Progressive multiple sclerosis 1

Pathological mechanisms in progressive multiple sclerosis

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A better understanding of the pathological mechanisms that drive neurodegeneration in individuals with multiple sclerosis is needed to develop therapies that will effectively treat patients in the primary and secondary progressive stages of the disease. We propose that the inflammatory demyelinating disease process in early multiple sclerosis triggers a cascade of events that lead to neurodegeneration and are amplified by pathogenic mechanisms related to brain ageing and accumulated disease burden. Key elements driving neurodegeneration include microglia activation, chronic oxidative injury, accumulation of mitochondrial damage in axons, and age-related iron accumulation in the human brain. Altered mitochondrial function in axons might be of particular importance. This process leads to chronic cell stress and imbalance of ionic homoeostasis, resulting in axonal and neuronal death. The evidence suggests that treatment of progressive multiple sclerosis should be based on a combination of anti-inflammatory, regenerative, and neuroprotective strategies.

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This is the first in a **Series** of three papers about progressive multiple sclerosis

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Introduction

Multiple sclerosis is a chronic inflammatory disease of the CNS that leads to focal plaques of primary demyelination and diffuse neurodegeneration in the grey and white matter of the brain and spinal cord.[1] In most patients, the disease starts with a relapsing-remitting course (RRMS), which is followed after several years by a secondary progressive phase (SPMS)`. Patients with primary progressive disease (PPMS) miss the relapsing and remitting stage and start with uninterrupted progression from disease onset.[2] When patients die within the first year of the disease, it is referred to as acute multiple sclerosis.[3] Current anti-inflammatory or immunosuppressive therapies are beneficial in patients with RRMS, but are not effective in patients with progressive disease.[4]

Although data have shown that the risk of disease development is determined partly by genetic factors related to immune function and activation,[5] and environmental factors such as Epstein-Barr virus infections,[6] the ultimate cause of multiple sclerosis is unknown. A commonly proposed idea is that multiple sclerosis is an autoimmune disease in which autoreactive T lymphocytes enter the CNS from the peripheral immune system in the initial stages of lesion formation (the outside-in hypothesis).[7] So far, no multiple sclerosis-specific autoimmune reaction has been identified. However, aggressive immunomodulatory treatments not only reduce relapses of the disease, but also reduce sustained disability progression, suggesting an important role for inflammation, at least in the early stages of the disease.[8] Alternatively, multiple sclerosis might be caused by a primary infection or neuronal disturbance within the brain, and inflammation might therefore occur as a secondary response to this initial trigger, which amplifies disease and tissue damage (the inside-out hypothesis).[9] Although infectious agents and specific alterations in CNS components that initiate a secondary immune reaction have not been identified in the brains of patients with multiple sclerosis, cortical atrophy can occur before substantial white matter demyelination and predicts future disease progression. While this finding could be taken as support for the inside-out hypothesis of multiple sclerosis, events that occur outside and inside the CNS are likely to determine the clinical outcome of the disease.

As outlined in this Series paper, many conflicting ideas have been proposed to explain disease progression and lesion formation in multiple sclerosis, all of which seem to be supported by firm and convincing data. We aim to provide a unifying picture by defining a cascade of immunological and neurodegenerative events that act in concert to induce multiple sclerosis-specific brain damage, but change in their relevance in the course of chronic disease evolution (figure 1; table).[1,10–33]

Neuropathological features of progressive multiple sclerosis

The most characteristic tissue injury in the multiple sclerosis brain is primary demyelination with partial preservation of axons,[3] but the prominent pathological feature of progressive multiple sclerosis is brain atrophy (figure 2).[34] Actively demyelinating plaques associated with inflammation and blood–brain barrier injury are seen mainly in patients with RRMS, and become rare in patients with progressive multiple sclerosis. A subset of lesions in progressive multiple sclerosis, which varies from case to case, shows low-grade myelin and axonal destruction at the white matter lesion margins (slowly expanding lesions, figure 2).[35] However, multiple sclerosis lesions rarely expand as a whole in chronic multiple sclerosis brains. Instead, they shrink, even in the presence of ongoing activity and expansion at the margins. This loss of lesion volume contributes substantially to brain atrophy and is caused partly by degeneration of chronically demyelinated axons. Axonal degeneration begins in acute or active multiple sclerosis lesions,[36,37] but does not initially cause neurological disability because the human CNS has a remarkable

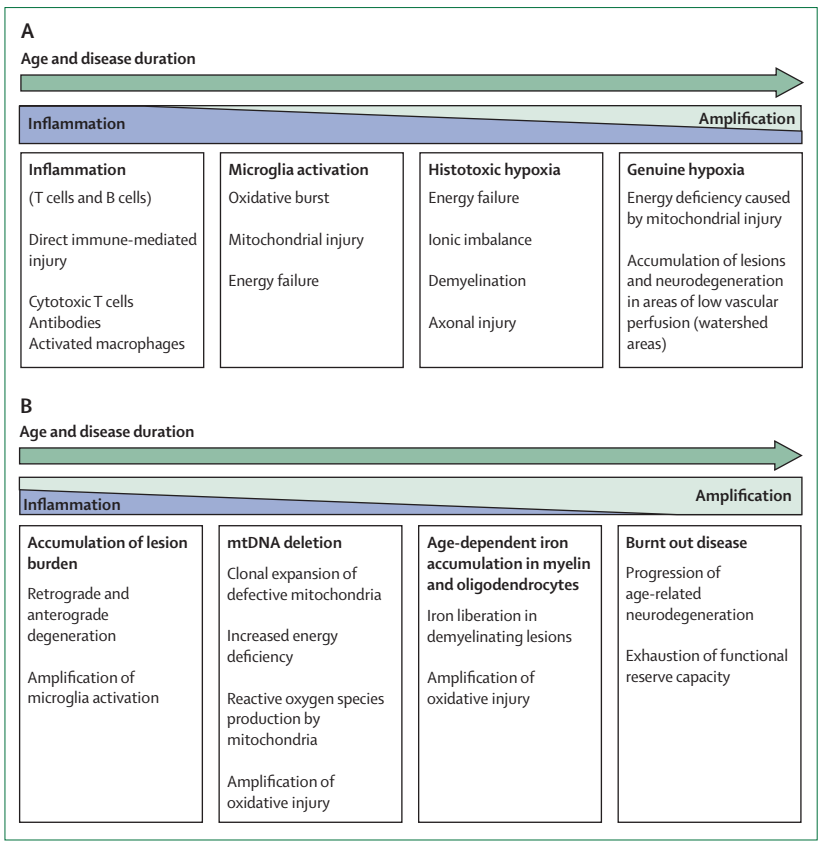

Figure 1: **Inflammatory demyelination and amplification factors for neurodegeneration in the multiple sclerosis brain**

Sequence of events, leading from (A) a predominantly inflammatory demyelinating disease in the early relapsing stage of multiple sclerosis to (B) neurodegeneration in the progressive stage. Although inflammation decreases in patients with age and disease duration, neurodegeneration is amplified by factors related to ageing and accumulation of pre-existing brain injury.

ability to compensate for axonal loss.[38,39] Most demyelinated axons survive acute demyelination, but do not survive chronic states of demyelination in most patients. The dynamics of axonal loss are not well documented and might vary from patient to patient and from lesion to lesion. Transected axons and axonal ovoids are present, but are not prominent features of chronic lesions, compared with acute lesions.[40] Chronic lesions persist for decades, while acute lesions exist for weeks. Thus, degeneration of chronically demyelinated axons is a prominent feature of the progressive multiple sclerosis brain and a major cause of irreversible neurological disability. In a mouse model of multiple sclerosis, permanent neurological disability was associated with a 38% loss of axons in the spinal cord.[41] Estimates of total axonal loss in chronic white matter lesions in severely disabled patients with multiple sclerosis can reach 60–70%.[38,42]

Another prominent pathological substrate of progressive multiple sclerosis is cortical demyelination (figure 2),[21,43] which seems to be one of the pathological substrates for cognitive disability, even in RRMS.[44,45] Different types of cortical lesion have been described and include leucocortical (corticosubcortical lesions, affecting white and grey matter), intracortical, and subpial lesions. Leucocortical lesions seem to start in the subcortical white matter and extend into the cortex. Active leucocortical lesions can be identified by the peripheral immune cell content of the white matter lesion. The cortical portions of acute leucocortical lesions contain increased numbers of immune cells, but these cells are substantially less abundant than those seen in subcortical white matter.[43] Leucocortical lesions are present in patients in the earliest stages of multiple sclerosis, and about 60% of subcortical white matter lesions enter the cortex.[46,47] Subpial lesions represent the most abundant type of cortical lesion and are most prominent in patients with progressive multiple sclerosis,[35] although they have also been described in patients with acute multiple sclerosis and RRMS who present with tumefactive white matter lesions.[47] Subpial lesions span long distances of the cortical ribbon and usually extend to cortical layers III or IV, but occasionally include all cortical layers, and rarely, if ever, invade the subcortical white matter.[48] These lesions are present in most chronic multiple sclerosis brains, but are absent from other inflammatory or non-inflammatory human brain diseases.[15,49] Subpial cortical lesions and neurodegeneration have been related to inflammation in the meninges of a subset of patients who have inflammatory infiltrates composed of T and B lymphocytes, plasma cells, and macrophages.[50,51] Lymphocyte infiltration in the cortical parenchyma is present in subpial cortical plaques in acute multiple sclerosis and RRMS,[21] but is sparse or absent in most patients with progressive multiple sclerosis. Active tissue damage is associated with microglia activation.[46,47] In addition to demyelination and oligodendrocyte loss, cortical lesions show neuritic transections, neuronal death, and reduced presynaptic terminals.[43,52] Grey matter demyelination also occurs in the cerebellar cortex,[53] hippocampus,[54] deep grey matter nuclei, and spinal cord.[55] Furthermore, synaptic loss in the demyelinated cortex[52] and hippocampus[56] is more prominent than neuronal loss. Analysis of neuronal miRNAs and neurotransmitter receptors in hippocampal multiple sclerosis lesions suggests that the synaptic alterations might partly be a secondary consequence of demyelination, and contribute to cognitive impairment of patients.[57]

Another characteristic feature of progressive multiple sclerosis is the diffuse pathology (microglia activation, axonal injury, and atrophy) in the normal-appearing white and grey matter.[35] These changes are present in early relapsing and remitting disease, but increase in severity with disease progression. Diffuse injury that is associated with microglia activation in the normal-appearing white matter can be more closely associated with cortical lesion volume than with white matter lesion load.[35] In the spinal cord, global atrophy can occur independently of focal white matter plaques.[58] MRI studies suggest that cortical atrophy might be more