neuroimaging study has shown that the relationship between GM atrophy and WM abnormalities is weaker in progressive patients relative to RRMS,9 suggesting independent pathological processes affecting these two compartments. Atrophy, although detected very early in disease course, is probably multifactorial and may be a late marker of neurodegeneration, hence the
emergence of imaging markers to better depict early neuronal dysfunction. A recent study using $^1$H magnetic resonance spectroscopy found decreased N-acetylaspartate (NAA) levels (underlying neuronal loss and/or impaired metabolism) in a cohort of 23 patients with radiologically isolated syndrome.\textsuperscript{10} Molecular imaging using a positron-emission tomography (PET) radioligand specific to neuronal integrity ($^{11}$C-flumazenil) has also demonstrated early neuronal damage in RRMS.\textsuperscript{11} A recent in vivo study using 7 Tesla cortical T$_2$* relaxation time found that subpial demyelination contributes to neurological disability independently of WM lesions.\textsuperscript{12} These studies among others provide evidence that neurodegeneration occurs at all MS stages, not necessarily associated with inflammation.

**Which are the potential factors influencing neurodegeneration independently of inflammation?**

A further key question is to identify factors explaining the heterogeneous susceptibility to neurodegeneration among MS patients, which would give clues to unravel the “clinico-radiological” paradox (i.e. discrepancies between disability and magnetic resonance imaging (MRI)-visible WM lesions).

Genetic background is thought to influence not only disease onset but also disease progression. A genome-wide association study has found a polymorphism in the sulfatase-modifying factor 1 gene and other related genes influencing in vivo brain glutamate levels, correlating with decreased NAA level and increased rate of atrophy.\textsuperscript{13} Strikingly, while MS is overall more prevalent in women than men, the female-to-male sex ratio is markedly lower in progressive MS,\textsuperscript{14} and male patients are more sensitive to GM atrophy and cognitive impairment.\textsuperscript{15} In line with these observations, a recent study using XY bone marrow chimeras of experimental autoimmune encephalomyelitis mice found more neuropathology in the spinal cord, cerebellum, and cerebral cortex of mice with XY CNS.\textsuperscript{16} Furthermore, the authors identified that the expression in cortical neurons of toll-like receptor 7 gene on the X chromosome, known to promote neurodegeneration, was higher in mice with XY compared with mice with XX CNS.

Recent advances in the knowledge of molecular pathways of neurodegeneration provide insight into the spreading of neuroaxonal pathology, including Wallerian and trans-neuronal degeneration, outside the original site of blood-brain barrier disruption. They comprise oxidative stress pathways dysfunction, closely associated with iron accumulation, dysfunction or impaired distribution of several ion channels,\textsuperscript{17} loss of metabolic support,\textsuperscript{18} and mitochondrial deficiency leading to energy failure.\textsuperscript{19} Despite being strongly associated with chronic activation of microglia and macrophages, these mechanisms tend to become self-sustaining, likely explaining continuous neurodegeneration inaccessible to anti-inflammatory treatments. Although this increased vulnerability mostly affects naked axons, neuronal abnormalities can also be detected in myelinated neurons, adding further complexity for designing neuroprotective strategies.

**Conclusion**

Neurodegeneration plays a central role in MS pathogenesis; it occurs early in the disease course and is a strong predictor of clinical disability. There is evidence that neurodegeneration is, at least partly, evolving per se independently of focal acute inflammation, influenced by genetic and metabolic background. These observations stress the need to pursue efforts to develop animal models of MS neurodegenerative pathology and in vivo biomarkers of neuronal function, in order to test putative neuroprotective agents eagerly expected in progressive MS.

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**References**


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Neurodegeneration in multiple sclerosis is a process separate from inflammation: No

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We consider that there are at least two phases in multiple sclerosis (MS): relapsing–remitting MS (RRMS) and secondary progressive MS (SPMS) (let us leave aside from the moment the question of primary progressive MS). The two clinical phenotypes suggest different pathological processes, as has been confirmed by numerous neuropathological and magnetic resonance imaging (MRI) studies.

My argument is that SPMS, characterised by steadily progressive, predictive disability, cerebral and spinal cord atrophy and neuroaxonal death is, purely and completely, a secondary effect of the preceding and ongoing inflammatory disease process.

The disappearance of hand surgeons in rheumatology

The management of rheumatoid arthritis, the corresponding disorder in rheumatology, has been revolutionised in the last ten years by the active management of the inflammatory process. Thus secondary contrac- tures, joint ankylosis and the need for prosthetic joint surgery has diminished by early medical intervention and the concept of ‘treating to target’ in rheumatology. Rheumatologists have the advantage over neurologists that their target is easily seen and palpable. It is also measurable with accessible biomarkers and radiological changes. Neurologists do not have these luxuries; their target is hidden, as discussed below.