MAIN THEME: MULTIPLE SCLEROSIS

Immunopathogenesis of multiple sclerosis

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Abstract: Immunopathogenesis of multiple sclerosis is a complex process involving T cell mediated autoimmunity at initial stage of disease. A long standing view that Th1 cells are critical for early inflammatory development of lesions is challenging by recent findings that Th1 helper cells with Th17 phenotype are even more important. A complex autoimmunity of MS is further complicated with evidence that CD8 cells, regulatory T cells, clonal expansion of B cells, cells of myelin lineage, antibodies and complement, as well as process intrinsic to central nervous system contribute to the tissue destruction. Although there are a lot of evidences about inflammatory phase of MS, far less is known about mechanisms involved in degenerative phase of disease. It is not known weather quantitative, or qualitative differences in inflammatory response contributes to destruction of the tissue, or as it was shown experimentally demyelination may sometimes occur independent of T cells.

Understanding of immunopathogenesis of MS especially regarding various stages of disease is necessary for clinicians in choosing optimal therapy of MS in individual patients. Influences of immunomodulatory treatment on various stages of MS immunopathogenesis are presented.

Key words: immunology, multiple sclerosis, immunologic basis for treatment

MS is regarded as autoimmune T cells mediated disease, characterized with multiphocal demyelination and axonal damage of central nervous system (CNS), based on a complex genetic background (1). Although it is accepted that activation of Cd4 cells and their differentiation into Th1 phenotype is a driving force in early phase of MS, but also important in the long-term evolution of disease, other components of immune system, such as antibodies, complement, CD8+ T cells, and factors produced by innate immune cells contribute to the lesion formation. Th1 cells were for a long time regarded as critical for development of demyelination in MS but recent data obtained from animal models as well as from MS patients indicate that T helper cells with Th17 phenotype may be even more important for inflammation. It was found that IL-17 mRNA is more abundant in blood and CSF of MS patient and IL23 critical for development of Th17 cells is higher in myeloid dendritic cells from patients with multiple sclerosis (5).

CD8+ cells also contribute to development of lesion in MS. In contrast to CD4+ cells that are found only at the edge of MS plaque, CD8+ cells are present also in perivascular regions. Besides this CD8+ cells recognize myelin proteins in MS patients with higher frequency than in healthy individuals, and myelin proteins are regarded, although it is not yet proved with certain, as specific target in MS. Therefore it is speculated that lesions in multiple sclerosis are initiated by CD4+, but amplification and damage is mediated by CD8+. This is supporting by data that CD8+ cells can directly attach and damage axons (3,6)

While in the past the role of B cells and the production of oligoclonal IgG in the brain and cerebrospinal fluid in patients with MS were mainly viewed as an epiphenomenon, more recent pathological findings in MS point to the important role of B cells in MS pathology. There are more and more evidences indicating that in MS, similar to other autoimmune diseases like rheumatoid arthritis, B cells aggregate into lymphoid-like structures. In MS such B cell ectopic lymphoid structures are found in intrameningeal follicles and in white matter. B cells are often infected with Epstein Barr (EBV) virus (7). These findings could explain continuous B cell and T cell activation in patients with severe SPMS and PMS. Although there is a lot of yet unsolved questions related on various B-cell-related mechanisms (e.g. B cell effectors and regulatory functions and others) it is clear that clonal expansion of B cells, and their antibody products, contributes to the hallmark of inflammation in the CNS in MS patients (7, 8).

Function of dendritic cells (DCs) in T cell response is also very important and influences the outcome of inflammatory response in MS. In EAE model myeloid DCs (CD 11b CD11c, CD45) are associated with presentation of antigen to active and to naïve T cells and therefore they may contribute to antigen spreading, and amplifying the inflammatory process, but also they contribute to maturation of Th17 cells (9).

In multiple sclerosis diffuse distribution of activated microglia was found, challenging that maybe such activation represent one of initial steps in lesion development and that it also may be answer to the fact that there is diffuse lesion of normal appearing white matter (10).

Formation of acute inflammatory lesions in MS is possible by breakdown of blood-brain barrier (BBB).Such lesions are commonly clinically silent, and are ten times more frequent, than clinically presenting symptoms. Disruption of BBB lasts for about a month and than resolves leaving the area of inflammatory damage. The outcome of such acute lesion is determined by immunological and genetic vulnerability factors of the central nervous system predicting also heterogeneity of MS (2, 3).

Beside acute inflammatory component degenerative process also exists in MS and contributes to the progression of disability. Although it is possible that degenerative process is independent of active immunological process, immune mechanism may contribute to its development. The cause of axonal damage is well established but the question is if immunological or non-immunological mechanisms are involved in mediation of the process. It is not yet known weather qualitative or quantitative difference in inflammatory response contribute to the degeneration of axons and neurons in CNS of MS patient. Based on pathological findings existence of four different pathological patterns are generally accepted (3).The types one and two are characterized with pronounced inflammation, but in type two deposits of complement and antibodies are dominant, indicating that in this type of disease myelin damage is mediated by antibody (3). This is also evident by an increase in intrathecally synthesized immunoglobulin G, indicating a clonal expansion of B cells. Besides, immunoglobulin G may be specific for causative agents in MS. Although such agent is not yet found, some studies showed that oligoclonal bands are directed against two different proteins of Epstein Barr (EBV) virus (11). On the other side antibody against MOG (myelin ologodendrocyte glycoprotein) can increase demyelination in marmoset EAE (12), and it was suspected that the same happened in MS patients (13), but it was not definitively confirmed (14).

An increase of inflammatory response could be due to various infiltrating cells, among them also regulatory cells but it could be also due to the processes associated with local CNS environment. Some studies point to the importance of various chemokines and their receptors in augmentation of CNS inflammation. Chemokine receptor CCL2 has been identified as potent chemo attractant of

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monocytes and dendritic cells, and it is assumed that its induction in astrocytes occurs by innate or adaptive activation (15). Experimentally was shown that over expression of chemokines receptors CCL2 in CNS may lead to minimal inflammation despite of substantial demyelination. This indicate that at least in some patients with MS initial step in the formation of lesion may be independent of immune cells, that means non immunologically driven(15).

The final pathway for axonal damage is probably calcium influx and mitochondrial collapse, probably with contribution of glutamate excitoxicity (16).

Involvement of a CD4+ T cell-mediated process as an initial in development of MS is consistent with the association of genetic risk with HLA class II molecules. Many studies confirmed that HLA class II genes have the largest risk for multiple sclerosis. In Western Europe these are HLA DRB genes of HLA DR-15 haplotype (17).

The most important question how and why autoimmune process starts in previously healthy individual is still questioned. Earlier standing that clonal depletion of self reactive T cells in thymus maintains the immunologic self tolerance was rejected by finding that potentially pathogenic autoreactive T cells are also present in the periphery of healthy individuals (18,19) . This point that some other regulatory mechanism must exist to prevent autoreactive T cells to start immune disorders (20). According to experimental findings the regulatory T cells play a key role in the control of self antigen reactive T cells and in the induction of peripheral tolerance (18). It was also found that autoreactive T cells in patients with autoimmune diseases are more easily activated compared to the same cells in healthy individuals (18). Recently it was found that CD4+ and CD25+ T cells prevent activation and effectors function of T cells. Although both subsets DCD4+ and CD25+ T cells are present at the same frequency in healthy individuals and in patients with MS, in MS patients CD 4+ and CD25+ T cells show primary regulatory defect of function. They are not able o suppress the proliferate response of CD4, CD25, +T cells target as it was possible with the same subset of healthy individual (19).

In MS it is not clear if Treg cells exert their effects in the periphery or at the site of disease, in the target organ, but regulatory T cells are definitively important part of complex autoimmunity in MS (20).

All this point to the conclusion that autoimmune disturbance in MS is characterized by the complex interplay of autoreactive T cells, B cells, antibodies, T regulatory cells complement as well as processes intrinsic to the CNS itself . These factors are also important in determining the stages of tissue damage and heterogeneity of the disease.

Another question is how to clinically apply results of scientific immunological studies? It is clear that immunological studies are fundamental for understanding the basic process that is ongoing in MS, and provide basis for development of pathogenetically adequate and effective therapy in MS. Influence of interferons beta on induction of anti-inflammatory cytokines IL 10 as well as inhibition of T-cells traffic by blocking metalloproteinases, and increasing a tissue inhibitor to matrix metalloproteinases is well known and correlate with reduction of disease activity (21).

Changes in the BBB permeability or local increase in expression of adhesion molecules contribute to disease activity. Interactions between endothelia cells and monocyte in acute MS lesions are well documented. It was shown that therapy with interferon beta in MS increases soluble vascular cell-adhesion molecules and causes reduction of endothelial adhesion cells thereby minimize the lymphocyte traffic into the CNS.

Recently was documented and confirmed by studies in MS patients, that monoclonal antibody directed at integrin alpha 4 (natalizumab) have special effect on adhesion cells resulting in profound reduction of disease activity (22).

Therapy with sphingosine-1 phosphate (SP1) receptor agonist (fingolimod) traps the lymphocytes in the lymph nodes and prevents their migration to peripheral tissue. Although the effectiveness of this medication is still studied results showed impressive reduction of disease activity pointing also to the importance of lymphocyte trafficking in the development of MS. (23)

A treatment that remove mononuclear cells by monoclonal antibody to CD 52 (alemtuzumab) also produce a profound reduction in inflammatory activity, and indicates importance of CD4 and CD8 cells in CNS inflammation in MS (24).

The exact function of B cells is not quite known, although it was shown that antibodies to myelin proteins contribute to demyelination. A trial with monoclonal antibody specific to CD 20 (Rituximab) showed a rapid reduction of acute disease activity shown by MRI, and is important for understanding the role of B cells in MS (25).

Reduction of activity in MS was also found with another monoclonal antibody- daclizumab. Explanation of such therapeutic goal is observation that daclizumab treated patients showed marked reduction of CD4 and CD25, FOX 3 type 1 regulatory cells (Tr1 cells) (26).

Conclusion: In MS inflammation is disregulated and inflammatory cells, pro-inflammatory cytokines, plasma proteins and cytotoxic agents predominate. Immunological studies suggested putative pathogenetic factors that may be important in the therapy of multiple sclerosis. Manipulations of immune response based on known pathogenesis of multiple sclerosis evolved in development of present immunomodulating treatment, but further researches and applications of new studies of even more effective therapies are ongoing.

An ideal therapy in the future would bring the immune system into balance by increasing anti-inflammatory agents and restorative molecules.

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Importance of neurophysiological investigations in the diagnosis of multiple sclerosis

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Introduction: Evoked potentials (EPs) are the electric responses of the nervous system (cortical response) to motor or sensory stimulations. Visual, acoustic or auditory (or auditory brain stem) and somatosensory evoked potentials (or responses) (VER/

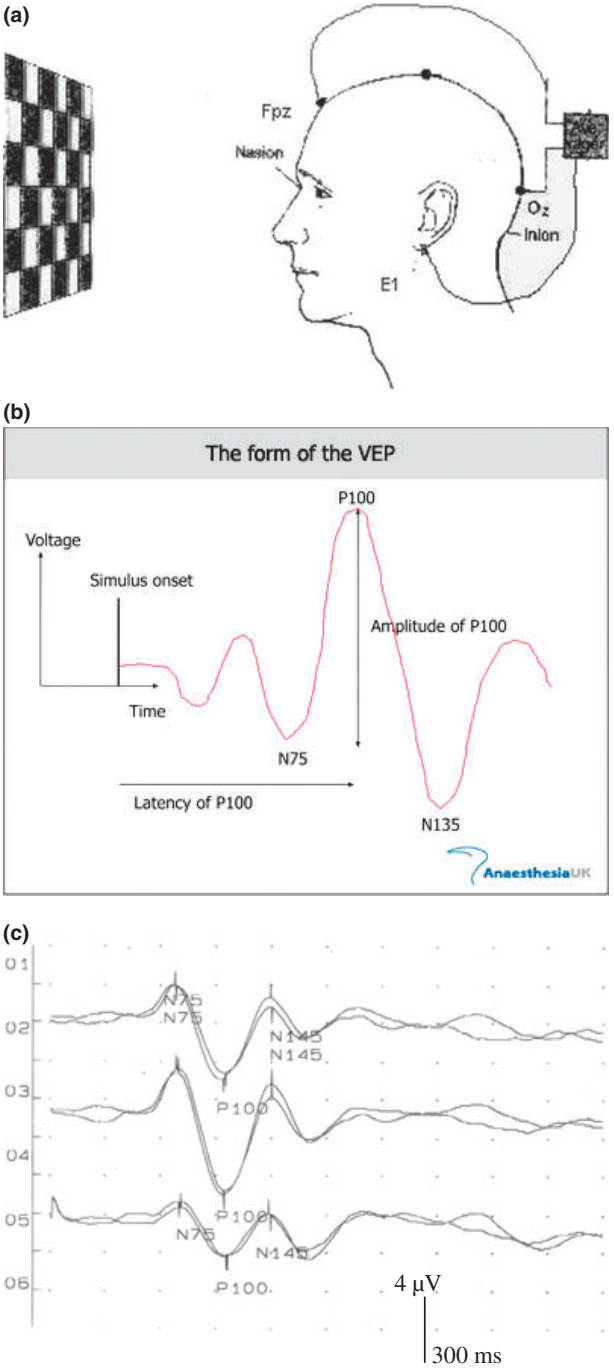


Fig. 1. a) Visual evoked potential. b) Norma visual evoked potential. c) Normal visual evoked potential.

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