SPECIAL ARTICLE

Multiple sclerosis: looking beyond autoimmunity

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'My dictionary gives the Latin root for falsity as *fallere*, which is the same root for the word failure.'—Lewis Thomas[1]

The chronic incurable disorder multiple sclerosis (MS) is characterized by neurodegeneration, multifocal demyelination and astroglial proliferation (gliosis).[2] The prevalence of MS is influenced by geography and genetics. In the Western world it is a leading cause of neurological disability in the young. The cause and exact pathogenesis are still unknown. Some see MS as a T-cell-driven autoimmune inflammatory disease, targeting the myelin sheaths in the central nervous system,[3] but there is no proof. Unlike autoimmune conditions such as rheumatoid arthritis, systemic lupus erythematosus or myasthenia gravis, MS has no specific immunological marker.[2,4]

An animal model that has been used in MS research is experimental allergic encephalomyelitis (EAE), in which demyelination is induced by sensitization against myelin basic protein. Clinically and pathologically, however, EAE resembles acute disseminated encephalomyelitis (ADEM) rather than MS.[2] Nonetheless, the EAE model has been used to drive the autoimmune theory and to develop treatments. An inflammatory hypothesis of demyelination also fails to explain various salient features of the disease (Box 1).[5–7] Here, we explain our view that research and treatment strategy in MS need to change direction.

HISTORICAL PERSPECTIVE

It was during the 1940s and 1950s that researchers became interested in experimentally induced demyelination. Hyperacute and acute demyelination (ADEM) in man came to be recognized as a complication of immunization with brain derived tissue (e.g. post-rabies-vaccine encephalomyelitis) and a similar 'allergic' basis of demyelination in MS was postulated. Adams made a detailed histological comparison of ADEM and MS in terms of morphological criteria for demyelinative disease—namely, destruction of myelin sheaths of nerve fibres; relative sparing of all other elements of nervous tissue (i.e. nerve cells, axis cylinders and supporting structures); and distribution of lesions, often perivenous, in multiple locations throughout the brain and spinal cord or to single foci spreading from one or more centres.[8] From Table 1, summarizing his observations, it is apparent that there are similarities but also important differences. Adams regarded the syndrome of acute bilateral optic neuritis and transverse myelitis (neuromyelitis optica, Devic's disease) as a regional variant of ADEM; the clinical syndrome of myelitis was judged merely a matter of localization within the spinal cord, where the tight confines of the pia and the oedema of very rapidly evolving lesions of ADEM led to infarction-necrosis (a condition seldom seen in the brain).

Subsequently, one of us (POB) showed that both EAE and ADEM are T-cell-dependent, organ-specific, autoimmune diseases of the central nervous system.[9,10] This has not been found true for MS, despite three decades of intensive research. Indirect evidence cited in support of an autoimmune pathogenesis for MS has likewise been found wanting (Table 2).

DISSOCIATION OF MS FROM EAE AND ADEM

The clinical, radiological, and histological differences between EAE and MS, we believe, argue against a common pathogenesis. EAE is typically a monophasic disorder, and even subacute or chronic relapsing models of EAE represent

Box 1 **Important facts about MS that cannot be explained by the concept of myelin-specific autoimmunity**

- Age effect of migration
- Geographic variation (higher prevalence in most northern latitudes)
- Maternal contribution to disease risk (Ref. 5)
- Early and extensive grey matter involvement (estimated number of deep grey matter lesions per gram wet weight is higher than in any other brain structure [Ref. 6])
- Progressive brain and spinal cord atrophy, beginning at the stage of clinically isolated demyelinating syndromes (Ref. 7)
- Selective anatomical localization, symmetry and sharp margins of plaques
- Absence of specific immunological marker
- Effect of stress
- General failure of immunotherapies that are highly successful in other organ-specific autoimmune diseases and transplant rejection
- Associations with Charcot–Marie–Tooth disease and neurofibromatosis-1 (Ref. 2)

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Table 1 **Comparative pathology of the demyelinative lesions in acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS)**

Pathological characteristics	*ADEM*	*Acute and chronic MS*
Distribution	Focal, regional or diffuse	Multifocal; as a rule entire central nervous system is affected in chronic MS
Age of lesions	Always same and uniform	Always of different ages (both in acute and chronic MS)
Size of lesions	0.1–1.0 mm	1.0 mm or less to 5+ cm
Relation of lesions to:		
Veins	Always	Prominent and usual
Pia	Usual	Rare
Degeneration of:		
Axis cylinders	Mild to severe	Mild to moderate
Nerve cells	Mild	Mild to moderate
Oligodendroglia	Restricted to lesions	Restricted to lesions
Astrocytosis	Mild	Marked in chronic MS
Tissue necrosis	May be severe	Rarely severe
Perivascular infiltration	Always and marked	Usually (but not always) present; prominent only in acute MS
Meningeal inflammation	Minimal to pronounced	None
Vascular damage and fibrin deposition	Constant and severe in hyperacute cases	Mild or none
Microglial proliferation	Marked, with pleomorphic forms	Pleomorphic forms in acute cases

Table 2 **Autoimmunity and multiple sclerosis (MS)**

Evidence used to support the concept of autoimmunity in MS	*Comments*
Predominance of women affected, as in rheumatoid arthritis and systemic lupus erythematosus	Predominance of women also seen in non-autoimmune disorders such as migraine
Association of other autoimmune diseases in affected individuals and families	Not proven in large epidemiological studies of MS
Association with HLA haplotypes	The strongest HLA links are observed with hereditary haemochromatosis and narcolepsy, metabolic and neurodegenerative diseases respectively
Antimyelin antibodies in serum	Antimyelin antibodies can be detected in neurological disorders other than MS, and some antimyelin antibodies have a reparative function
Oligoclonal bands in cerebrospinal fluid	These bands are reported in other neurological diseases such as subacute sclerosing panencephalitis and neurosyphilis, conditions that are not autoimmune. Oligoclonal-band-negative cases of MS have been reported
Specific T-cell response identified during MS relapses	No T-cell response is unique or specific in MS
Partial therapeutic response of relapses to beta-interferons, glatiramer and other immunotherapies	Relapse prevention in MS may not translate into disability prevention. No immunotherapy has reduced long-term disability in MS

recurrent challenges to some encephalitogenic antigen, a phenomenon that has not been shown to apply in MS. The progressive and global brain and spinal cord atrophy that characterizes the human disease from its earliest stages[7] has not been reproduced in animals with EAE. EAE and ADEM also differ from MS in that the uninvolved white matter is normal.[11]

One of the characteristic histological features of EAE is destruction of cerebral endothelial cells by an immunological mechanism, and this is seen in human cases of ADEM after immunization (post-rabies vaccine encephalomyelitis) or endotoxic shock,[12] but not in MS. Even from the early days it was acknowledged that chronic relapsing MS had pathological features that were absent in acute or subacute

EAE, such as the large sizes and confluence of individual demyelinating lesions ('plaques'), the shadow plaques and the appearance of fresh lesions at the borders of the older ones 'as though the pathological process had spread in a succession of waves from a more central focus'.[8] Furthermore, there are inherent pitfalls in the assumption of a common pathogenesis based on morphological similarities alone, when the range of histological responses to injury is so limited within the nervous system. For example, ischaemic brain tissue will look much the same in cerebral infarcts due to systemic lupus, cardioembolic stroke or thrombotic stroke, though the pathogenesis and treatment will differ. Morphological issues apart, an important reason for questioning the extrapolation of EAE to MS pathogenesis is the failure to identify an encephalitogenic marker specific for MS. In Devic's disease (a variant of ADEM), Lennon *et al.* have now found an antibody that localizes with laminin at the blood-brain barrier.[13] We would recommend immunosuppression in Devic's disease but not in MS.

BEYOND AUTOIMMUNITY IN MS

The definition of MS as a T-cell-specific autoimmune demyelinative disease is in our view too narrow. First, nearly 60 years of EAE-based research yielded not a single MS-halting therapy. This in itself should be an important reason to consider a shift in research direction. Although the existing disease-modifying therapies reduce relapse rates in some patients by up to one-third there is little evidence that the common features of fatigue, pain, depression and cognitive decline are positively influenced.[14] There is also a concern, theoretical at present, that early benefit of reduced relapse rates may later be offset by accelerated brain atrophy.[15]

Second, neurodegeneration is now regarded as an important component in MS. It is neurodegeneration rather than demyelination that contributes to long-term disability. Several pathological and MRI studies indicate that grey matter involvement is early and extensive. Axonal transection may be degenerative, inflammatory or both, but brain and spinal cord atrophy is considered to be the direct result of neurodegeneration. If we accept axonal degeneration and neuronal loss to be essential features, then MS no longer fulfils the original criteria of a primary demyelinative disease and comparison with EAE becomes even less apposite. Longitudinal studies of brain volume in MS teach us that the rate of brain atrophy is independent of the disease subtype;[16] in other words, whether the disease is classed as relapsing–remitting or progressive, the loss of brain volume is the same and is due to neurodegeneration. While the concept of clinical and pathogenic heterogeneity[17] has been proposed to identify an inflammatory subgroup in necropsy studies, it is clear that all patients, whatever their clinical phenotype, require neuroprotection.

Third, the most neglected aspect of MS research is prevention, and we believe that this again is explained by the erroneous assumption of autoimmunity. Several potentially modifiable environmental factors are associated with the risk of developing MS. One is infectious mononucleosis due to Epstein–Barr virus (EBV), which emerged in a large case-control study of MS and virus infection among US women (Nurses' Health Study I and II) as the single most important risk factor.[18] Currently, the search for an effective EBV vaccine is focused on prevention of lymphoproliferative disorders and nasopharyngeal carcinoma in susceptible populations,[19] but such a vaccine has huge potential for reducing the risk of several other debilitating clinical syndromes including MS. Smoking is another modifiable risk factor;[20] in female nurses there was a clear dose-response relation between cigarette consumption and MS, and in a general population the risk of MS was higher in smokers than in never-smokers.[21] Clearly, smoking needs to be especially discouraged, from the time of diagnosis, in a patient with MS.

Finally, of all the environmental risk factors associated with MS, vitamin D seems the most easily modified.[22] In a longitudinal follow-up study of over 90 000 women, those taking vitamin D supplements had a 40% lower incidence of MS than those who did not.[23] MS is rare in the tropics and a direct relation between sunlight exposure and MS has been confirmed in epidemiological studies since 1960.[24] Therefore an argument can be made for vitamin D supplementation to reduce the risk of MS in areas of high disease prevalence in the northern latitudes where solar exposure is inadequate for vitamin D synthesis throughout the year.[22]

CONCLUSIONS

After six decades of autoimmune and EAE-based research, the time has come for a change in direction. For basic scientists, the challenge is to develop a new animal model of MS that replicates both demyelination and neurodegeneration. Solvent-induced demyelination might be such a model, in view of the association between solvent exposure and MS risk.[25,26] For clinicians the task is to evaluate existing neuroprotective treatments. Possible candidate agents for randomized trials in early MS are antioxidants such as coenzyme Q_{10},[27] omega-3-essential fatty acids,[28] minocyclin,[29] and cannabinoids,[30] alone or in combination.

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