MULTIPLE SCLEROSIS IS PRIMARILY A NEURODEGENERATIVE DISEASE

Abhijit Chaudhuri
UK

The precise cause and pathogenesis of multiple sclerosis (MS) are yet 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 has not yet delivered a cure. The primary role of inflammation in the human disease is presumed, rather than proven. It is likely that the very modest inflammatory changes present in MS plaques represent the secondary effect of myelin injury and degradation triggered by a yet unknown process of metabolic stress. Disabilities in MS are the direct consequence of neurodegeneration that invariably occurs in every clinical phenotypes of the disease (relapsing –remitting, primary and secondary progressive MS). Indeed, degenerative changes in both grey and white matter are well recognised even in the very early stage of the clinical disease. Axonal loss is an early feature in MS and in chronic disease, there is significant loss of brain volume that occurs irrespective of the severity of inflammatory process and spinal cord atrophy correlates best with walking impairment. In addition, cognitive impairment is reported in over two-thirds of patients with MS and no anti-inflammatory treatment has ever been shown to reverse progressive disability from degeneration of neurons, axons and synapses in the central nervous system that characterise the disease.

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. There is no firm evidence that inflammatory changes are directed towards specific targets and there is no target antigen or pathogenic antibody in MS. Inflammatory changes are recognised in Alzheimer's disease lesions and HLA-association has been established for Parkinson's disease; however both Alzheimer's and Parkinson's diseases are prototype degenerative disorders of human central nervous system. In all likelihood, disease pathogenesis and disease progression in MS are metabolically influenced and are controlled by the oxidative stress in genetically and environmentally susceptible individuals. Anti-inflammatory therapy may have a marginal therapeutic benefit in neurodegenerative diseases by limiting the process of oxidative injury and the experience of immunotherapy in MS does not prove its causation.

Reference

1. *Chaudhuri A, Behan PO. Multiple sclerosis is not an autoimmune disease. Arch Neurol 2004; 61: 1610-1612.*
2. *Barnett MH, Prineas JW. Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. Ann Neurol 2004; 55: 458-468.*
3. *Trapp BD, Nave K-A. Multiple sclerosis: an immune or neurodegenerative disorder? Annual Review of Neuroscience 2008; 31: 247-269.*