Multiple Sclerosis: A Literature Review

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Abstract

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). The pathogenesis of MS consists of an inflammatory and a neurodegenerative phase, which can be subdivided into a relapse-remitting phase, a primary and a secondary phase. This review will evaluate current research on the pathogenesis and management of MS. A characteristic of MS is the infiltration by immune cells across the blood-brain barrier that stimulates inflammation. It is unclear whether this reaction can be contributed to actions within the CNS or outside in the periphery. Specific focus on the autoimmune reaction of T and B cells have been at the center for most theories concerning the cause of MS. However, the specific antigen for the induction of the inflammation remains yet to be discovered. There is no cure for MS, but Alemtuzumab, Glatiramer, and Natalizumab inhibit lymphocyte activation and activate self-repair mechanisms in lesion areas.

Introduction

MS, or multiple sclerosis, is a chronic inflammatory demyelinating disease of the Central Nervous System (CNS). Symptoms of the disease can include sensory and visual deficits, motor impairments, fatigue, pain and problems in cognition [1]. Globally, a total of approximately 1 million patients are diagnosed with MS, and women outnumber men two to one. The disease is considered to be autoimmune, because autoreactive lymphocytes mount aberrant responses against CNS autoantigens [2]. The pathogenesis of MS consists of an inflammatory and a neurodegenerative phase, with a subdivision in a relapse-remitting phase, a primary and a secondary chronic-progressive state [3].

Because of the early onset of MS, a considerable burden in terms of both healthcare and societal costs is inevitable [4]. There has not yet been an absolute cure, causing health care for MS patient to be costly. The pharmaceutical costs of MS have risen over the previous few years with the development and treatment of disease-modifying drugs, which delay the progression and development of long-term disabilities. Besides the financial aspect, patients are most likely to undergo MS-related symptoms during their early life, interfering with their career and family life. Therefore, research into MS remains profoundly important for not only the individual, but also for the society as a whole. This review will evaluate current research on the pathogenesis and management of MS.

Description of the physiological process of MS

Pathogenesis. MS commonly begins in early adolescence, characterized by an autoimmune inflammatory reaction against components of the myelin sheath surrounding the nerves of the CNS, with lesions in the nervous tissue as a result. These first symptoms often last a few days to weeks, followed by a phase called the relapsing-remitting phase. The course of MS and symptomatology are heterogeneous. This stage can last up until 10 years from the point of the first symptoms, but one-third of the patients will progress to a secondary chronic-progressive state, which is characterized by an inability to walk and without distinct attack. The disease however advances silently. Some patients progress earlier into the second phase, which will then be classified as primary-progressive MS. The earlier phase of relapse-remitting of MS may have a stimulating influence on the autoimmune reaction [3].

The lesions, which are a distinct characteristic of MS, are caused by immune cell infiltration across the blood-brain barrier that stimulates inflammation. Consequently, this causes demyelination and neuroaxonal degeneration. A loss in movement can therefore be attributed to loss in neuronal activity. The cause of MS however, remains a medical and neuroscientific mystery. However, MS occurs more
often in those who are at a genetic risk, but environmental conditions can also influence its onset.

It remains unclear whether the inflammations are triggered in the CNS itself, or that influences from outside the CNS (periphery) have a stimulating effect. In animal models, an MS-like condition can be induced after onset of a disease called experimental autoimmune encephalomyelitis, or EAE. Similar to the peripheral invasion hypothesis, in this model myelin-derived proteins or peptides in adjuvant are administered, or passive transfer of activated myelin-specific CD4+ T cells will be applied. This results in the suspected activation and/or homing of pathogenic CD4+ T helper cells in the draining lymph nodes. These cells cross the blood-brain barrier in a fashion which remains to be unknown, but suspected to be at the choroid plexus. However, it should be noted that the described model is initiated in different ways, and that the underlying mechanisms may also differ, having implications for its use.

MS is still considered a CD4+ T helper cell (T1) mediated autoimmune disease, based on the cellular composition of brain and cerebrospinal fluid infiltrating cells and data from EAE. The importance of CD4+ T cells in MS is based on the overlapping symptoms between EAE and MS. One of which is the discovery of certain major histocompatibility (HHC) class II molecules, representing the strongest genetic risk factor for MS, presumably via their role as antigen-presenting molecules to CD4+ T cells [1]. Additionally, reactive oxygen species (ROS) and reactive nitrogen species cause chronic inflammation in patients with MS. These ROS most likely promote mitochondrial injury as a result of the accumulation of detrimental mitochondrial DNA mutation. Consequently, this promotes metabolic stress, protein misfolding in the endoplasmic reticulum, energy deficiency and a loss of neuronal fitness [2].

The role of T and B cells. The idea that lesions are initiated by CD4+ T helper cells in acute MS can be simply demonstrated in EAE. However, although it is not the main focus in MS research, the importance of CD4+ T cells cannot be overlooked. The presence of CD8+ T cells can be found by simply looking at the site of the patient’s inflammatory lesions. What is particularly interesting is that CD8+ T cells are not only present at the lesions, but also at the perivascular regions. CD4+ T cells are on the other hand only present at the lesion edge. Interestingly, a higher number of autoreactive CD8+ T cells that interact with myelin sheet antigens have been found in patients with MS as compared to a healthy control [5].

Another study also found that CD4+ CD25+ regulatory T cells display impaired function in patients with MS [6]. A deficit in the control of autoreactive CD4+ T cells, and therefore an autoimmune reaction chain of the patient, can provide vital clues on the progression of the disease. Central tolerance is subjective to the deletion of most autoreactive T cells. This process however has its flaws, resulting in some autoreactive T cells being released into the periphery. With an impaired function of CD4+ CD5+ regulatory T cells in MS patients, the CNS directed autoreactive B cells and T cells can be activated in the periphery to become aggressive effector cells by molecular mimicry, novel autoantigen presentation, recognition sequestered CNS antigen released into the periphery or bystander activation. Once activated, both CD8+ T cytotoxic cells and CD4+ T helper cells can infiltrate the CNS, causing inflammation and nerve damage [2].

The presence of T cells during the early stages of MS is widely recognized. As demyelination is a key feature of MS, myelin protein-derived antigens have been hypothesized to be the main autoreactive targets. CD8+ T cells are found in higher numbers than CD4+ T cells in white matter and in grey matter cortical demyelinating lesions, and the number of CD8+ T cells closely correlates with axonal damage. As compared to T cells, CNS infiltrating B cells vary more in number throughout the progression of the disease. Locations of B cells include the meninges, parenchyma and CFS [2]. Maybe one of the largest questions involved in MS is to which antigen(s) this autoimmune reaction is targeted. Multiple immune responses to several components of a supramolecular structure, like the myelin sheath in MS patients, have been proven to be a place of interest. A key immune response is targeted to certain regions of myelin basic protein. Further research is required to pinpoint the exact reaction between the antigen and the immune reaction [7].

The process of infiltrating the CNS. To start the immunological reaction and as a consequence inflammation, lymphocytes need to penetrate the blood-brain barrier first. This process involves multiple steps and is still not completely understood. There are specialized capillary endothelial cells in the CNS
that are nonfenestrated and connected through tight junctions. During the inflammatory response, tumor necrosis factor (TNF)-alpha and interferon (INF) -gamma induce these capillary endothelial cells to express vascular cell adhesion molecules (VCAM) and MHC class II molecules. Activated T cells express integrin, such as VLA-4 and other molecules such as CD4, which can bind VCAM and MHC class II molecules, respectively. Once activated, any T cell expressing VLA-4, can bind to adhesion molecules on the surface of inflamed endothelium and spread throughout the endothelium. In EAE, blockade of VLA-4 reverses clinical paralysis and prevents further relapses in the chronic model of this disease. In acute MS lesions, VLA-4 is found on T cells that collect the perivascular lymphocyte cuff, a region around veins and capillaries that is limited by the extracellular matrix. Once the activated lymphocytes have extravasated, they must still pass through a barrier of extracellular matrix, comprised of type IV collagen before they can enter the CNS [7].

**Diagnosis and treatment**

In the case of MS, no single clinical feature or diagnostic test is sufficient. However, a recent clinical revision has established a few guidelines based on objective evidence of dissemination, objective determined clinical signs, and radiological and laboratory investigations. An attack refers to an episode of neurological disturbance of the kind seen in MS. To make a diagnosis of MS, objective evidence of a second lesion is required to demonstrate dissemination in space. This can be provided by an MRI scan of the brain. There must be a minimum of 3 months between the clinical event and evidence for a new lesion. An abnormal cerebrospinal fluid (CSF) finding with evidence of inflammation and immune abnormality is also essential in the diagnosis of MS [8].

There has not yet been a cure for MS, with multiple treatments aiming at halting demyelination and inflammation and facilitating a faster recovery from attacks. Infiltration of immune cells from the periphery, in the relapse-remitting phase, has been the main target for currently available therapies for MS. Without directly indicating either CD4+ or CD8+ T cells, a treatment that removes lymphomononuclear cells by means of an antibody (alemtuzumab) to CD52 has produced a profound reduction in inflammatory activity and thus indicates involvement of these cells in the CNS inflammation of MS. The proposed mechanism of action is interference with adhesion molecules and cell migration. However, antibodies against CD52 may have also serious side effects. IFN-beta, a potent inhibitor of gelatinase B activity, has been used relatively successful in clinical trials. In relapsing-remitting MS, this drug reduced exacerbation rates and slows the progression of the relapse-remitting phase. Side effects of IFN-beta include symptoms of flue: fever, chills, sweat, and headaches. Commonly, these manifestations last no more than 24 hours [9].

Glatiramer (GA) is the only MS drug that has a copolymer as its active ingredient and is one of the most widely prescribed first-line treatments of relapse-remitting MS. Interestingly, the active component in GA has not yet been established, because of the complexity and variability of its working. However, immune cells triggered by GA promote growth factors, generating suppression of the inflammation and enhancing self-repair mechanisms, which counters the lesions caused by MS [10]. Furthermore, Natalizumab is a “humanized monoclonal antibody that binds specifically to the alpha-chain of alpha4-integrins, inhibiting the binding of leukocytes to VCAM-1 expressed on activated brain vessels, inhibiting activation of lymphocytes into inflammatory MS lesions.” [11].

**Conclusion & Summary**

Although research into the pathogenesis of MS has been extensive, the exact cause of the neuroinflammation has yet to be discovered. The role of CD4+ T helper cells and CD8+ T cells cannot be underestimated, and might provide vital clues towards its pathogenesis. The process of infiltrating the CNS and crossing the blood-brain barrier consists of multiple steps. The reaction cascade to a suspected antigen within the protein of the myelin sheet in MS patients remains to be the subject of research, with special focus on pinpointing the precise antigen. Diagnosis of MS in patients requires at least two lesions in the CNS, which can be examined by the use of MRI imaging techniques. A period of at least three months must be established between the appearance and evidence of a new lesion. Current treatment is mostly aimed at the treatment of the symptoms of MS, no cure has yet been found. The use of alemtuzumab has been found to be an effective treatment, because of its anti-inflammatory effects.
Additionally, Glatiramer is one of the most widely prescribed first-line treatments of relapse-remitting MS, promoting the suppression of the inflammation, and enhancing self-repair mechanisms, which counters the lesions caused by MS. Natalizumab also inhibits the binding of leukocytes to VCAM-1 in relapse-remitting MS, inhibiting activation of lymphocytes.

References


