

Multiple sclerosis – novel insights and new therapeutic strategies

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Purpose of review

This review focuses on novel aspects of the pathogenesis and advances in the therapy of multiple sclerosis (MS).

Recent findings

Recent observations suggest that early lesion development in MS may start in some forms with oligodendrocyte death and that inflammation appears as a secondary phenomenon only. The lack of sufficient remyelination in MS may be the result of a disturbed function of basic helix-loop-helix transcription factors. Clinically the identification of patients with a clinically isolated syndrome at high risk to develop clinically definite MS remains difficult; the predictive value of serum antibodies against myelin proteins remains controversial. The role of neutralizing antibodies in interferon therapy is discussed. New therapeutic approaches in MS are emerging.

Summary

The existing view on the pathogenesis of MS is still changing. The original assumption that cell-mediated demyelination is the key event in lesion development dictating clinical disability is critically reviewed and alternative pathways have been suggested. Oligodendrocyte death, axonal loss, the role of CD8⁺ T lymphocytes, T regulatory cells, and B lymphocytes have come into the focus of newly evolving concepts in MS pathogenesis. A deepened understanding of the immunopathogenesis of this disease translates into innovative therapeutic approaches, such as blockade of $\alpha 4$ integrins by a humanized monoclonal antibody. In various animal models cell-replacement strategies yield promising results; however, turning these findings into an effective therapy in MS patients has a long way to go.

Keywords

B lymphocytes, CD8, CIS, MOG, natural history, neutralizing antibodies, pathology, regulatory T cells

Abbreviations

CIS	clinically isolated syndrome
CNS	central nervous system
EAE	experimental autoimmune encephalomyelitis
EBV	Epstein-Barr virus
FDA	US Food and Drug Administration
HERV	human endogenous retrovirus
MOG	myelin oligodendrocyte glycoprotein
MRI	magnetic resonance imaging
MS	multiple sclerosis
NAb	neutralizing antibody
RRMS	relapsing-remitting multiple sclerosis
SPMS	secondary progressive multiple sclerosis
TAL	therapy-related acute leukemia

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Introduction

Multiple sclerosis (MS) is considered a prototype inflammatory autoimmune disorder of the central nervous system (CNS). The etiology of this disease remains unknown, but an interplay between as-yet unidentified environmental factors and susceptibility genes appears most likely [1]. In consequence, these factors trigger a cascade, involving an inflammatory response within the CNS that results in demyelination, oligodendrocyte death, axonal damage, gliosis, and neurodegeneration. How these complex traits translate into the clinical presentation of the disease is a focus of ongoing research. A better understanding of the sequential evolution of the MS lesion, the development of clinical surrogate markers which would allow to define patients at higher risk, and increased awareness of the natural course of the disease will pave the way for an optimized treatment approach, utilizing currently approved and promising experimental drugs that may hopefully become available in the near future.

Insights from neuropathology

MS is considered a prototypic immune-mediated demyelinating disease of the CNS. Its morphological hallmarks are demyelination, inflammation, gliosis, and axonal damage [2,3], although heterogeneity of lesion pathology has been recognized. Four patterns of demyelination have been delineated [4]. Evidence gained from studies in animal models supports the concept of a strategic role of inflammation in the pathogenesis of MS [5]. Changes on magnetic resonance imaging (MRI) are indicative of blood-brain barrier disruption and CNS inflammation,

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correlate albeit moderately with clinical disability, and have apparently some predictive value for the course of the disease [6]. Immunomodulatory and immunosuppressive treatment strategies are proven to reduce relapse rate in MS patients [7]. Nevertheless, the reason why the immune system starts to attack the myelin sheath remains enigmatic. A recent publication by Barnett and Prineas [8^{*}] raises the possibility that the immune response in MS is secondary to a primary disease mechanism. The authors had the opportunity to analyze the brain of a young patient with relapsing-remitting MS (RRMS) who died within 17 h of the onset of a new symptomatic and fatal brainstem lesion. They observed extensive apoptosis of oligodendrocytes in a circumscribed small area and propose this as the initial event in lesion formation. Oligodendrocyte death would cause activation of resident microglia which phagocytose the debris. As part of the apoptotic pathway, activated complement is deposited on the myelin sheath, which within a few days appears vacuolated and attracts monocytes. This view of MS lesion formation proposes oligodendrocyte death as the primary cause of inflammation in the MS brain [9]. Leukocyte recruitment appears necessary for the removal of apoptotic membranes. The authors tried to confirm these observations in postmortem tissue from patients with early MS. In six out of 11 brains, a total of nine lesions also contained apoptotic oligodendrocytes, similar to the picture in the 14-year-old patient. On the other hand, in five other early MS cases and six patients with long-standing MS, such lesions were not depictable. Thus, this study underlines the heterogeneity of MS pathology. The pattern observed falls into the spectrum of a type 3 lesion according to Lucchinetti *et al.* [4]. Hence, there is clearly no need to completely change our view of the pathogenesis of MS. What causes oligodendrocyte death remains elusive; nevertheless, several possible pathways have been suggested, such as a virus infection of oligodendrocytes [4], hypoxic stress secondary to ischemia or an immune-mediated vasculitis [10–12], or damage inflicted by cytokines and other immune mediators derived from activated microglia in what one might call friendly fire [13–16]. Further studies are required to identify the specific factors governing lesion development of each subtype in MS. It remains to be seen from extended pathological studies whether the proposed four subtypes represent truly distinct patterns unique to the natural history of one individual's disease or a spectrum whose expression changes as the disease evolves during the patient's lifetime.

The possible contribution of CD8⁺ T lymphocytes as effector cells mediating CNS damage is receiving increasing attention. These cells outnumber CD4⁺ T cells in active plaques. Clonally expanded CD8⁺ T cells have been found within MS lesions [17] as well as in the cerebrospinal fluid of MS patients [18]. In a recent

study several identical expanded CD8⁺ T cell clones could be retrieved from the brain and cerebrospinal fluid, and some from the blood of MS patients [19^{*}]. Interestingly, some of the brain-infiltrating CD8⁺ T cell clones persisted for more than 5 years in the cerebrospinal fluid and/or blood, underlining the putative role of this cell population in perpetuating disease progression in MS.

The antigen(s) recognized by these CD8⁺ T lymphocytes are yet to be determined. All attempts to identify the target antigen(s) in MS have to date either yielded no or controversial results. Viral antigens would represent obvious candidates; alternatively, CD8⁺ T cells might recognize genuine CNS autoantigens, such as myelin constituents. The most attractive aspect of CD8⁺ T cells is their ability to recognize HLA class I-associated antigens. This may allow them to attack directly neurons and oligodendroglia which can only secondarily be targeted by CD4⁺ T cells [20]. These findings, however, do not exclude that CD4⁺ T lymphocytes have an equally important role in MS pathogenesis.

Increasing attention has been directed towards the role of CD4⁺ CD25⁺ regulatory T cells because of their contribution to the maintenance of peripheral tolerance. Breakdown of peripheral tolerance to neural self-antigens is considered key in the development of the autoaggressive immune response. Deletion of this regulatory T cell population causes spontaneous autoimmune disease in mice [21^{**}]. In the peripheral blood of patients with MS a significant decrease in the effector function of CD4⁺ CD25^{hi} regulatory T cells compared with healthy donors has been reported, suggesting functional alterations of suppressor cells in MS [22^{*}]. However, this finding has not been confirmed by others [23^{*}]. Other control functions have been attributed to natural killer (NK) cells that exert regulatory effects on memory T cells in an antigen-non-specific fashion in MS patients [24].

The detection of ectopic B-cell follicle-like structures with germinal centers in the cerebral meninges of two out of three patients with secondary progressive MS (SPMS) provides further clues in our understanding how humoral autoimmunity may be maintained in MS [25^{*}]. The meninges have been identified as possible sites of B-cell follicles in the animal model of experimental autoimmune encephalomyelitis as well [26]. In line with this finding, centroblasts, which are usually restricted to the lymph nodes, were detected in the cerebrospinal fluid [27]. Clonal accumulation of B cells and plasma cells in the cerebrospinal fluid has now been confirmed by single-cell PCR analysis [28,29]. Clonal expansion of B lymphocytes can be detected in the cerebrospinal fluid of MS patients early in the disease process, emphasizing that

specific stimulation of B-cell expansion in the CNS of MS patients occurs upstream in the immunopathogenetic cascade [29,30]. Further studies will shed light on the role of various subpopulations of immunocompetent cells and their interplay in MS [31].

Besides tissue destruction mediated by immunocompetent cells the lack of sufficient remyelination in MS is currently the focus of various research avenues. A recent report suggests that activation of oligodendrocyte progenitors, which are often present in abundance in the CNS, may be dependent on signals regulating the subcellular localization and/or activity of the basic helix-loop-helix transcription factor Olig1 [32**]. Further insights into the molecular mechanisms of Olig1 function may have therapeutic implications given that this factor appears to propagate repair in the damaged MS brain [33].

Natural history and prognostic factors

Natural-history studies provide crucial information in a number of ways. They form the basis for disease cost analysis, are relevant for the deployment of health-care resources, and play an indispensable role in the evaluation of efficacy in clinical trials. The natural history of MS has taught us that, over time, the majority of MS patients will exhibit progressive neurologic deterioration. Approximately 50% of patients diagnosed with MS will require the use of a cane to ambulate safely within 10 years, and 25 years from the time of diagnosis approximately 90% of MS patients have transitioned to a progressive form of the disease and sustain substantial clinical disability [34,35].

Pittock *et al.* [36*,37*] reassessed the 1991 Olmsted County MS prevalence cohort in 2001. Although survival was reduced and 30% of patients progressed clinically to needing a cane or wheelchair, or worse, over the 10-year follow-up period, most remained clinically stable or progressed only minimally [36*]. The distribution of clinical disability in the Olmsted community remained stable for 10 years, suggesting that progression of disability for patients with RRMS or SPMS may be more favorable than reported previously. Once a certain clinical threshold of disability was reached, disease progression accelerated and the chance of developing significant disability rose [37*]. Similarly, a study in northern Sweden obtaining data from an incidence cohort and a prevalence population suggests that the clinical course of MS may be slightly more benign than anticipated [38]. These observations, demonstrating that MS-related disability in the vast majority of individuals in a large community may change only modestly over 10 years, have a number of implications; moreover, an increased knowledge of the natural history of MS is important for the design and interpretation of randomized clinical trials [39].

Time to accrued disability is apparently influenced strongly by the number of exacerbations during the early phases of the disease. Although clinically isolated syndromes (CISs) and RRMS are not classified as progressive forms of the disease, irreversible deficits can be established with each exacerbation and as such contribute to persistent clinical impairment and disability. Consequently, MS treatment should be initiated at the earliest possible time point to prevent accumulation of irreversible deficits. Based on the CHAMPS study the US Food and Drug Administration (FDA) approved the use of intramuscular interferon β -1a in patients with CISs and an MRI result suggestive of MS [40]. Decisions regarding the initiation of immunomodulatory therapy are influenced by concerns about adverse events and cost-benefit considerations at present. Thus, it is an ongoing debate how to define those patients that are at high risk of deterioration since early prognostic factors are lacking. The implementation of MRI has provided the means to stratify patients with higher risk of recurrent disease on the basis of the number and size of CNS lesions at their initial presentation [41–43]. **A re-analysis of the optic neuritis trial revealed that the 10-year risk of MS following an initial episode of acute optic neuritis is significantly higher if there is a single brain MRI lesion.** On the other hand, even when brain lesions were seen on MRI, only 40% of the patients developed clinical MS after 10 years [44], and the clinical course was benign in most cases [45]. Along this line, a recent study confirms that patients with CISs presenting with optic neuritis have a smaller risk to convert to definite MS compared to other clinical topographies. Interestingly, in optic neuritis the baseline MRI was normal in nearly 50% [46]. These data underline the critical role of MRI and the need for better surrogate markers [47**,48], especially since MRI remains an expensive and logistically difficult examination to perform.

Recently, Berger and co-workers [49] provided evidence that the analysis of serum antibodies against myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP) in patients with CISs might be a precise method to predict the early conversion to clinically definite MS. The authors could demonstrate that patients with anti-MOG and anti-MBP IgM antibodies experienced relapses more often and earlier than patients without these antibodies. The adjusted hazard ratio for the development of clinically definite MS was 76.5 among those seropositive patients, and 31.6 among those who were seropositive only for anti-MOG antibodies compared with the seronegative patients. These data, however, do not clarify the pathogenetic role of these antibodies. It remains to be established whether these myelin-reactive antibodies contribute to initial tissue damage, reflect a response to injury, or participate in a protective or remyelinating response to parenchymal destruction [50,51].

Another group was able to identify IgM antibodies against native glycosylated MOG in patients during the first demyelinating event and higher MOG-specific IgG antibodies in patients during relapses and in secondary chronic progressive forms by ELISA [52]. On the other hand, a third group, using a liquid-phase radio-binding assay, did not find any difference in the expression level of anti-MOG antibodies between MS patients and controls [53]. Because the solid-phase technique measures high-affinity antibodies, it is possible that the discrepancy is due to a low-affinity MOG binding of the IgM antibodies. Additional studies are needed to clarify the role of anti-MOG antibodies in MS. If the observations described by Berger *et al.* [49] could be confirmed by others, such a test would improve the quality of the diagnostic and prognostic information that can be used to guide treatment decision and strategies in the future. Currently ongoing trials in CIS patients will provide an excellent opportunity for such research.

Recently, a putative marker for neuromyelitis optica (Devic's disease; NMO-IgG) has been described [54*]. This autoantibody, with a reported sensitivity of 73% and specificity of 91% for neuromyelitis optica, may be helpful in distinguishing neuromyelitis optica from MS. Moreover, these studies underline the critical role of the humoral immune response in inflammatory demyelination of the CNS.

The role of viral agents in the pathogenesis of MS has received support from recent epidemiological investigations. A number of studies demonstrated higher Epstein-Barr virus (EBV) antibody titers, higher virus load, and altered T-cell responses in MS patients [55–58]. In a recent study, pediatric MS patients were analyzed for antibody titers against common viruses including EBV, cytomegalovirus, parvovirus B19, herpes simplex virus, and varicella zoster. Some 83% of pediatric MS patients compared with 42% of emergency-department and healthy controls had antibodies against EBV. A slightly higher reactivity was also noted for herpes simplex virus-1 but for none of the other pathogens [59]. The same group reported a reduced MS risk for individuals who had an extended exposure to an infant sibling during childhood. Interestingly, childhood exposure was associated with lower IgG antibody titers against EBV [60*]. The authors conclude that late exposure to EBV may contribute to the development of MS. Other groups report a strong association with active infections with the neurotropic herpesvirus 6 (HHV-6) in a subset of patients with RRMS [61]. Such observations find support by a recent study in which HHV-6 was detected to a higher degree in oligodendrocytes within MS lesions and the normal appearing white matter when compared to control samples [62].

Human endogenous retroviruses (HERVs) have also been implicated in the pathogenesis of MS. The functional consequences of HERV expression in glia cells were recently addressed by Antony and colleagues [63]. The authors reported that the HERV-W-encoded glycoprotein syncytin is upregulated in astrocytes within acute demyelinating MS lesions. Syncytin expression was cytotoxic for oligodendrocytes due to the release of redox reactants. These findings provide an explanation of how HERVs may mediate damage during neuroinflammation.

Immunomodulatory drugs and antibodies

In recent years, efficacy of interferon β and glatiramer acetate in the treatment of RRMS was demonstrated in a number of phase III trials. Moreover, interferon β was also shown to be efficacious in CISs in patients at risk from developing clinically definite MS as well as in secondary progressive forms of MS. Recently, a combined analysis of the European and North American [64] placebo-controlled studies with interferon β -1b in SPMS was published. These studies had yielded divergent results regarding their primary outcome of sustained disease progression. The aggregate data, subject to *post-hoc* analysis, suggest that both continuing relapse activity and pronounced disability progression might help to identify those patients with SPMS who are more likely to benefit from interferon therapy [65*].

Like many other proteins, interferons are potentially immunogenic, especially those produced by recombinant gene-expression technologies [66]. In several studies the appearance of neutralizing antibodies (NABs) under treatment with interferon β has been documented. The reported frequencies and titers of NABs vary considerably depending on administration, preparation, and the type of assay being used [67]. The presence of these NABs may be associated with a reduction in clinical effectiveness [68]. In a recently published study Sorensen and co-workers [69] measured NABs every 12 months for up to 60 months in 541 patients with MS under interferon therapy using an antiviral neutralization bioassay. Although the authors observed that patients during antibody-positive periods exhibited a significantly higher relapse rate compared to their antibody-negative periods, disease progression, as measured by the expanded disability status scale (EDSS), was not affected during this short observation period. It is of note, though, that for most of the β interferons no impact on disease progression has been documented in RRMS [7]. Moreover, the appearance of NABs in the serum of patients treated with interferon may be transient [70]. Thus, further studies are warranted to evaluate the clinical implications of NABs against interferons in greater detail.

Long-term treatment with glatiramer acetate also induces the development of serum antibodies [71]. One study