SECTION EDITOR: E. S. ROACH, MD

Multiple Sclerosis Is Not an Autoimmune Disease

Abhijit Chaudhuri, DM, MD, PhD, FACP, FRCP; Peter O. Behan, DSc, MD, FRCP, FACP

Disease is very old and nothing about it has changed. It is we who change as we learn to recognize what was formerly imperceptible.

J. M. Charcot

The cause of multiple sclerosis (MS) and its pathogenesis are unknown, but 2 main theories have emerged: a viral cause and an autoimmune cause. In the past half century, however, research and therapy have been driven by the autoimmune hypothesis. We propose that MS is not an autoimmune disease but a genetically determined disorder characterized by metabolically dependent neurodegeneration.

AUTOIMMUNITY AND MS

The idea that MS may be a central nervous system, myelin-specific autoimmune disease is based on 2 sets of observations. The first is that fatal cases of acute disseminated encephalomyelitis (ADEM) have sleevelike, perivenous myelin damage up to 2 mm in diameter, in association with cellular infiltrates. The second observation is that animals inoculated with brain material develop experimental, allergic encephalomyelitis (EAE), which clinically, histologically, and immunologically is identical to ADEM. It has been repeatedly demonstrated that ADEM and EAE are organ-specific autoimmune disorders caused by T-cell sensitization to encephalitogenic myelin basic protein.[1-3] Both EAE and ADEM are acute, monophasic neurological syndromes where limited myelin damage follows endothelial cell injury.[4]

The confluent demyelinating lesions in patients with MS are entirely different. Indeed, lymphocytic infiltration is not regarded as 1 of the diagnostic criteria. The MS plaque has a well-defined edge and a scant lymphocytic infiltrate that is absent in one third of all plaques. In patients with MS, the normal-appearing gray and white matter are always involved with the disease process, extending well beyond the borders of the plaque as seen in the T_2-weighted magnetic resonance (MR) brain images. In the diffusion tensor MR imaging, there is a progressive decline in fractional anisotropy extending from the normal-appearing white matter to the plaque with the most extensive changes seen at the center of the plaque paralleling the decrease in the magnetization transfer ratio.[4] White matter abnormalities in ADEM are different, however, and do not extend beyond the focal areas of injury. Unlike MS, the magnetization transfer ratio of the uninvolved brain and spinal cord in ADEM is identical to that of normal tissue. The evolution of the plaques in patients with MS as seen in MR spectroscopy is different from ADEM.

Extrapolation of EAE data to MS is guided purely by faith rather than by science. Even the most exhaustive experiments have yielded inconclusive results. Autoreactive T-cell clones to brain antigens are also found in the blood of healthy individuals. The cornerstone of the autoimmune hypothesis is that sensitized T cells attack putative myelin antigens, and that T-cell–dependent inflammation is responsible for the local breakdown of the blood-brain barrier and subsequent influx of the immune components that lead to MS lesions. However, there is no evidence that these processes cause the typical demyelinating plaques seen in patients with MS or are disease specific. Transplanting EAE data to human MS is not science but an example of monumental incredulity that has only hindered proper MS research. Myelin-antigen reactive T cells are present in the peripheral blood and cerebrospinal fluid of patients in a variety of neurological disorders and show a 7-fold rise after acute stroke, where it is considered to be a response to acute brain injury rather than its cause.[5]

Numerous detailed immunological analyses of the inflammatory cells have been reported without any evidence that demyelination is directly caused by such cells. Similarly, nonspecific cellular infiltrates are found in many conditions including adrenoleukodystrophy, amyotrophic lateral sclerosis, and in the spinal cord of patients even 40 years after an attack of poliomyelitis.[4] Others have argued that complement activation at the edge of some of the MS plaques is sufficient evidence to support an immunopathogenesis. However, complement activation and lymphocytic infiltration are also observed in the brains of patients with neurological infections, head injury, cerebrovascular ischemia, and neurodegenerative diseases.[6] Many studies confirm that demyelination in the MS plaque may occur in the absence of mononuclear cells.[4]

Oligoclonal bands in the cerebrospinal fluid are present not only in patients with MS but also in patients with a variety of other nonimmune conditions. Despite the voluminous literature on immunological abnormalities claimed to be present in the peripheral blood and cerebrospinal fluid of MS patients, none has been found to be specific. Claims have been made that antimyelin antibodies predict or modify the course of MS and may therefore contribute to the dis-

Author Affiliations: Division of Clinical Neurology, University of Glasgow, Scotland.

ease pathogenesis.[7] Antimyelin antibodies in patients with MS are a nonspecific feature (an epiphenomenon) because these antibodies have been shown to be present in patients with closed head injury, stroke, amyotrophic lateral sclerosis, and subacute sclerosing panencephalitis.[8]

MS THERAPY BASED ON AUTOIMMUNITY

Unlike other autoimmune diseases such as rheumatoid arthritis or myasthenia gravis, no association with disease-specific immune markers or other systemic autoimmune diseases exists in patients with MS. The age effect on migration and risk of acquiring MS and the geographic variations in disease prevalence cannot be explained by the autoimmune hypothesis. Despite the fact that MS does not fulfill the criteria of an autoimmune disease, this has not deterred researchers from attempts at using varied immunotherapies over the years, and having treatment fatalities on occasions (**Figure 1**). None of these therapies is effective or safe for long-term use. Optimism at the launch of each new MS immunotherapy is dampened by the ensuing failure, only to be followed by renewed expectations of yet another new treatment. Therapeutic endeavors based on faith and hype are doomed to fail, and the saga of MS immunotherapy is a particularly good example.[9] In general, MS immunotherapy has been guided by the false hope that a reduction of relapse rates in the short-term will limit significant disability among patients in the long-term. However, epidemiological studies have shown that there is a biological dissociation between relapses and progression in patients with MS even at a modest level of disability.[10] The 2 most widely prescribed therapies for MS (β interferon and glatiramer acetate) have no effect on the progressive forms of the disease (primary or secondary MS), although relapse rates may be reduced by about one third in some patients. A response rate of one third is considered to be a powerful placebo effect in treatment trials.[4] In women, the effect of pregnancy on relapse remission is superior to both β interferon and glatiramer; however, disability progression is not influenced by the reduced relapse rate during pregnancy.[11] The therapeutic effect of mitoxantrone in patients with secondary progressive MS is not convincing.[12]

MS IS A METABOLICALLY DEPENDENT, NEURODEGENERATIVE DISEASE

It is our contention that MS relapses are primarily caused by metabolic changes influencing glial and neuronal function that lead to a breakdown in the blood-brain barrier. Proton MR spectroscopy studies have confirmed that widespread neuronal loss is present even at the earliest clinical stage of the disease and is largely independent of inflammation.[13] *N*-Acetyl aspartate is considered to be a marker of the functional neuronal mass, and a reduced total brain *N*-acetyl aspartateis an excellent predictor of relapses in patients with MS. Treatments using natalizumab, which are effective in reducing the permeability of the blood-brain barrier,[14] may not reduce the disease progression that occurs as a direct result of neuronal loss. This is because immune mechanisms are not responsible for neuronal loss and progressive brain and spinal cord atrophy in MS. Demyelination in MS spares the subcortical U-fibers that are typically involved in oligodendroglial infection and demyelination (progressive multifocal leukoencephalopathy). Symmetry of lesions and sparing of the U-fibers on T_2-weighed MR images are compatible with metabolically inherited white matter diseases.[15]

Relapse-related acute symptoms in patients with MS are caused by physiological blockade of conduction, and even though conduction abnormalities may continue to persist, functional recovery (remission) occurs in the early stage of the disease. There is significant involvement of the gray matter that often manifests early as neurobehavioral, cognitive, and paroxysmal symptoms that are not explained by myelin loss. Pathologically, gray matter involvement is always present in patients with MS where progressive brain atrophy is common in longitudinal MR studies. A recent study[16] of the thalamic gray matter of MS patients has confirmed substantial neuronal loss (30%-35% reduction) and concluded that neurodegeneration may make a major contribution to the pathogenesis. There is also evidence from MR spectroscopy that neuronal metabolic dysfunction and neuronal loss is closely associated with disease progression and disability.[4] In MS, as axons and their myelin sheaths break down in the metabolically compromised brain, their effective repair and regeneration are blocked by inhibitory factors from astroglia and oli-

Currently licensed treatments:
- Interferon beta, glatiramer acetate, mitoxantrone, and natalizumab

Other treatments advocated or used in trials:
- Adrenocorticotrophic hormone
- Interferon alfa
- Altered peptide ligands
- Antilymphocyte globulin
- Azathioprine
- Bone marrow transplantation
- Campath 1-H
- Chimeric monoclonal antibodies to CD4 cells
- Chlorambucil
- 2-Chlorodeoxyadenosine (Cladirabine)
- Cyclophosphamide
- Cyclosporin
- Deoxyspergualine
- Interferon gamma
- Human immunoglobulin
- Infliximab
- Interleukin 10
- Inthrathecal PPD
- Isoprinosine
- Lenercept
- Linomide
- Methotrexate
- Methylprednisolone
- Mycophenolic acid
- Myloral (oral myelin)
- Oral copolymer
- Paclitaxel
- Photopheresis
- Plasma exchange (plasmapheresis)
- Rapamycin (Sirolimus, Wyeth-Ayerst Laboratories, St David, Pa)
- Sulfasalazine
- Tacrolimus (Fijisawa Healthcare, Inc, Deerfield, Ill)
- T-cell vaccination
- T-cell receptor peptide vaccination
- Total body or lymphoid irradiation
- Transfer factor
- Transforming growth factor β2

Figure 1. Immunotherapies in multiple sclerosis. Photopheresis is exposing peripheral blood lymphocytes in extracorporeal circulation to photoactivated 8-methoxypsoralen and reinfusing these cells to "target unirradiated T cells of the same pathogenic clone." PPD indicates purified protein derivative of the tubercle bacilli.

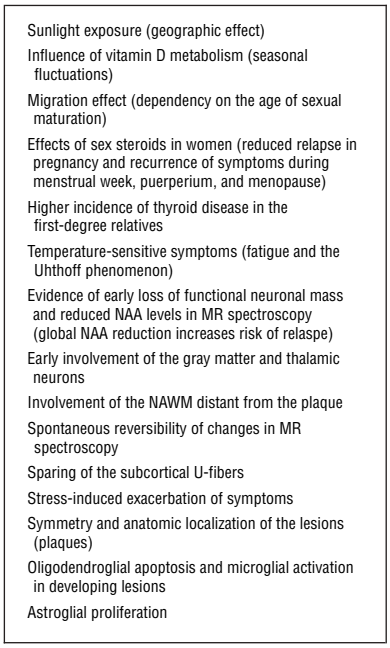

Figure 2. Features suggestive of possible metabolic regulation of disease process in multiple sclerosis. NAA indicates *N*-acetyl aspartate; MR, magnetic resonance; NAWM, normal-appearing white matter.

godendrocytes that, in turn, stimulate astroglial proliferation as evidenced by a reduction in the fractional anisotropy of the diffusion tensor MR images.[17] **Figure 2** summarizes the features that are in keeping with a metabolic regulation of the disease. We know that exposure to sunlight is protective in patients with MS[18] and vitamin D levels may be one of the key metabolic regulators in the "at-risk" individuals who carry the MS susceptibility gene or genes.

CONCLUSIONS

Our view is that the extrapolation of data on EAE to MS and its application for research and therapy is fundamentally flawed. This has been repeatedly demonstrated by the EAE models, where effective treatments are hardly ever successful in preventing disability in patients with MS. We concur with the view that

T-cell subsets, T-cell clones specific for myelin basic protein, and rodent models of central nervous system inflammation induced by a nasty concoction of myelin, Freund's adjuvant and pertussis toxin have not yet led to the anticipated insights into disease mechanisms that might permit a mechanistic understanding of the disease or a rational approach to therapy.[19]

Epidemiological studies and data from the new MR techniques cast serious doubt on the role of inflammation in patients with MS. There is increasing evidence that the primary mechanism of disease is neuronal and glial and not autoimmune demyelination. Abnormal neuronal metabolism appears to be the key determinant of disease progression in patients with MS. Autoimmune MS research raises the spectre of monumental incredulity; the documented failure of immunotherapy should be required reading for the clinicians and future grant applicants. Future MS therapies must be targeted to neuroprotection, and dietary vitamin D supplementation should be considered in all susceptible individuals.

NOTE ADDED DURING FINAL SUBMISSION

At the time of the final submission of this manuscript, Barnett and Prineas[20] have published pathological findings of the newly forming demyelinating lesion in 12 patients who died with acute MS. Extensive oligodendrocyte apoptosis and microglial activation with virtual absence of the lymphocytes or myelin phagocytes were the changes observed in the developing lesions, supporting our contention that the current laboratory model (EAE) and the autoimmune hypothesis of MS are both incorrect and inappropriate.

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Correspondence: Abhijit Chaudhuri, Department of Neurology, Institute of Neurological Sciences, 1345 Govan Rd, Glasgow, Scotland G51 4TF (ac54p@udcf.gla.ac.uk).
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