Multiple Sclerosis: Immunologic Aspects

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ABSTRACT

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS). Although the causes are not known, the pathogenesis likely involves complex relationships between autoimmunity, immunogenetics, immunologic deficiency and viral infection. The evidence for such interrelationships is discussed.

Introduction

Multiple sclerosis (MS) is a disease of the central nervous system (CNS) of unknown cause. Although toxic, metabolic and dietary etiologies have been proposed, most of the recent progress and interest in multiple sclerosis has been in the interrelated areas of autoimmunity, immunogenetics, immunodeficiency states and viral infection. The disease is variable in its clinical course and often is of long duration. Epidemiologic, immunologic, genetic and virologic studies suggest the possibility of a multifactorial pathogenesis and the search for a single simple "cause" of MS may be naive. It would seem more likely that a complex pathogenesis involving immunogenetics and autoimmunity as well as immunodeficiency and viral infection will be found to be involved in the pathogenesis of multiple sclerosis.

Immunogenetics

Recent immunogenetic research has provided some exciting clues to the pathogenesis of MS. Several groups of investigators have now reported a disproportionate number of MS patients in the serologically defined HL-A types 3, 7 and W18.22,42 The incidence of these HL-A types is 40 percent in MS and 10 percent in the control population. However, 60 percent of patients with MS do not possess these three HL-A antigens. Jersild et al.26 have also identified a mixed leukocyte reaction (MLR) defined antigenic determinant linked to the FOUR (second locus)66 HL-A site which has been called the 7a determinant. In a Danish population, it was noted that 60 percent of all patients with MS and 90 percent of MS patients with the serologically defined HL-A 7 determinant fail to recognize the 7a determinant as a foreign antigen in the MLR.25 These subjects therefore carry the 7a antigenic determinant on their cells. In a small number of families studied, the presence of the 7a determinant was "bred true", meaning that the inability to recognize 7a as foreign is inherited, not acquired as a result of having MS.25 While the previous data might well explain the increased family incidence of MS43 as well as partially explaining the geographic distribution of
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MS, there are patients with MS who have the ability to react to the 7a determinant (do not carry the 7a marker) as well as normals who carry the 7a determinant. This makes a simple genetic defect unlikely to be the sole cause of MS. It has been suggested that the presence of a 7a marker is associated with inability to mount a cell-mediated response to myxovirus infection (specific immunodeficiency) leading to a persistent viral infection and an increase in the humoral response to the virus as well. In addition, it has been postulated that identity with or shared antigenicity between the 7a determinant and certain myxoviruses could lead to inability to recognize the virus as foreign.

Other immune genetic clues suggest that variability in the development of experimental allergic encephalomyelitis (EAE) in several species is genetically determined. In rats this variability seems to follow a pattern compatible with gene control of immune reactivity. EAE is considered to be a possible model for acute MS and is an experimental autoimmune disease.

Immunodeficiency

There has been recent interest in the possibility that an immunodeficiency state exists in multiple sclerosis. Although there is no evidence that a severe generalized defect in the immune system is present, it is possible that a subtle generalized or specific immune defect could exist in patients with MS. Such a deficit could allow a persistent viral infection or cause an inability to eliminate a forbidden "autodestructive" clone of immune cells, which in turn might generate an autoimmune disease. Depression of skin test reactivity to standard secondary antigens and to primary antigens, dinitrochlorobenzene (DNCB) and keyhole limpet hemocyanin (KLH), has been reported by one group to occur in MS. Suppression of phytohemagglutinin (PHA) induced in vitro lymphocyte response has also been described. However, others have not found either depressed skin test reactivity, or an abnormal response to PHA, or depressed reactivity to standard antigens such as PPD. Recent studies describe an increase in T (thymic independent) lymphocytes in subjects with MS and a decrease in T (thymic dependent) lymphocytes in the blood of patients with acute MS. However, serial studies will be required to determine the cause-and-effect relationship to exacerbations and progression of disease. Anti-lymphocyte antibodies and serum factors capable of inhibiting in vitro DNA and/or RNA turnover have been reported to occur in MS. It is conceivable that these factors could depress T lymphocytes and protect the patient by supressing a T-cell mediated autoimmune response.

Viral Infection

The evidence that multiple sclerosis is caused by a virus is in general indirect and includes (1) a higher disease incidence in temperate climates; (2) a higher incidence in middle and upper class economic groups with better sanitation perhaps analogous to the situation with poliomyelitis; and (3) increase in antibodies to measles as well as to other viruses. The specificity of the latter observation is uncertain because an increase in myxovirus antibody titers has also been found in connective tissue diseases. More recently it has been reported that peripheral blood cells from patients with MS show less inhibition of in vitro migration of their buffy coat cells in the presence of measles virus but not other viruses. Neither study was performed using purified or well-characterized viral antigens. It has been suggested, as mentioned previously, that these observations might represent the effects of a specific or subtle immunologic deficiency, perhaps linked to the 7a MLR determinant. Cells from patients treated with transfer factor regain
the ability to react \textit{in vitro} to the viral antigens\textsuperscript{25} but whether or not transfer factor will prove to have a beneficial effect on the clinical course of MS is not known.

Other recent developments related to the possible role of viruses in the pathogenesis of MS are (1) the isolation of a virus from the brain of two MS patients\textsuperscript{63} related to, but not identical to, other parainfluenza viruses; (2) observation with electron microscopy (EM) of viral-like particles in brains of patients with MS.\textsuperscript{17,50,51} It should be noted, however, that other autopsy and biopsy specimens have failed to yield virus, and doubts have been expressed about the specificity as well as the viral nature of these particles observed by EM.\textsuperscript{17,51}

\textbf{Autoimmunity}

There have been intensive efforts for the past thirty years to establish MS as an autoimmune disease of the CNS. Much of this effort was stimulated by similarities between MS and experimental allergic encephalomyelitis (EAE),\textsuperscript{1,48} a disease that can be induced in a wide variety of animals by injection of myelinated CNS, myelin or the active encephalitogenic protein, myelin basic protein (BP).\textsuperscript{28} EAE is generally considered to be caused by a cell-mediated hypersensitivity reaction to BP as manifested by (1) passive transfer with cells\textsuperscript{47} but not serum; (2) correlation with skin tests to BP\textsuperscript{57} but not with antibody to BP;\textsuperscript{38} (3) inhibition by neonatal thymectomy but not by bursectomy and irradiation;\textsuperscript{10} (4) demonstration of "cell-mediated immunity" by \textit{in vitro} parameters that may correlate with delayed hypersensitivity;\textsuperscript{14,39,52} (5) predominance of mononuclear cells in a perivascular pattern similar to classic delayed hypersensitivity reactions;\textsuperscript{1,48} and (6) variation in susceptibility to EAE of different inbred strains of certain species, as already mentioned.\textsuperscript{21,34,61,65} There are other features of EAE which relate to MS. These include the ability of serum from animals with EAE produced by sensitization with whole CNS,\textsuperscript{11} but not by BP,\textsuperscript{55} to produce both \textit{in vitro} demyelination of CNS cultures and \textit{in vitro} inhibition of myelination.\textsuperscript{29} Increase in cerebrospinal fluid (CSF) \(\gamma\)-globulin is found in EAE,\textsuperscript{27} as well as in MS.

With these features of EAE in mind, what are the clues suggesting an autoimmune etiology of MS? "Acute" MS lesions show perivascular mononuclear cell cuffing indistinguishable from that of EAE,\textsuperscript{45,51} and the pathology of the post-rabies vaccination neuroparalytic accidents reported from Japan forms a continuum between EAE and MS.\textsuperscript{40} However, despite the production of a reproducible recurrent form of EAE in the rat\textsuperscript{44} no classic MS plaques have been produced in EAE animals. Sera from patients with MS in acute exacerbation are capable of inducing \textit{in vitro} demyelination of CNS cultures as well as \textit{in vitro} glial toxic factors.\textsuperscript{1,11,48} However, in EAE and in human neurologic diseases including amyotrophic lateral sclerosis (ALS),\textsuperscript{1,11,48} the demyelinating antibodies in serum seem to be directed, at least in part, at galactocerebroside, a non-encephalitogenic CNS antigen.\textsuperscript{20} There is an increase in antmyelin antibodies by immunofluorescence in MS but patients with ALS also have increased antimyelin antibody titers.\textsuperscript{18,40} Anti-BP antibodies do not occur in MS sera or CSF.\textsuperscript{33,36} The increase in CSF \(\gamma\)-globulin in MS\textsuperscript{55} occurs in an oligoclonal pattern\textsuperscript{55} but other diseases such as SSPE and Guillain-Barre syndrome show this same pattern. ACTH, which will modify or prevent EAE,\textsuperscript{42} has been shown to shorten acute attacks of MS\textsuperscript{54} but corticosteroids have other effects on the organism besides that of immunsupression. As noted earlier, the increased incidence of HL-A types 3, 7 and W18 as well as the 7a MLR determinant can be used to support an autoimmune or a viral etiology of MS, or both. Thus, autoimmunity in MS is a reasonable hypothesis, but its precise mechanism cannot be stated.

Much of the recent work on autoimmunity in MS has centered on the use of "\textit{in vitro} correlates of cell-mediated immunity".
Reactivity to whole CNS or BP has been studied using such measures as in vitro lymphocyte proliferative response,\textsuperscript{6,15,22,37} indirect macrophage migration\textsuperscript{4,7,53,58} and inhibition of buffy coat cell migration.\textsuperscript{8,62} The results have been contradictory; some groups report reactivity in MS only or to a greater degree in MS when compared to other CNS diseases.\textsuperscript{4,15,22,58} Others find equal reactivity in MS, normals, and patients with other CNS diseases.\textsuperscript{5,19,53} and still others find no reactivity in any groups.\textsuperscript{6,7,37,62} The reasons for these divergent results are not clear but differences in techniques, antigens and stages of disease studied do not explain completely the disparities. A more definitive answer as to reactivity to CNS components may come when several different groups study a sufficient number of patients longitudinally by several techniques.

Conclusions

The myriad of clues to the pathogenesis of MS are frequently confusing or conflicting. It should be remembered that these may represent different aspects of a multifactorial disease. On the basis of present knowledge, a reasonable synthesis might be a viral infection, facilitated by a genetic predisposition or genetically controlled immune defect, serving as the triggering event for an autoimmune reaction. This could occur through any one of several mechanisms. Such mechanisms include (1) shared antigenicity between virus and CNS antigen; (2) formation of a neo-antigen under control of part of the viral genetic apparatus; (3) a haptene-carrier complex formed between a portion of the virus and a CNS structural component; (4) an asymptomatic viral infection of the CNS allowing the exposure of a "hidden" antigen; (5) a viral infection acting as an adjuvant in an autoimmune reaction; and (f) damage to the CNS during an immunologic reaction directed against a virus latent in the CNS. It is obvious from the data presented in this paper that much remains to be done in both experimental and clinical studies in order to determine the relative importance and roles of these or other possibilities.

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References


