Multiple sclerosis: a unique immunopathological syndrome of the central nervous system

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Multiple sclerosis: a clinical neurological syndrome mediated by immune phenomena

Multiple sclerosis (MS) is the most common, disabling neurological syndrome of young adults. The etiology is idiopathic, yet most authorities agree that the immune system is crucial in the pathogenesis of the recurrent and chronic injury to the central nervous system (CNS). Nearly identical histopathological findings occur in MS and related clinical syndromes, designated as “demyelinating diseases.” Clinical presentation differentiates MS from the monophasic syndromes (optic neuritis, acute transverse myelitis, and Marburg disease) and the less-common relapsing syndromes (Devic’s disease, Balo’s concentric sclerosis). A chronic progressive variant of MS is also well recognized.

The primary pathological feature of demyelinating diseases is a focal loss of CNS myelin in the white matter, the areas of concentrated, parallel myelinated axons within the CNS. Oligodendroglia produce and maintain the myelin. This multilamellar lipid structure permits rapid, saltatory conduction of action potentials and mechanically separates CNS axons. The focal nature of demyelinating disease contrasts with the diffuse myelin loss of toxic or metabolic injuries, such as occurs in leukodystrophy, myelinolysis, radiation, and nutritional compromise. The great magnitude of myelin loss relative to the perivascular inflammatory infiltrate differentiates MS from the more cellular inflammatory response of acute disseminated encephalomyelitis.

Demyelinating disease afflicts 0.2% of individuals in high prevalence areas, and incidence is increasing. MS is not associated with other immune diseases [104]. Genetic studies reveal weak associations with major histocompatibility complex (MHC) and T cell receptor (TCR) genes and only moderate concordance in monozygous twins, supporting a polygenic inheritance for susceptibility and severity, as well as environmental factors.

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Diagnosis is dependent upon clinical findings often in association with typical magnetic resonance (MR) imaging or immunological findings of cerebrospinal fluid (CSF). Less commonly biopsy or post-mortem examination are required to demonstrate typical histopathology. The characteristic focal inflammatory events in brain and spinal cord leave areas of increased water and decreased lipids visible with MR imaging. Paramagnetic contrast enhances these areas in acute lesions where inflammation perturbs the blood-brain barrier (BBB) [55]. Chronic inflammation in the brain and meninges also results in characteristic changes in the CSF.

Clinical neurological deficits depend primarily upon the location of the inflammation. Impairment is due to multifactorial axonal dysfunction, in part due to inflammation, edema, disordered axonal sodium channels, BBB abnormalities, demyelination, and axonal loss. The most common clinical deficits include impairment of visual acuity, double vision, abnormal sensation, incoordination, spastic weakness, tremor, mood disorders, and fatigue. Significant intellectual impairment is uncommon except in advanced stages of the disease, and most cerebral lesions are silent clinically. Lesions tend to cluster in the periventricular areas, but can occur almost anywhere within the CNS white matter.

The temporal pattern and progression of the disease are unpredictable. About half of cases have minimal progression, whereas about 10% of cases have a severe course which results in death due to MS or complications of the marked disability [76]. The most typical pattern is one of a relapsing-remitting deficit, but with time the attack rate decreases, the inter-attack disability increases, and eventually a progressive disease emerges. The primary chronic progressive variant has few or no distinct exacerbations. Large, fulminating and frequently life-threatening demyelinating lesions [55] are the least common presentation. In all of these clinical syndromes, the essential pathological lesion is similar.

Therapies for MS have targeted the immune response, mostly with limited benefit. Anti-inflammatory treatment with short courses of high-dose intravenous corticosteroids shorten exacerbations, may improve immune and inflammatory parameters, and prolong the interval to further neurological symptoms following an attack of optic neuritis [7]. Whereas clinical trials with interferon (IFN-γ) resulted in increased exacerbations [57], IFN-α suppresses the severity of exacerbations but does not alter disease progression [1]. IFN-β has similar actions to IFN-α, and, although larger active lesions are fewer on MR images [58], no difference in disability results over 3 years.

A hypothesized failure of self-tolerance, which could underlie autoimmunity, has spurred ongoing attempts to promote immunological tolerance by administration of proteins mimicking myelin antigens. Anti-proliferative and immunosuppressive treatments have been used with limited benefit and with significant toxicities. Attempts to modulate the disease through manipulation of blood components have had limited efficacy. Plasmapheresis (removal of the plasma) has a short-term benefit of less than 3 months [100], but may have an important role in the treatment of acute fulminating demyelinating disease [74]. Immunoglobulin (Ig) may improve function in optic neuritis [96] and is currently being studied as a way of promoting remyelination in double-blinded controlled trial.