

DISABILITY PROGRESSION IN MS IS DUE TO A NEURODEGENERATIVE DISEASE PROCESS

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Multiple sclerosis (MS) is a chronic and disabling disease of the central nervous system (CNS) the precise cause and pathogenesis of which remain unknown. The notion that MS is an inflammatory disease is largely based on an artificial model of experimentally induced demyelination after sensitisation to myelin basic protein (experimental allergic encephalomyelitis or EAE). The superficial resemblance between MS and EAE has underpinned past and present research and therapeutic developments in MS for over 60 years but is yet to achieve the therapeutic goal of limiting long term disability. The introduction of beta interferon in MS therapeutics was hailed as a major success of the immune-inflammatory hypothesis and the treatment was shown to reduce relapse rates and suppress MRI changes in white matter associated with demyelination. Twenty years later, it is clearly evident that beta-interferon was not associated with a reduction in progression of disability in patients with relapsing-remitting MS (Shirani et al, 2012). Moreover, beta interferon and related immunomodulatory drugs are ineffective in primary and secondary progressive MS where disability progression is independent of relapses, the biological model of inflammation.

Despite extensive and often laborious attempts over the years, not a single antigen or antibody has been proved to be a candidate for cell-mediated or humoral immunopathogenesis in MS. The rational inference, clearly, has to be that the modest inflammatory changes in demyelinating lesions are secondary to tissue injury from a primary neurodegenerative process. This view would be supported by the pathological observation that acute demyelination in MS can evolve without inflammatory cells (Barnett and Prineas, 2004). Pathological studies have also revealed that during the evolution of demyelinating plaque, the first changes appear at inner myelin sheaths, often in areas beyond areas of inflammation, when outer myelin sheaths are still intact, an observation that would be incompatible with an immunological injury targeted to the myelin from a cell or antibody mediated disease pathogenesis. Ultrastructural examination has also confirmed that the structural evidence of myelin injury in MS is present beyond areas of maximal inflammation (Rodriguez and Scheithauer 1994), confirming that inflammation and immunological changes in MS evolve in spatial dissociation from demyelinating lesions and cannot be regarded as causal. Several key histopathological features in MS cannot be explained by the assumption of myelin-directed inflammatory pathogenesis. Loss of retinal nerve fibres, early changes in grey matter and thalamic neurodegeneration, involvement of normal-appearing white matter, chronic axonal necrosis and hypoxic neuronal changes occur often at sites distant to inflammatory changes and lymphocytic infiltrates. In addition, oligodendrocyte apoptosis and microglial activation has been reported in acute MS in the absence of lymphocytes and macrophage activation. Axonal loss is an early feature in MS (Trapp and Nave, 2008) and there is no evidence of widespread IgG deposition or complement activated injury of myelinated axons and neurons to suggest that the degenerative process in MS is a consequence of immune-mediated inflammatory tissue injury. In chronic MS, there is hardly ever any evidence of inflammation in diffusely abnormal white and grey matter where myelin and axonal density is reduced. Progressive loss of brain volume occurs relentlessly over a period of time in chronic MS and loss of brain volume occurs irrespective of the severity of inflammatory process.

Epidemiological observations clearly suggest that the influence of clinical variables-and relapses-on the course of irreversible disability in MS is limited to the time of onset to the attainment of early walking impairment (EDSS score of 4.0) and subsequent progression of disability occurs in a self-perpetuating

pathway independent of clinical variables and inflammation has only a limited effect on neurodegeneration responsible for progressive disability (Confraveux et al, 2003) that results in the requirement of mobility assistance (EDSS score of 6.0 and above) in symptomatic patients after a median time of 20 years. Cervical spinal cord atrophy correlates best with walking impairment in chronic MS. Cognitive impairment is recognised in over two-thirds of patients with MS and dementia in younger patients with secondary progressive disease often presents a major problem.

The progression of disability in MS is due to irreversible and irreparable axonal and neuronal injury that is an inevitable consequence of natural history of the disease. Degenerative changes in both grey and white matter are well recognised even in the very early stage of the clinical disease. No anti-inflammatory treatment has ever been shown to reverse progressive disability from degeneration of neurons, axons and synapses in the CNS that are the pathological hallmarks of MS. Future shift of the treatment paradigm in MS to early disease prevention with vitamin D supplementation and deceleration of its intrinsic pace of tissue degeneration with neuroprotective therapy would be of greatest benefit to all patients regardless of their clinical phenotypes.

Reference

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