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Multiple Sclerosis: Neuroimmunologic Puzzle

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MS is the most common neuroimmunologic disease in the United States with current estimates indicating that some 250,000 individuals may be afflicted.[9, 31] The disease is a major cause of disability among working-age Americans, with the highest incidence of definite diagnosis in the 20 to 40 age group. The cause of the disease is unknown but evidence suggests both genetic and environmental factors play a role. A number of excellent reviews describing various aspects of MS are available.[2, 7, 25, 45, 58, 73] This article will briefly review the major characteristics of MS and will then focus on neuroimmunologic findings that may be encountered by the clinical immunopathology laboratory.

EPIDEMIOLOGY

Analyses of risk factors in MS have indicated that both hereditary and environmental factors appear to be involved in development of the disease. There is a north-south gradient for the disease that is independent of heredity, and in the United States, those born and raised above the 37th parallel have a 1.9-fold greater risk of developing MS than do individuals born and raised below the 37th parallel. Commonly, MS begins in the third and fourth decades with a mean age of onset in the United States of 33 years. Women are affected 1.7 times as often as men.

Epidemiologic studies of MS in other countries have shown that there is a higher risk above the 40th parallel in both the Northern and Southern hemispheres (prevalence greater than 40 out of 100,000). Between this latitude and the Tropics of Capricorn and Cancer, there is a medium-risk zone (20 to 39 out of 100,000), and between the Tropics themselves, there is a low-risk zone (fewer than 19 out of 100,000). These observations have been considered to be marred by regional differences in medical care, but

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are supported by other observations indicating that when persons born in low-risk areas migrate to high-risk areas, they still have a lower incidence of disease than do people born in high-risk zones. The later in life the migration occurs, the lower the risk of MS.

The conclusion drawn from these findings is that an environmental agent must contribute to the incidence of MS. Support for this concept has also come from observations of clustered cases such as those reported in the Faroe Islands.[32] No cases of MS were recognized prior to World War II, but between 1943 and 1960, 24 cases appeared, and only one additional case has appeared since 1960. Such clustering of cases in space and time strongly suggests the introduction of an environmental infective agent, possibly related to the stationing of the British Army in the Faroes just before the epidemic began. The long period of time between the arrival of British soldiers and the onset of MS cases suggested that the putative infectious agent acted with considerable latency.

Epidemiologic studies of MS have also suggested that genetic factors may play a role in susceptibility. MS is rare or absent in some populations such as the Bantu, Orientals, and Gypsies. The last group shares a common environment with other Northern Europeans in whom the disease is relatively common. These population differences are found regardless of the influence of the north-south gradient upon local incidence of disease. Other evidence for a genetic influence on the incidence of MS comes from population studies indicating an overrepresentation of HLA-B7 and DR2 histocompatibility antigens among patients with MS. These studies have given rise to speculation that environmental factors may be implicated in the incidence of MS, and because the putative agent appears to act after a long latent period, they have suggested that incidence is also related to a genetically susceptible host. Thus, the current understanding of MS implicates both environmental factors and genetic susceptibilities in the incidence of the disease.

CLINICAL ASPECTS AND DIAGNOSIS

Clinically, MS presents a varied spectrum of symptoms and disease course. The course of MS may be relatively benign; exacerbating-remitting, progressive from onset; or exacerbating-remitting, becoming progressive. In previous years, early diagnosis of MS was difficult, and further, there was no advantage to early diagnosis in terms of patient welfare. Although there is no specific treatment for MS, advantages in medicine have allowed for earlier diagnosis and a markedly improved prognosis. With standard medical maneuvers, such as treatment of pneumonia, prevention and treatment of pulmonary emboli, prevention and treatment of pressure sores, and treatment of neurogenic bladder, the mean life expectancy of patients with MS has increased from 10 to 35 years after onset.

Criteria for diagnosis of MS were fundamentally revised in 1983 to reflect new technologies available for early diagnosis.[52] The major item in the differential diagnosis of early MS is hysteria, and neuropathologic confirmation of MS is not possible during life. Therefore, objective clinical

testing procedures have been emphasized. The new diagnostic criteria recognized the ability of new neuroimaging techniques such as computed tomography and nuclear magnetic resonance to identify silent CNS lesions. The ability of evoked potential testing to similarly identify silent lesions was also acknowledged. In addition, these criteria recognized that qualitative or quantitative abnormalities of IgG may be detected in the cerebrospinal fluid (CSF) of more than 90 per cent of all patients with definite MS. Thus, to fulfill the new diagnostic criteria, the numbers of clinical episodes of neurologic dysfunction are counted, CNS lesions are detected by clinical examination and by various clinical diagnostic techniques as mentioned previously, and in addition, the degree of certainty of diagnosis can be enhanced by the knowledge that IgG abnormalities are present in CSF. By these criteria, Clinically Definite MS is indicated if two episodes of neurologic dysfunction have occurred and if at least two CNS lesions are detected. Laboratory-Supported Definite MS is indicated if one or two attacks have occurred, one or two CNS lesions are present, and in addition, CSF testing demonstrates IgG abnormalities. The new diagnostic criteria are essential for objective recognition of MS cases for inclusion in clinical therapeutic trials, epidemiologic surveys, or other research studies. These diagnostic aids also require careful interpretation however, because all of the tests involved are nonspecific. The quality of laboratory support may affect results, and in addition, each abnormality detected has a differential diagnosis including MS.

HISTOPATHOLOGY

When Charcot coined the term "sclerose en plaques" for MS, he considered glial scarring (sclerosis) to be the primary pathogenetic process.[14] The disease is now generally considered to be primarily one of demyelination, characterized by destruction of myelin sheaths within the CNS with the preservation of neuron axis cylinders.[2, 3] Lymphocytic cuffing about blood vessels and infiltration of brain parenchyma often accompany the demyelinating process. MS lesions have been classified according to the amount and type of myelin breakdown product present and also according to the numbers and types of cells in or about the lesions. Acute or active lesions have been seen only rarely and have been noted in patients who died within a few years after onset of disease. These lesions appear hypercellular with numerous lymphocytes and macrophages infiltrating the demyelinated tissue.[53, 54] Lesions have a pinkish color. Proliferation of hypertrophic astrocytes is characteristic of the lesion margins. Subacute (active) lesions appear grayish-yellow and have been characterized by peripheral hypercellularity and increased enzyme activity in the phagocytes, astrocytes, and lymphoid cells appearing at the edges of the lesions. The lesions observed most frequently in MS cases are the grayish chronic or inactive lesions characterized by little or no evidence of recent myelin breakdown. In chronic plaques, normal parenchyma has been replaced by parallel rows of dense glial fibers along preserved but naked (demyelinated) axons. Reactive and occasionally multinucleated astrocytes appear at the

edges of the plaques. Oligodendroglia, the myelin-synthesizing cells of the brain, are absent from the lesion centers.

Immunohistochemical studies of MS lesions have detected abundant IgG deposits in chronic MS plaques as well as the presence of IgG-positive plasma cells and reactive astrocytes containing IgG.[19, 22, 60] Identification of T-lymphocytes by monoclonal antisera have indicated that helper/inducer T cells (T4) appear to be common in active lesions and extend into adjacent normal-appearing white matter. Numerous suppressor/cytotoxic T cells (T8) have been found most commonly in perivascular cuffs.[66] Macrophages displaying Ia antigens were found in the center and edges of plaques. Recent studies have detected Ia antigens on endothelial cells throughout MS brain, and on reactive astrocytes located predominantly within active lesions and on the margins of chronic lesions.[67] Ia antigen display by macrophages is associated with the capacity to present antigen to T-lymphocytes.[69] These results are intriguing and suggest that in MS, antigen presentation may be carried out in the CNS by Ia antigen-bearing astrocytes or endothelial cells. Antigen presentation by endogenous brain cells to infiltrating T-helper lymphocytes might thus contribute to initiation and perpetuation of the MS inflammatory process. These findings are supported by results from studies of experimental animals showing that both endothelial cells and astrocytes are capable of Ia antigen expression and antigen presentation when under the influence of T-cell lymphokines.[23, 44] None of these immunohistopathologic findings, however, have provided any clues to identification of the etiologic agent that triggers the inflammatory process.

EXPERIMENTAL MODELS AND PATHOGENESIS

Observations from experimentally-induced demyelinating diseases in laboratory animals have suggested that autoimmune reactivity to brain components can induce demyelination. The major experimental model of MS, experimental allergic encephalomyelitis (EAE), may be induced by inoculation of animals with myelin antigens.[4, 30] Acute EAE is a monophasic and fatal disease that is similar not to MS, but to postvaccination encephalomyelitis. This model has been useful in demonstrating that demyelination may be a T cell–mediated injury. Recently, a chronic relapsing model of EAE has been developed.[82] The pathology of this model is similar in many respects to that of MS. Chronic EAE is inducible in mice and guinea pigs and, like the acute EAE model, is characterized by T cell–mediated autoimmune reactivity to myelin antigens.

Because of results of epidemiologic studies in MS, there has been a considerable search for a viral agent in pathogenesis. Viruses have been identified in two demyelinating disorders of man—progressive multifocal leukoencephalopathy (PML) and subacute sclerosing panencephalitis (SSPE). Measles virus is associated with SSPE, which begins in early childhood following measles infection. Two closely related papovaviruses, JC and SV40, have been identified in PML, which typically occurs following some underlying immunodeficiency.[47] There are two well-characterized animal models of virally-induced demyelination.[17, 77] Both murine corona-

virus JHM and Theiler's murine encephalitis virus have been shown to produce a chronic demyelinative disease that may be associated with sensitization to myelin antigens. Lymphocytes from infected animals can induce demyelination when subsequently injected into uninfected recipients. In these experiments, lymphocytes were shown not to contain virus, so that virus transfer did not account for production of the disease in recipient animals. This finding suggests that viral infection in a genetically susceptible host may trigger subsequent autoimmune demyelination.

DNA hybridization techniques have been used to search for the presence of viral genomes in MS brain tissue. Results have indicated that DNA from measles, herpes simplex, and other viruses may be found as often in MS as in non-MS cases, suggesting that viral genes may be deposited frequently in the CNS as a consequence of common viral infections. No viral genomic material specific to MS has been identified, and by immunologic methods, no consistent patterns of viral antigens have been detected in MS brain.[58] Antibodies to a number of common viruses are found in both MS sera and CSF, but unlike SSPE, in which the bulk of CSF IgG is directed against measles virus, most of the IgG in MS CSF has no detectable antiviral activity.[63, 76]

CEREBROSPINAL FLUID ABNORMALITIES

CSF constituents are derived principally from blood, but in MS, several lines of evidence indicate that CSF IgG may be derived from within the CNS. Kabat was the first to note that gamma globulin in MS CSF increased disproportionately to the total amount of CSF protein, and he suggested that this finding was due to antibody synthesis within the CNS.[29] Subsequently, several investigators examined the source of CSF IgG by radiolabeled exchange techniques. In these studies, CSF and blood were sequentially monitored for concentration of radiolabeled IgG or albumin that had been previously inoculated intravenously. Results indicated that in non-MS and healthy individuals, CSF IgG was derived mainly from blood, but in MS, CSF IgG was also supplied by another source.[76] In other studies, IgG was detected in soluble protein extracts of MS brain tissues and was found to display the same characteristics as CSF IgG. Evidence for the presence of IgG-secreting plasma cells in MS brain emerged from immunohistochemical studies in which IgG was also found to be deposited in MS plaques.[22] All of these findings indicate that although the CNS does not have organized lymphoid tissue, in MS, lymphoid cells can migrate into the CNS and appear to be responsible for intrathecal production of IgG, which spills over into the CSF. The phenomenon of intrathecal IgG synthesis is not specific to MS, however, but is also found frequently in other inflammatory neurologic diseases, principally those of a chronic, infectious nature.

Other abnormalities in MS CSF have been detected but not as frequently as those involving IgG. In CSF from the majority (65 to 70 per cent) of patients with MS, leukocyte counts and total protein levels are within normal range.[76] Such findings contrast with those seen in the majority

of patients with infectious neurologic diseases in which both of these factors are elevated. Methods for quantitating the IgG abnormality also vary in sensitivity.[26, 28, 61] The measurement of IgG only in CSF and expression of values in milligrams per deciliter or as a fraction of total CSF protein or albumin yield abnormal results in only approximately 70 per cent of MS cases.[61] More sensitive methods for quantitating CSF IgG require measurement of both serum and CSF IgG and albumin levels. By performing one or another mathematical calculation with these values, an expression of intrathecal IgG synthesis can be derived that is abnormal in up to 95 per cent of MS cases.

Two formulas popular in the United States have been the Tourtellotte formula[62] and the Link IgG index.[39, 61] Both formulas require measurement of CSF albumin to indicate an altered blood-brain barrier (BBB), which in itself would lead to increased CSF IgG. The ratio of CSF to serum albumin is used to express BBB permeability. Serum values of IgG and albumin are measured to correct for the contribution of serum to CSF by diffusion. Quantitation of CSF albumin and IgG in the clinical laboratory has been carried out by electroimmunodiffusion and more recently by laser nephelometry.[42] Such analyses require determination of serum and CSF albumin and IgG values in normal individuals or from appropriate patient controls such as individuals who present with spine pain, normal neurologic examination, normal myelogram, normal CSF protein, and normal CSF leukocyte count.[42, 61] The Link index (CSF/Serum IgG ÷ CSF/Serum Albumin) expresses intrathecal IgG synthesis as a relative value, whereas Tourtellotte's formula expresses IgG synthesis as an absolute value of milligrams of IgG synthesized per day.[64] Tourtellotte's formula is as follows:

$$\left[\left(\mathrm{IgG_{CSF}} - \frac{\mathrm{IgG_{serum}}}{369}\right) - \left(\left[\mathrm{Alb_{CSF}} - \frac{\mathrm{Alb_{serum}}}{230}\right]\left[\frac{\mathrm{IgG_{serum}}}{\mathrm{Alb_{serum}}}\right] 0.43\right)\right] \times 5$$

Concentrations are given in milligrams per deciliter. The constant, 369, was obtained by taking the ratio of mean serum to CSF IgG as determined from measurements in a group of normal individuals. Similarly, the constant, 230, represented the ratio of mean serum to CSF albumin from the same control group. The first portion of the formula, which deals with IgG values, calculates the amount of residual CSF IgG remaining after subtracting the amount diffused from serum. The second half of the formula calculates CSF albumin in a similar manner and, by subtracting the albumin values from IgG values, corrects the formula for excess IgG appearing in CSF due to a damaged BBB. The second half of the formula also relates albumin and IgG on a molar basis. The basic formula calculates milligrams of IgG synthesized per 100 ml of CSF. Because approximately 500 ml of CSF is synthesized each day, the result of the equation is then multiplied by 5 to give the amount of CSF IgG synthesized daily.

The concepts and assumptions of both Tourtellotte's and Link's calculations have recently been reviewed and are not without controversy.[80] The assumption made in Tourtellotte's formula that IgG and albumin cross the BBB in a fixed proportional relationship has been challenged, as has the

formula's failure to consider catabolic rates of CSF IgG.[37] The validity of the Link index has also been questioned.[65] Nevertheless, the sensitivity of these formulas in enhancing the clinical diagnosis of MS is quite comparable, although data from our institution indicate slightly higher sensitivity with Tourtellotte's formula.[11]

The most striking immunologic anomaly found in CSF from over 90 per cent of patients with clinically definite MS is an IgG that is qualitatively different from serum IgG. The abnormal IgG may be detected by agarose electrophoresis or isoelectrofocusing on polyacrylamide gel and appears in the form of two or more prominent, discrete bands migrating in the cathodal or gamma region on electrophoresis and in the high alkaline (pH>7.5) area on isoelectrofocusing.[27, 33, 48] This abnormal IgG has been called oligoclonal because of its electrophoretic pattern of restricted heterogeneity.[33] Identification of the oligoclonal bands as IgG has been confirmed by a number of techniques, an example of which is immunofixation.[13] In this method, cellulose acetate strips soaked with antiserum to human IgG are placed over the gels and the antiserum is allowed to combine with the CSF protein. After the gels have been washed and stained, areas where antibody has complexed with CSF IgG are visible as intense, discrete bands that match in number and position the oligoclonal bands visualized in the same CSF specimen by routine biochemical staining.

A requirement of proper interpretation of oligoclonal band results is the simultaneous testing of patient serum along with CSF, at comparable IgG concentrations. CSF oligoclonal bands should be either undetectable or only slightly detectable in serum, indicating synthesis within the CNS. The isoelectrofocusing method is more sensitive and produces higher resolution of oligoclonal bands than does electrophoresis,[27, 35] but a higher rate of false-positive results has been reported with isoelectric focusing, as compared with electrophoresis.[26] As in quantitative CSF IgG assays, oligoclonal bands are not specific to MS but have been found in a number of inflammatory neurologic diseases, including CNS syphilis, viral meningitis or encephalitis, fungal meningitis, tuberculous meningitis, SSPE, progressive rubella panencephalitis, CNS lupus erythematosus, and Guillain-Barré syndrome.[15, 27, 43] Occasionally, oligoclonal bands have been detected in CSF from patients with brain tumors, sarcoidosis, amyotrophic lateral sclerosis, spinal osteoarthritis, Alzheimer's disease, temporal arteritis, and other diseases.[15, 21, 43, 58]

Lefvert and Link have proposed that use of the Link IgG index together with oligoclonal band testing is the most sensitive combination of laboratory assays in MS diagnosis. Unlike the quantitative method for determining intrathecal IgG synthesis, which yields results that may fluctuate with the course of disease and with treatment, oligoclonal bands, once developed in MS CSF, persist relatively unchanged throughout the disease. The numbers and migration patterns of oligoclonal bands vary widely and are essentially patient-specific. MS oligoclonal IgG has been characterized as predominantly IgG_1 subclass,[38] and Glm(1) allotype.[57] Some oligoclonal bands have been reported to contain free lambda light chains.[36] Discrete oligoclonal bands have been shown to contain both kappa and

lambda chains by immunofixation, indicating that each band does not represent a homogeneous IgG population.[36, 38, 76]

The antigenic specificity of the bulk of oligoclonal IgG in MS, as mentioned previously, has not yet been identified despite numerous efforts. In the infectious neurologic disease SSPE, oligoclonal IgG bands can be shown to react with measles virus, indicating that the CSF IgG has antibody activity against measles virus antigens.[70] Similar findings have been reported with treponemal antibody in neurosyphilis.[72] In MS, however, minor portions of oligoclonal IgG have been shown to contain reactivity against brain tissues, viruses, and autoantigens, including nucleic acids, erythrocytes, and smooth muscle.[34, 71, 76] Rheumatoid factor activity has also been identified. Two different hypotheses have been proposed to explain this oligoclonal IgG. One considers that the IgG represents an immune response against a specific antigen that has not yet been identified. The second school of thought considers the oligoclonal IgG to be a nonspecific "nonsense" antibody induced by some activating stimulus present in MS brain. Proponents of the latter hypothesis have cited evidence such as the heterogeneity of antibody specificities found in MS oligoclonal IgG, and data indicating that the oligoclonal pattern of IgG isolated from individual MS plaques differs with each plaque. Other evidence cited in favor of the latter hypothesis is that normal B-lymphocytes stimulated by a nonspecific mitogen in the presence of helper T-lymphocytes also produce oligoclonal IgG.

In connection with the hypothesis that oligoclonal IgG represents specific antibody, many investigators have attempted to study the idiotypic profile of oligoclonal IgG by using the eluted bands as antigenic material with which to inoculate experimental animals.[20] Antisera produced by these animals have then been used to search for the presence of idiotypic (combining site) specificities that would be common to a number of MS CSF samples. The theory behind such experiments proposes that demonstration of an idiotypic specificity common to several different MS CSF specimens would imply the presence of a common antibody response to a specific antigen. In SSPE, once again, these experiments have demonstrated the presence of common idiotypic profiles in CSF IgG, but as yet no common patterns have emerged in MS. Another line of investigation somewhat similar to this has been to test MS CSF IgG for the presence of antibody directed against autologous idiotypic antigens.[58] Researchers carrying out these studies have theorized that oligoclonal IgG may represent an immunoregulatory antibody response in MS that is directed against an antigen-combining site on some other antibody molecule or lymphocyte receptor. If MS oligoclonal IgG displayed anti-idiotypic reactivity, it might ultimately lead to identification of the original triggering antigen. Studies to address this question are still in progress.

A CSF abnormality that occurs only transiently in MS is the presence of myelin basic protein (MBP) or MBP fragments. MBP, a peptide of approximately 169 amino acids, has a molecular weight in humans of 18,500 daltons and comprises 30 per cent of the total protein associated with the myelin sheath.[18] During episodes of CNS myelin destruction, MBP fragments are released and appear in the CSF.[16] In MS, MBP can be detected

in CSF within 5 to 15 days after the onset of neurologic symptoms indicative of acute exacerbations. The presence of MBP in CSF is not specific for MS but is also found in other conditions in which myelin breakdown occurs, for example, SSPE, Guillain-Barré syndrome, cerebrovascular disease, or the leukoencephalopathy resulting from irradiation and chemotherapy for treatment of leukemia.[10, 81] Detection of MBP in CSF is not used as a diagnostic aid in MS but is helpful in monitoring disease activity. The molecular weights and composition of MBP fragments detected in CSF have been reported to vary with disease, with higher molecular weight fragments appearing in stroke or neurosurgical patients, and lower molecular weight fragments associated with MS CSF.[79, 81] Standardized reagents for MBP radioimmunoassay are not yet available, and the sensitivity of the assay in MS has been reported to be enhanced by using antibody specific for peptides 43 to 88 of the MBP molecule. The entire MBP molecule contains several antigenic domains; therefore, antisera specificities may vary. The dominant molecular species of MBP present in MS CSF appears to contain peptides 43 to 88.[79] The presence of MBP in MS CSF is not related to total CSF protein or IgG and rapidly becomes undetectable after the initial signs of exacerbation.

CSF lymphocytes, although they appear in low numbers, have also been studied in MS, and data indicate that these cells are in an activated state. An increase in the percentage of MS CSF lymphocytes in the G_1 phase (RNA synthesis) and a slight increase of cells in the S phase (DNA synthesis) have been reported by flow cytometric analysis.[49] Comparable increases were not found in controls. In another investigation, a high proportion of T cells in MS CSF were found to display the Ta_1 surface marker, an activation antigen.[24] Long-term cell lines have been established from MS CSF lymphocytes by using interleukin-2–containing media to promote T-lymphocyte growth. These cloned CSF T-lymphocytes have been found to demonstrate reactivities to a number of different antigens, including myelin basic protein, measles virus, and tetanus toxoid.[12, 58] Thus far, no single reactivity appears to be characteristic of MS CSF lymphocytes, but such studies are still in progress.

SYSTEMIC IMMUNOLOGIC ABNORMALITIES

Despite numerous research efforts, there is as yet no evidence in MS to support the existence of either a humoral or cell-mediated immune response to any CNS constituent. MS sera have been examined for the presence of antibodies to oligodendroglia, but results have been difficult to interpret because of the presence of IgG-binding Fc receptors on oligodendrocytes and on microglia within the brain cell preparations.[1, 68] Determination of antibody to myelin basic protein has been complicated by the propensity of myelin basic protein to nonspecifically bind IgG.[59] Cell-mediated immunity to CSF components has not been conclusively demonstrated in MS owing to the high reactivity often observed in normal individuals and disease controls.[58] The presence of circulating immune complexes is also not characteristic of MS.[58]

The most intriguing systemic immunologic findings in MS have been the demonstrations of alterations in T-suppressor-cell activities.[5, 6] Suppressor-cell function has been evaluated by exposing cells to the lectin Concanavalin A, which activates suppressor activity. Addition of such activated suppressor cells to fresh lymphocyte cultures from the same donor results in a reduced proliferative response of the fresh cells. Similarly, T-suppressor cells may reduce B-cell immunoglobulin secretion. In MS, these capacities have been found to be impaired in patients with progressive disease and in those undergoing acute exacerbations. Suppressor activity appears to return to normal levels when patients enter remission.

Results from studies of T-lymphocyte subsets using monoclonal antibodies have generally confirmed findings from functional studies of T-suppressor cells in MS. Diminished numbers of T8-bearing (suppressor/cytotoxic) lymphocytes have been associated with progressive MS.[51, 56] Similar changes have been found occasionally during disease exacerbations and have also been reported in CSF lymphocytes.[50, 56] Monitoring changes in T-cell subsets has not been shown to be a sensitive indicator of acute relapse however, because such changes have not been consistently observed in all patients.[8, 51] MS T-lymphocytes have been reported to have a reduced density of T8 marker,[55] and this finding has been suggested to be related to modulation by prostaglandin E, which is released by activated monocytes in circulation.[46, 75] Evidence for activated T-lymphocytes in MS circulation has been derived from flow cytometric studies using monoclonal antibodies to activation antigens. Increased numbers of T-lymphocytes bearing the activation antigen, Ta_1, have been reported in progressive MS, whereas increases in other activation markers, including the Ia marker and interleukin-2 receptor, were not detected.[24] These findings suggest chronic immunologic activation in MS and perturbed immunoregulation.[74, 78] Whether such findings play a role in the chronic remitting and relapsing nature of MS remains to be established.

SUMMARY

Multiple sclerosis (MS), a chronic disease with a relapsing and remitting course, is the most common neuroimmunologic condition in the United States. The hallmarks of the disease are focal demyelination and inflammation within the central nervous system (CNS). Because histopathologic changes can be identified only at autopsy, attention has been directed at formulating standardized clinical and laboratory procedures to aid in MS diagnosis. Currently, there are no MS-specific clinical or laboratory tests, but detection of abnormality in cerebrospinal fluid (CSF) IgG is important in supporting clinical evidence of disease. A number of other immunologic abnormalities have been recognized in MS, including the presence of T- and B-lymphocytes within the CNS and alterations in circulating suppressor T-lymphocytes. These findings have been interpreted as indicating disturbed immunoregulation associated with a chronic autoimmune response within the CNS. Evidence implicates viral infection in the pathogenesis of MS but the cause of the disease remains unknown.

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