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Etiopathogenesis of multiple sclerosis

ABSTRACT

Multiple sclerosis (MS) is an inflammatory demyelinating disease that is specific to the central nervous system (CNS). It is the most common cause of chronic neurological disability among young adults. The clinical course is quite variable, but the most common form is characterized by relapsing neurological deficits. Morphologically, MS is characterized by the presence of areas (plaque) of myelin destruction with relative axonal preservation and T-cell predominant perivascular inflammation in the white matter of CNS. Plaques (active, inactive, recent and old) can occur at different sites in the CNS with some sites of predilection. Etiopathogenesis. Despite the formulation of many hypotheses, and the study of many factors that appear to contribute to the etiology of MS, no single cause has been confirmed. It is probable that several factors are involved: genetic, environmental, viral and autoimmune. Indirect evidence suggests that MS is a T cell-mediated autoimmune disease involving a neural antigen (myelin component) in some individuals susceptible to MS by their genetic constitution and by exposure to an unknown environmental trigger, possibly a virus infection early in their life. In the recent years there are many studies about the role of cytokines in pathogenetic events involved in MS. Some of them may promote disease such as IFN-γ and TNF-α, while others (IL-4, IL-10) may limit disease, or contribute to downregulation of disease, such as IFN-β. The clinical trials showed that IFN-β administered intrathecally significantly reduce the rate and the severity of exacerbations in relapsing/remitting MS.

KEYWORDS: Multiple sclerosis + etiology + physiopathology; Autoimmunity; Demyelinating Diseases

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating disease that is specific to the central nervous system (CNS) (1). It is the most common cause of chronic neurological disability among young adults during their most productive years. Patients can display a wide variety of neurological symptoms and signs such as double vision, nystagmus, slurred speech, tremor, spastic/ataxic gait etc. MS is classified according to its clinical course into several categories: relapsing-remitting (the most common variant), progressive, and benign. Most patients with MS die from the complications of immobility (such as infection), approximately twenty years after beginning of the disease.

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MORPHOLOGICAL CHANGES

Grossly, MS is characterized by disseminated white matter lesions (plaques) which are rounded or irregularly shaped, well limited areas of different size and age. The older lesions appear grayish, translucent and firm, while the recent lesions tend to be softer and pinkish in colour. Plaques can occur at different sites in the CNS with some sites of predilection, such as the periventricular white matter - especially at the lateral angles of the lateral ventricles, the optic nerves, the brainstem, the cerebellum and the spinal cord. Plaques may rarely spread into the gray matter. In these lesions neuronal cell bodies are remarkably spared.

Microscopically, plaque lesions contain demyelination, perivascular inflammation and glial cell changes. Demyelination is characterized in myelin stains (Luxol fast blue, Kluver Barrera) by discoloration of the myelin with clear-cut and regular borders. Myelin-axonal dissociation is a cardinal feature, and silver impregnations (Bodian, Bielschowski) demonstrate a network of preserved axons in the plaque. The myelin breakdown products (sudanophilic lipids) are phagocytosed by macrophages present in active plaques. Inactive plaques are demyelinated, but do not contain myelin breakdown products. Perivascular inflammation is consisted of perivenular T-cells and other mononuclear cuffing , which are often conspicuous in recent plaques, and less pronounced or absent in old plaques.

Glial cell changes. Typically, the oligodendrocytes have disappeared. It is demonstrated that early in the course of the disease, more oligodendrocytes are preserved in the plaque, thus some degree of remyelination remains possible. There is proliferation of astrocytes, which is maximal at the periphery of the plaque. Gliosis becomes progressively more fibrillary toward the center.

ETIOPATHOGENESIS

The etiopathogenesis of MS is incompletely understood, although it is clear that several factors are involved: genetic, environmental, viral and autoimmune.

Genetic factors. There is strong evidence of genetic (probably polygenic) predisposition for MS. The incidence of MS in first degree relatives is 20 times higher than in general population. Monozygotic twin studies show the concordance rate of 27% (2). Genetic loci that influence immune system regulation are important in MS susceptibility. Different HLA associations are reported within ethnic groups and some associations remain very stable in patients with MS. In north European populations MS has been linked with the Class I HLAs A3 and B7, and especially Class II HLAs DR2, DQW1, DQA1, and DQB1 (3). However, this relationship is not universal and MS is linked to alleles other than DR2 in some populations (e.g. Jordanian Arabs and Japanese). Although Class II MHC alleles increase the risk for MS, no specific allele has yet been identified that is necessary for the development of MS. It is likely that other genes such as genes for T-cell receptor (TCR) and tumor necrosis factor-alpha (TNF-α) are involved as well, for which a systemic search is currently being undertaken (3,4). Initial reports linking MS to the myelin basic protein (MBP) gene have not been confirmed.

It is possible that although genetic factors increase susceptibility to MS their effect is only apparent in the appropriate environmental conditions.

Environmental factors. MS onset occurs between the ages 20 and 40. Like other immuno-mediated diseases, females are affected more often than males, with a ratio that approaches 2:1. Race is another factor that affects susceptibility to MS. In general, whites are more susceptible to MS than are blacks or orientals.There is a very specific geographic distribution of this disease around the world. A significantly higher incidence of the disease is found in the northernmost latitudes of the northern and the southern hemispheres compared to southernmost latitudes. This observation is based on the incidence of the disease in Scandinavia, northern United States and Canada, as well as Australia and New Zealand. Migration between regions of different lat-

itude at an early age (before 15 years) is associated with a change in risk. There is clear and consistent evidence that migration from a high-risk to a low-risk area while young results in a reduction in MS risk (2). "Epidemics" of MS have been reported (e.g., Faroe Islands after they were occupied by British troops in World War II) and these provide further evidence of importance of environmental factors in MS. A specific "point agent" for these "epidemics" never was identified.

Infectious agents. Infectious agents have been proposed in the pathogenesis of the MS. Support for the viral hypothesis is seen in fact that MS patients consistently exibit abnormal immune responses to a number of viral antigens including elevated antibody titres in the blood and spinal fluid to several viruses. Some viruses (e.g., HSV, measles, para-influenza type etc.) have been found in the CNS of the patients with MS (5), but no consistent pattern has emerged. There is considerable interest in a theory that exposure to a virus may lead to immunopathologic condition resulting in MS. One possible explanation for this is molecular mimicry between viral and CNS proteins so that antiviral response is mediated against myelin. In MS, homology between viral peptides and myelin antigens is established. Viral persistency, latency and periodic inactivation could be of possible significance. Viral infections also are known to provoke relapses of the disease. Another possibility is that autoimmunity results from super antigenic stimulation of T-cells by viral or bacterial proteins. Super antigens may bind to specific T-cell receptor proteins, producing non-specific stimulation of a large number of T-cells. This may result in clonal expansion of T-cells reactive to myelin or oligodendrocyte antigens.

Autoimmune causes. Autoimmune nature of MS has long been suspected. In MS immune dysfunction can be detected locally in CNS, CSF, as well as in peripheral circulation. It is known that patients with MS have inflammation and demyelination in their CNS and oligoclonal bands in their cerebrospinal fluid. This increase in CSF immunoglobulin is the result of proliferation of B cells within the nervous system. The target epitopes of these antibodies are widely variable. These observations suggested that the demyelination is not mediated through an antibody-dependent mechanism. A dysregulated immune system no longer prevents memory T-cells from becoming activated against myelin, entering the CNS, and mediating damage associated with the disease. Particularly interesting were investigations on the response of T-lymphocytes from patients with MS for reactivity with myelin basic protein (MBP). No specific oligoclonality was found to help differentiate patients with MS. However, it remains possible that other myelin proteins such as myelin oligodendrocyte glycoprotein (MOG), proteolipid protein (PLP), myelin-associated glicoprotein (MAG), and others may also play a role in pathogenesis of MS (4,5). While there is no direct evidence implicating autoreactive T cells or myelin specific antibodies in the pathogenesis of MS, the fact that relapsing and remitting neurological illness can be induced in genetically suscetible strains of animals by sensitizing them to components of myelin, as well as that chronic form of EAE resembles MS, suggests that these may be related disorders with a common pathogenesis. Also, there are some reports in literature that human subjects injected with preparations containing neural tissue developed lessions in the CNS resembling the lesions of acute MS (1). Indirect evidence suggests that MS is a T cell-mediated autoimmune disease involving a neural antigen (myelin components) in some individuals susceptible to MS by their genetic constitution and by exposure to an unknown environmental factor, possibly a virus infection early in life.

THE ROLE OF PARTICULAR IMMUNE SYSTEM COMPONENTS IN MS

T-lymphocyte

T-lymphocytes become activated by some as yet unknown mechanism. Adhesion molecules on endothelial cells (ICAM-1, ELAM-1,VACAM-1) allow activated T- lymphocytes to enter the CNS in search of their target antigen. They cannot recognize their target antigen unless it is presented to them by antigen presenting cells. Activated T-lymphocyte accumulate around small venules.These are predominantly the helper variety of T-lymphocyte (TH1 - which augment T-lymphocyte and macrophage activation). When a sufficient number of T-lymphocytes are present, inflammation begins. The receptors that T-lymphocytes use to bind to their antigen consist of two glycoprotein sub-units. The $\alpha\beta$T-lymphocytes are likely to be specific for MBP, PLP and MOG. Such cells are present in blood and more frequent in the CSF. $\gamma\delta$T-lymphocytes has been described in MS plaques, where they multiply in clones. In vitro, $\gamma\delta$T-lymphocytes, lyse olidogendrocytes, possibly by recognising antigens known as heat chock proteins (HSP) that are expressed by stressed oligodendrocytes (6). One possible scenario is that $\alpha\beta$T-lymphocytes initiate the inflammatory process by attacking myelin. This stresses oligodendrocytes which consequently express HSPs. $\gamma\delta$T-lymphocytes are then recruited and may further destroy oligodendrocytes. Some T-lymphocytes enhance polyclonal B-lymphocytes responses, eather directly or through the release of cytokines; other suppress B-lymphocyte responses.

B-lymphocytes. MS plaques also contain B-lymphocytes and plasma cells. It seems that there is an antigenic stimulus to B-lymphocytes within the plaque according to B-lymphocytes clones in some plaques. Antibodies directed against myelin surface antigen may aid demyelination by activating complement via the classical pathway. B-lymphocytes may affect T-lymphocytes, by expressing HLA Class II antigens and presenting antigens to T-lymphocytes.

Complement. In patients with MS, CSF studies suggest a role of complement in the disease process. Two short-lived by-products of complement activation, called C3a and C4a, can be detected in the CSF of MS patients. Also, complement component C9 (part of the membrane attack complex) is depleted from the CSF of MS patients. Membrane attack complexes on oligodendrocytes surfaces allow rapid entry of excess calcium into the cell. This is greater when antibody and complement are used together. Antibodies against MOG promote greater complement-mediated calcium influx than those against MBP. By-products of the complement pathway attract and activate macrophages. Also, complement may act as an opsonin on the myelin surface.

Macrophages. Macrophages are some of the most abundant infiltrating cells found in histopathological studies of MS. Myelin breakdown occurs mainly in the presence of infiltrating macrophages and local macrophages activity. Much evidence suggests that, in MS, macrophages physically remove myelin from axons by phagocytosis. In the early stages of demyelination, superficial layers of myelin can be seen attached to receptor-rich areas on the surface of macrophages (coated pits areas). This suggests that receptor-mediated phagocytosis is taking place. In MS, non-immune mediated phagocytosis probably occurs as well as antibody- and complement-mediated phagocytosis. It remains unclear whether macrophages initiate the damage to myelin and oligodendrocytes or merely remove tissue alredy damaged by other immune mechanisms. No consistent changes in myelin are known to precede phagocytosis of myelin in MS. This suggests that macrophages may initiate the demyelination. Activated monocytes/macrophages secrete various cytokines, oxygen-free radicals and proteolytic enzymes. In MS plaques, macrophages may function as antigen presenting cells. HLA Class II expression occurs mainly on microglial/macrophage like cells.

Cytokines

In the recent years there are many studies about the role of different cytokines in pathogenetic events involved in MS. Some of them may promote disease such as TNF-α and IFN-γ, while others (IL-4, IL-10) may limit disease, or contribute to downregulation of disease, such as IFN-β (7). TNF-α is secreted by activated macrophages, and occurs in active MS plaque. It may

damage myelin and oligodendrocytes directly through an effect on ion channels. Levels of TNF-α correlate well with BBB damage in the brains of MS patients. It may cause BBB disruption by damaging vascular endothelial cells. TNF-α acts synergistically with IFNγ to induce HLA Class II molecules. Therefore it may promote the inflammatory response by stimulating antigen presentation. IFN-γ has antiprolifetative, antiviral and immunoregulatory functions. In MS patients, IFN-γ is produced by T-lymphocytes in response to myelin antigens, especially during relapses. It may potentiate the immune response by activating other T-lymphocytes, and attracting them into plaques. It may do this by inducing adhaesion molecules which help lymphocytes to cross the blood-brain barrier and control their migration to sites of inflammation. It induces macrophages to express HLA Class II molecules, permitting them to present myelin antigens to activated T-lymphocytes. IFNγ stimulates macrophages to produce another cytokene, such as TNF-α, thereby enhancing myelin destruction. It can potentiate antibody-mediated demyelination also. In MS there is a relationship between acute exacerbations and common viral infections. This may be an immunological side-effect as a result of the body producing IFNγ for its antiviral properties. IFN-β tends to inhibit the activity of IFN-γ and down-regulates IFN-γ production. Decrease cytokine release from T-lymphocytes, and, by counteracting interferon gamma's augmentation of MHC-derived proteins, it inhibits T-lymphocyte proliferation. Also it improves suppressor T-lymphocyte function.The clinical trials showed that IFN-β administered intrathecally significantly reduce the rate and the severity of exacerbations in relapsing/remitting MS with minimal side effects (7).

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