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*Review*

# Multiple sclerosis: An overview of the disease and current concepts of its pathophysiology

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**The oligodendrocytes, myelin-producing cells in the central nervous system (CNS), have an essential role in "multiple sclerosis". This disease is of unknown etiology, and thus, of a variable prognosis. The main pathologic feature is the injury to the myelin and loss of oligodendrocytes in the CNS. Studies of animal models, demonstrating that autoreactive T cells (CD4 or CD8) can result in inflammatory demyelination of the central nervous system, support the theory that multiple sclerosis is an immune-mediated disorder involving one or more antigens located in the myelin of central nervous system cells (neurons and glia). About the disorder´s pathology, important findings have been made regarding inflammation, adhesion-molecules, ion-channel alterations and the process of neurodegeneration in the progression of the multiple sclerosis plaque. The progress made so far in the pathogenesis of the disease will allow a better understanding of the mechanisms involved in its progression and so, more specific treatments can be developed to ensure a better quality of life of the affected patients.**

**Key words:** Oligodendrocytes, multiple sclerosis, myelin, demyelination, plaque, immune response, autoimmunity, pathogenesis.

## INTRODUCTION

Multiple sclerosis is a chronic disease, of unknown etiology, in which symptoms vary on each patient. This enigmatic, progressive and relapsing disorder of the white matter, continues to challenge researchers, who try to understand the pathogenesis of the disease and prevent its progression. Multiple sclerosis typically begins in early adulthood and has a variable course. Fifty percent of patients will need assistance to walk within the first fifteen years of the after onset of the disease. Both clinical and imaging manifestations of disease activity have been improved by new therapies, although the long-term benefit from these treatments requires further study (Noseworthy et al., 2000). Classically, multiple sclerosis has been known as an autoimmune disease. Recent literature and studies of *in vitro* and *in vivo* have

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**Table 1.** Multiple sclerosis symptoms.

| Multiple sclerosis | |
|---|---|
| **Visual** | Pain<br>Blindness in one eye<br>Double vision<br>Green-red color distortion |
| **Sensory** | Emotionlessness<br>Insensitivity |
| **Motor** | Clumsiness<br>Painfulness<br>Absence of coordination<br>Limitation in their extremities |
| **Others** | Discomfort<br>Lightheadedness<br>Spinning feeling |

demonstrated that there are other factors involved in the pathogenesis of the disease and there isn't one unique cause. In other words, multiple sclerosis is a multifactorial disease. The objective of the present review is to briefly present an overview of the disease, of normal immune response and the actual knowledge in the study of multiple sclerosis pathogenesis, which will allow changing the perspective and approach for its treatment.

## Multiple sclerosis

Multiple sclerosis (MS), also known as disseminated sclerosis, is a chronic and disabling neurological disease, which develops in people between fifteen and forty years old and is characterized by a disturbance in myelination (Lucchinetti et al., 2001). Therefore, it will affect the conduction of nerve impulses and the integrity of signals. Clinically, it is characterized as alterations in movement and sensitivity. This will be further discussed. In MS, the brainstem is primarily altered zone in the central nervous system (CNS), followed by the spinal cord white matter.

## Clinical manifestations of MS

Symptoms depend on the degree and area of involvement. The initial symptom of MS is often double vision, red-green color distortion, or even blindness in one eye. There may be different kinds of symptoms; sensory symptoms are among the most common presenting symptoms, sensitive symptoms, such as tingling in the skin, paresthesias, pain, Lhermitte's sign(temporary paresthesias in arms and legs while bending) and Uhthoff phenomenon electrical transmission of the nervous system or worsening of symptoms in demyelinating disorders when exposed to elevating temperatures). Initially these can consist of an absence of sensation or can involve positive, uncomfortable sensations including pain or tingling; motor symptoms, as motor dysfunction, unsteady gait, dysmetria, among others; vegetative symptoms, like bladder and sexual dysfunction, constipation or diarrhea, etc. as well as cognitive impairment and affective disorders (Table 1).

## Natural evolution of the disease

In the natural evolution of the disease, it is necessary to recognize the clinical and prognostic presentations of MS, as each one of them has a different course. This has great implications in the patient's quality of life. So, it can be said that MS is a heterogeneous disease (Prat and Antel, 2005). These presentations are:

### *Relapsing-remitting multiple sclerosis*

It is characterized by episodes of neurologic dysfunction with clinical recovery but each one leaves a neurologic deficit. Its duration is very variable; from days to months.

### *Benign multiple sclerosis*

Symptoms are merely of sensorial kind. There is no worsening over time, and the clinical manifestations are not permanent.

### *Primary progressive multiple sclerosis*

The symptoms will worsen over time slowly, there are no "episodes" of neurologic dysfunction, but its course is progressive and incipient. There may be little improvement (Weinshenker et al., 1989).

### *Secondary progressive multiple sclerosis*

Since the beginning of the disease, the patients present a progressive deteriorating course, with episodes of acute dysfunction and later recovery, as a relapsing-remitting pattern (Rose and Carlson, 2007).

### Prognostic factors

There are some factors that have a direct impact on the patient's prognosis.

#### *Favorable factors*

Favorable factors include an early onset of disease, feminine gender, the relapsing-remitting clinical course and sensitive symptoms or optic neuritis as initial manifestations.

#### *Factors of worse prognosis*

Factors of worse prognosis late onset of the disease (beyond the age of forty), masculine gender, motor or cerebellar symptoms as initial manifestations, frequent episodes during the first five years, a short lapse between the first and second episodes, progressive course of the disease. The death causes in these individuals are associated with the neurologic deficits and the mobility limitation. The respiratory infections and pulmonary thromboembolism are in the top of the list. However, in young people, suicide represents an important mortality cause (Riise et al., 2003).

### Elements of the normal immune response

The human body is constantly exposed to injury by strange agents, either microorganisms, as bacteria, virus, fungi or parasites, or isolated macromolecules. However, there are several defense mechanisms to protect the body against these agents (Cudrici et al., 2006). These mechanisms are:

#### *Natural defense mechanisms*

Those in constant functioning, like skin which stands as an impermeable barrier that prevents the entrance of these agents to the body; secretions as saliva or tears, that contain the lysozyme enzyme which has some bactericide action; the acid environment in organs like the stomach or the vagina that inhibit the bacterian development, among others.

#### *Inespecific defense mechanisms*

When the invasive agent enters the body, the inespecific defense mechanisms act in charge of cells as macrophages and neutrophils, which attack indistinctly against any strange substance.

#### *Specific defense mechanisms*

The ones in charge of this defense mechanism are the *lymphocytes*. There are two types of lymphocytes which have structural and functional differences:

**T lymphocytes:** It represents the 60 to 70% of the lymphocytes in the blood stream. According to the differentiation molecules present in the cell membrane (CD from cluster differentiation), T lymphocytes are subdivided in; CD4 T lymphocytes or T helpers and CD8 T lymphocytes or cytotoxic lymphocytes.

**B lymphocytes:** It represents 10 to 20% of the total amount of lymphocytes. The CD4 T lymphocytes are the key cells to start the immune response; they activate when an antigen-presenting cell (macrophage) presents them the captured antigens during the unspecific defense response. Once activated, the CD4 T cells may stimulate the CD8 T cells, which multiply and attack in a direct and specific way the antigen that produced their stimulation. This is called the cellular immune response. On the other hand, the CD4 T cells may stimulate the B lymphocytes, which also multiply and differentiate to plasmatic cells, which produce specialized proteins called immuno-globulins or antibodies that attach to the antigen and destroy it (Rudick, 2001).

## FACTORS INVOLVED IN MS DEVELOPMENT

Multiple sclerosis is a complex disease, with genetic predisposing factors that interact with environmental ones. It is known that it is more common in people of Caucasian race of northern Europe. In studies with monocigotic twins, there has been a genetic concordance of 15 to 50%, compared to a concordance of 3 to 5% in dicigotic twins, which reveals an important genetic participation. Also, there is a strong environmental influence as some patients present the disease while others do not. The risk of presenting MS increases 2 to 4% among people who have a family member with the disease, while in general population it is estimated in 0.1% (Rivera-Olmos, 2007).

### Genetic factors

The most important genetic influence has to do with

major histocompatibility class II molecules, but it requires the interactions of various genes to be a susceptible genotype to MS (poligenicity). It has been identified in chromosome 6p21 the human leucocyte antigen (HLA) and the mayor histocompatibility complex (MHC). Recently, it has been considered other regions as the alpha-receptor of interleukin 7 (IL-7RA), the interferon 5-regulator factor gene and the alpha-receptor of interleukin 1 (IL-2RA) (Alcina et al., 2009; Balabanov et al., 2007).

### Environmental factors

Some specific genes can influence in susceptibility of one person but not from other; therefore it requires environmental elements to "activate" them. Among these ones, it includes the "geographic region" where MS is more frequent; this is attributed to the poles, as those are regions with less amount of solar light. There are some studies that associate this feature with "vitamin D" synthesis and function. It has been documented that vitamin D interacts with the HLA-DRB1, influencing its expression. In MS, it has been demonstrated that patients have low levels of vitamin D. This can be explained as there is a further separation from the equator and less conversion and cutaneous activation of vitamin D. One of the environmental factors considered is tobacco consume; however, this has not been completely explained although there is a hypothesis which states that nicotine, as other substances from tobacco smoke, produces an immunotoxic effect and alters the cell T antigen-mediated signalization (Wekerle and Honifeld, 2003). In "dietary" aspects, during the 1950's decade, some studies documented certain protective effect against MS in subjects that consumed great amounts of fish; other investigators found that a big amount of calories from animal fats increased the risk. Moreover, it has been stated that linoleic acid consume is a protective factor against MS.

The viruses have been targeted as possible factors involved in MS pathogenesis (Forman et al., 2006; Sotelo et al., 2007). The measles, Rubella, Epstein-Barr, Herpes type 6 and Herpes-Zoster virus are most mentioned and associated with the origin of the disease. In a recent study made in Mexico, through real time PCR, Varicella-Zoster virus DNA was found in 95% of patients with MS during an exacerbation of the disease (Franklin and Nelson, 2003; Gronning et al., 1993).

## INFLAMMATION AS THE PILLAR OF THE DISEASE

In multiple sclerosis, there is a whole cascade of events occurring in the central nervous system. There is an actual active inflammatory process occurring. The encephalon is one of the privileged sites in the human body, as it is protected by an anatomical and functional barrier, the "blood-brain barrier", which stands as a defense mechanism against microorganisms, toxins, etc. However, in multiple sclerosis, there is a disruption of this barrier, allowing lymphocytes and other cells and factors involved in inflammation to enter the central nervous system and start the inflammatory process. T and B lymphocytes, macrophages, plasma cells and others such as dendritic cells have been implicated in the pathogenesis of MS (Frohman et al., 2006). The regulation of these immune components, by either receptor activation or cytokine release, is what triggers the pathogenic process. Which antigen starts this response is an unknown matter up to now (Hemmer et al., 2002).

### Humoral response

Some cells are directly implicated in damage to myelin or oligodendrocytes, while others have regulatory function or cause damage through indirect mechanisms, such as immunoglobulin production (Huseby et al., 2001). More specifically, antibodies against molecules expressed on the extracellular surface of myelin and oligodendrocytes, like glycolipids, are synthesized (Genain et al., 1999). In models of multiple sclerosis, such as experimental autoimmune encephalomyelitis (EAE), complement activation stimulates the creation of antibodies. The fact of finding elevated antibody levels and oligoclonal IgG bands in the cerebrospinal fluid, which are actually some of the most important tests for diagnosing MS, supports the involvement of humoral immunity in the pathogenesis of MS. Also, another key point for this argument is the actual recognition of ectopic lymphoid follicle-like structures with active germinal centers in the meninges that serve as a continuous source of B cells and their products (Husted, 2006).

### Cellular response

#### *Macrophages*

Macrophages have their role in MS pathogenesis producing substances that cause direct tissue injury, such as proteases, lipases, cytotoxic cytokines, reactive oxygen species and nitric oxide radicals. The later ones have demonstrated to be an important part in damage to oligodendrocytes and axons. A mechanism of synthesis is through cell stress, provoked by mitochondrial injury and hypoxia. Other relevant molecule produced by

macrophages is “osteopontin”. It is highly expressed in MS and contributes to inflammation perpetuation. Its action mechanism; it stimulates monocyte recruitment (monocytes are macrophage immature forms), causes T-cell apoptosis inhibition (provoking tissue injury indirectly) and produces proinflammatory cytokines (Chang et al., 2002). Other factors contribute to oligodendrocyte toxicity, such as an excess of excitatory neurotransmitter (glutamate), T cell products (perforin/lymphotoxin), interaction of fas antigen with fas-ligand (implicated in apoptosis), etc.

## Lymphocytes

### *CD8 T lymphocytes*

CD8 cells have classically been implicated in damage to oligodendrocytes and their axons, because of their direct cytotoxic effect. This is achieved through recognition of class I peptide epitopes on the surfaces of axons. Among their effects observed in MS, CD8 cells can transect axons, induce oligodendrocyte death and promote vascular permeability (Blakemore, 2008).

### *CD4 T lymphocytes/T helpers*

Besides the CD8+ T cells, the T helper cells are also involved in MS pathogenesis. As mentioned above, CD4 effector cells have the function of activating and directing other immune cells, and are particularly important in the immune system. There are two major subtypes of cells, known as Th1 and Th2, which have several differences between them, but the main one is the immune response promoted by each one of them. Th1 cells trigger the cellular immune system, while Th2 cells stimulate the humoral immune system. This polarization from CD4 lymphocytes depends on the exposure to certain types of interleukins (IL) (Imitola et al., 2006). It has been described that MS is primarily a Th1 cell-mediated disease, with proliferation of cytokines that up-regulate cytotoxic cells, including IL-2, □-IFN, and TNF-□. In spite of this, there has been demonstrated that Th2 cells can participate in autoimmune processes. Specifically, in MS there is formation of antibodies against myelin-oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP), important components of myelin covering. This contribution from Th2 cells aggravates the Th1 autoimmune process (Saikali et al., 2007). Subtypes of Th1 cells are the Th17 CD4 cells. Specifically, these cells are relevant in MS as they produce proinflammatory cytokines involved in myelin damage, such as IL-17, TNF-a and IL-6. It has been seen that IL-17 is expressed in MS lesions. IL-6 has the effect of inhibiting the negative regulation of Th17 cells, so it acts as a positive feedback to keep the inflammatory process active. Besides Th1 and Th2 derived cells from naïve CD4 lymphocytes, there is another type of cell that comes from these ones; the regulatory T cells (T reg).

T regs are in charge of regulating not only Th1/Th2 function, but also the activity of IL-17. Besides, it has been demonstrated that patients with MS have reduced T reg function.

## Dendritic cells

Dendritic cells (DC) are antigen-presenting cells, which are the primary cells that recognize foreign antigens and induce cell differentiation by the release of certain cytokines. In MS, there is evidence that DC appears in the cerebral spinal fluid (CSF) circulation to survey inflamed CNS tissue and they remain in an active state. So, there is a constant synthesis, release of IL and cell induction and this may be the primary source of the disease pathogenesis. Specifically, TLR-9 (toll-like receptor 9) and MyD88 (myeloid differentiation factor 88) have been found to be essential mediators for the induction of EAE in experimental models.

## Other relevant considerations

Another factor that may have to do with MS pathogenesis is the “progenitor cell pool”. Oligodendrocytes appear to be reduced in active stages of disease and in sites of active local inflammation. However, in areas of remyelination or inactive inflammatory process, there seems to be a recovery in the number of these myelin producing cells. This may be attributed to progenitor cells which differentiate into mature oligodendrocytes. However, in sites of intense tissue destruction, at active sites of demyelination, there is absence not only of oligodendrocytes, but also of progenitor cells. This could be an interesting starting point of future study for new therapeutic approaches (Wolfgan, 2007). The difficulty in clinical recovery with each episode that occurs may be influenced by “axon destruction” and not only myelin disruption. This is supported by the evidence of *in vivo* studies that show reduced levels of N-acetyl-aspartate, a neuronal marker, in brain lesions in relapsing-remitting multiple sclerosis. It has been seen that duration of clinical active disease does not have to do with damage to the white matter, but the “background of active tissue inflammation”, as there may be periods of clinical remission and still there is damage occurring at the same time or there may be more overt clinical manifestations

but progression of the disease may delay more time. The main problem then may not be a lack of myelin repair, but the process of remyelination may be unstable as long as the inflammation remains active. This may be a reason why some patients have a different evolution within the natural history of the disease (Lassmann, 2008).

**How does damage occur in MS?**

If an individual younger than 15 years and genetically susceptible is exposed, for a minimum of two years and during periods of intense proliferation of oligodendrocytes, to an environmental factor, up to now no well defined (probably viral), he will develop a cross reaction between the environmental antigen "X" and the myelin components and/or their producing cells (oligodendrocytes) or even non-myelin proteins (alpha, beta, cristalin, phosphodiesterases, S-100 proteins). This leads to sensitization (permanent memory) of T cells, but are inactive against myelin and/or the oligodendrocytes, which have turned into auto-antigens due to the cross reaction. When the right antigen enters the body, it is phagocytized by the macrophages. Once in the surface of the antigen-presenting cells, the MHC-antigen complex is recognized by the receptor in the surface of the CD4+ cells. From this moment, T cells are turned into activated T helper cells (Th1) capable of crossing the brain-blood barrier. It has been described that MS is primarily a Th1 cell-mediated disease, with proliferation of cytokines that up-regulate cytotoxic cells, including IL-2, $\gamma$-IFN, and TNF-$\alpha$. As Th1 cells, T lymphocytes induce a proinflammatory immune response characterized by: proliferation of T cells (clonal expansion), proinflammatory cytokines release (IL-2 stimulates the production of $\gamma$-IFN, IL-12, $\alpha$-TNF, $\beta$-TNF and lymphotoxin), activation of B cells and macrophages by other proinflammatory cytokines (which intensifies the immune response), antibody production and release of anti-inflammatory cytokines (IL-1, IL-4, IL-10) through Th2 subtype (Kasper and Shoemaker, 2010).

The effect of the proinflammatory cytokines, together with the effect of local factors in the CNS (as metabolic stress), generates Th1 cell attraction to the vascular endothelium and amplification of the expression of the endothelial adhesion molecules receptors, of E-selectins and integrins. These allow cells to cross the blood-brain barrier. At the same time, proteases (as the matrix-metalloproteinase) degrade the extracellular matrix molecules of the endothelial cells, causing a break in the blood-brain barrier and favoring even more the cell migration. Within the CNS, the TH1 cells are reactivated by antigen-presenting cells, but this time the antigen is not exogenous, but an own antigen (as a myelin protein); this generates an "amplification of the immune response" whose components recognize the autoantigens of the CNS and cause demyelination. At this point, the autoimmunity process can be suppressed, or it can continue with the process of demyelination. Apparently, the suppression is secondary to the action of the Th2 cells which secrete anti-inflammatory lymphokines and the subsequent "cleaning" of the inflammatory infiltrate and edema remission. The autoimmune process stops without generating demyelination; however, if there was cytokine and immunoglobulin (IgG) secretion, as well as blood-brain barrier breakage, there will be clinical manifestations, but of reversible nature (Zhou et al., 2006). Demyelination is the characteristic that defines MS; it presents when the myelin destruction exceeds its production. It predominates in the optic nerves, periventricular white matter, brainstem, cerebellum, and spinal cord white matter. Regardless of the demyelination mechanism, the immediate consequence is the reversible blockage of the nerve conduction.

Sometimes, after demyelination, there is a remyelination process. This is characterized by being incomplete (aberrant) generally limited to active demyelination zones; but also it is possible to watch these in chronic lesions, as some conserve an important number of oligodendrocytes precursor cells. The axons are not the primary target in MS, but their damage or loss is the main cause of irreversible neurologic disability and the main determinant of the secondary progressive presentation of the disease (Kantarci et al., 1998). It is a continuum process due to the axon vulnerability to inflammatory response mediators. The process initiates from the earliest stages of the disease and continues in patients with a disease evolution greater than ten years, independently of the clinical course (Kuhlmann et al., 2002).

**CONCLUSIONS**

Multiple sclerosis is a chronic, heterogeneous and complex disease, in terms of origin, pathophysiology, illness course, progression mechanisms and treatment response. The main feature is the involvement of the myelin and loss of oligodendrocytes in the CNS due to an active inflammatory process. Its development is determined by the intervention of genetic and environmental factors. Within the genetic factors, there are multiple genes that predispose or increase the risk of developing the disease (genetic susceptibility), making it harder for investigators to determine the heritage pattern of expression. Among the environmental factors, it has been proposed several ones; however, there is no convincing evidence that one has a greater impact than

other, although the viral theory has been the most solid one. From the population point of view, it has important consequences, as it affects young and economically active individuals and their quality of life. The advances in molecular biology will allow identifying more specific genes involved in the genetic susceptibility and in the development of the disease. And so, this will allow implementing more specific therapies. In future, this is promising, as it could not only affect the sick individual, but it would prevent its appearance in subjects with family risk.

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