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PHARMACOTHERAPY

A PATHOPHYSIOLOGIC APPROACH

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Multiple Sclerosis

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KEY CONCEPTS

1. The etiology of multiple sclerosis (MS) is unknown, but it appears to be autoimmune in nature. Currently there is no cure.
2. MS is characterized by CNS demyelination and axonal damage.
3. MS is classified by the nature of progression over time into several categories, which have different clinical presentations and responses to therapy.
4. Although studies do not support the general use of any of the FDA-approved disease-modifying therapies (DMTs) in patients with progressive forms of the illness, information derived from multiple studies suggests younger patients with progressive illness and those with either superimposed acute relapses or enhancing lesions on magnetic resonance imaging (MRI) scans may benefit from some of the presently used DMTs.
5. Diagnosis of MS requires evidence of dissemination of lesions over time and in multiple parts of the CNS and/or optic nerve, and is made primarily on the basis of clinical symptoms and examination. Diagnostic criteria also allow for the use of MRI, spinal fluid evaluation, optical coherence tomography, and evoked potentials to aid in the diagnosis.
6. Exacerbations or relapses of MS can be disabling. When this is the case exacerbations and relapses are treated with high-dose glucocorticoids, such as methylprednisolone IV, with onset of clinical response typically within 3 to 5 days.
7. Treatment of relapsing-remitting multiple sclerosis (RRMS) with the DMTs interferon-β (IFN-β) (Avonex, Betaseron, Rebif, Extavia), glatiramer acetate (Copaxone), natalizumab (Tysabri), mitoxantrone (Novantrone), fingolimod (Gilenya), teriflunomide (Aubagio), and dimethyl fumarate (Tecfidera) can reduce annual relapse rate, lessen severity of relapses, slow progression of changes on MRI scans, slow progression of disability, and slow cognitive decline. In addition, they have been shown to reduce the likelihood of developing a second attack after a first clinically isolated syndrome (CIS) consistent with MS.
8. In most cases, treatment with DMTs should begin promptly after the diagnosis of relapsing-remitting MS, or after a CIS if the brain MRI is suggestive of high risk of further attacks. Natalizumab and other choices that have been associated with problematic adverse events should be reserved for those patients who have failed
9. The definition of treatment inadequacy for RRMS remains unclear, and therapy changes after "treatment failure" should be individualized.
10. Patients suffering with MS frequently have symptoms such as spasticity, bladder dysfunction, fatigue, neuropathic pain, cognitive dysfunction, and depression that can require treatment. Patients must be counseled that therapies such as IFN-β and glatiramer acetate will not relieve these symptoms. Depression is common in MS and can pose the risk of suicide.

Multiple sclerosis (MS) is an inflammatory disease of the CNS that affects approximately 1 in 200 women and fewer men in the United States.[1] The term "multiple sclerosis" refers to two characteristics of the disease: numerous affected areas of the brain and spinal cord (CNS) producing multiple neurologic symptoms that accrue over time, and the characteristic plaques or sclerosed areas that are the hallmark of the disease.

1 Although MS was first described almost 140 years ago, the cause remains a mystery, and a cure is still unavailable. Nevertheless, many advances have been made in treating and managing the disease complications and improving the quality-of-life of affected individuals.

EPIDEMIOLOGY

Epidemiologic aspects of MS have been reviewed in many publications.[1–5] MS affects approximately 400,000 people in the United States and 2.5 million people worldwide.[6] MS is usually diagnosed between the ages of 15 and 45 years; peak incidence occurs in the fourth decade. Approximately 10,000 new cases are diagnosed per year in the United States. Women are afflicted more than men by a ratio of 2:1. Men usually develop the first signs of MS at a later age than women, and are more likely to develop a progressive form of the disease. The most important factors in determination of risk for developing the disease are geography, age, environmental influences, and genetics. In general, disease prevalence is higher the greater the distance from the equator; within the United States the prevalence of MS is higher in states above the 37th parallel. Recent studies, however, suggest a waning latitude gradient as demonstrated by a substantial increase in MS incidence in Mediterranean regions. Rising incidence of MS in females appears to be associated with urbanization. As an example, recent reports suggest that MS incidence markedly rose on Crete among female subjects residing in urban settings or relocating at a young age from rural areas; this

MS occurs more frequently in whites of Scandinavian ancestry than in other ethnic groups. In addition, an inverse relationship between MS risk and 25-hydroxyvitamin D levels has been proposed.[1,2]

Etiology

It is thought that genetically susceptible individuals ≤15 years of age who have lived in a high-risk area for at least 2 years and were exposed to a crucial environmental agent are at risk for developing MS. Interestingly, an individual who migrates from a low- to high-risk area prior to the age of 15 years acquires the same chance of developing MS as those who live in a high-risk area all their lives.[2] If the move is made from a high- to a low-risk area, the individual retains the high risk if the move is made after the age of 15 years, but acquires the lower risk if the move is made prior to this age.[2] Smoking cigarettes has been associated with both an increased risk of developing MS and with more severe progression of disability.[3,4]

Viral or bacterial infections may be an important environmental cause of MS. Although no clear association has been identified, certain infections might participate in the pathogenesis of MS by initiating or activating autoreactive immune cells in genetically susceptible individuals, leading to subsequent demyelination. Evidence to support a viral etiology includes increased immunoglobulin G (IgG) synthesis in the CNS, increased antibody titers to certain viruses, and epidemiologic studies that indicate a childhood exposure factor, suggesting that "viral" infections may precipitate exacerbations. In addition, viruses have been shown to cause diseases with prolonged incubation periods, myelin destruction, and a relapsing-remitting course in both humans and experimental animal models.[5-10]

Although numerous viruses have a proposed association with MS, the greatest evidence supports Epstein–Barr virus (EBV). Links of EBV infection to MS pathology are yet largely hypothetical. Autoreactive T-cells could be activated by EBV through molecular mimicry, whereby sequence similarities between EBV and self-peptides are sufficient to result in the cross-activation of autoreactive T- or B-cells. Other potential mechanisms of demyelination include enhanced breakdown and presentation of self-antigens, expression of viral superantigens, or bystander activation.[11] Antibody titers to Epstein–Barr nuclear antigen (EBNA) complex are higher in MS patients versus controls, especially if blood is collected ≥5 years before onset. These titers increase over time in MS patients (controls are unchanged), and a fourfold increase in EBNA titers over time results in a threefold increased risk of developing MS (almost an 18-fold increase in those with first samples before age 20).[12] Interestingly, one paper notes individuals positive for *HLA DRB1*1501* have a 24-fold increased risk of developing MS when they also have antibodies to certain epitopes within EBNA-1 compared with others.[13] This is consistent with a genetic-environmental interaction. In addition, anti-EBNA titers have been associated with relapsing-remitting multiple sclerosis (RRMS), conversion of clinically isolated syndrome (CIS) to clinically definite multiple sclerosis (CDMS, confirmed diagnosis of MS), and with magnetic resonance imaging (MRI) measures such as gadolinium-enhancing lesions, change in T_2 lesion volume ($r = 0.27$; $P = 0.044$), and Expanded Disability Status Scale (EDSS) score ($r = 0.3$; $P = 0.035$). Zivadinov et al. also found anti-EBNA and anti-vascular cell adhesion (VCA) titers associated with gray matter atrophy in MS.[14] While Serafini et al. have claimed to identify evidence of abortive infection in a significant number of MS patients,[15] others have not been able to replicate these findings.[16] The majority of data would lead to a conclusion that exposure to EBV is somehow associated with developing MS, but does not support the concept of an active or aborting EBV infection directly causing MS.

The familial recurrence rate of MS is approximately 5%, with siblings being the most commonly reported relationship,[2] and a concordance rate among monozygotic twins of approximately 25%. This is consistent with the idea that an environmental agent is important in the etiology of MS, but also suggests a role for one or more genes. Genes that lie within the major histocompatibility complex (MHC), which is located on the sixth chromosome in humans, have been linked to MS.[17,18] Recent data show a significant association of risk with mutations in the interleukin-2α (IL-2α) and interleukin-7α (IL-7α) receptor genes.[17-19] African Americans are significantly less likely to be diagnosed with MS compared with whites, although there is emerging evidence that they are more likely to have a severe disease course[20] and respond less well to interferon (IFN) therapy.[21] A locus on chromosome 1 may be associated with increased susceptibility in African Americans.[22]

PATHOPHYSIOLOGY

The basic physiologic derangement in MS is stripping of the myelin sheath surrounding CNS axons. This activity is associated with an inflammatory, perivenular infiltrate consisting of T and B lymphocytes, macrophages, antibodies, and complement.[23] Demyelination renders axons susceptible to damage, which becomes irreversible when they are severed. Irreversible axonal damage correlates with disability and can be visualized as hypointense lesions, or "black holes," on T_1-weighted MRI.[24,25]

It is well accepted that MS lesions are heterogeneous, which may be due in part to differences in the stage of evolution of the lesions over time, differences in underlying immunopathogenesis, or a combination. Briefly stated, acute lesions show demyelination and axonal destruction with lymphocytic activity consistent with an inflammatory state. In contrast, more chronic lesions display less inflammatory lymphocytes with active remyelination.[10] Although traditional descriptions have focused on white matter as the sole location of MS lesions, more recent studies have clearly identified cortical and subcortical gray matter lesions both pathologically[26] and radiographically.[26] In addition, a subset of patients with progressive MS are noted to have abnormalities consistent with B-cell follicles in the meninges.[27]

Just as the full dimensions of the neuropathology are uncertain, so is the pathogenesis of the MS lesion. Substantial evidence suggests it is an autoimmune process directed against myelin and oligodendrocytes, the cells that make myelin[10] (Fig. 39-1). A new concept of T-cell entry into the CNS suggests that the initial lymphocyte invasion in MS may proceed through the ventricles, toward the choroid plexus along a CCL 20 gradient that attracts activated Th17 cells.[27] The actual mediator of myelin and axonal destruction has not been established, but may reflect a combination of macrophages, antibodies, destructive cytokines, and reactive oxygen intermediates. The exact trigger for activation of T-cells in the periphery remains unclear, but the T-cells in MS patients recognize myelin basic protein (MBP), proteolipid protein, myelin oligodendrocyte glycoprotein, and myelin-associated glycoprotein. T-helper subtypes can be either pathogenic or protective in MS. Furthermore, theory holds that certain T-cell subsets are not terminally differentiated, but instead engender a level of plasticity that allows for their conversion from pathogenic to protective and vice versa under certain conditions (Fig. 39-2).[28] In patients with stable or mild disease, increased numbers of cells are found that express messenger RNA (mRNA) for transforming growth factor-β (TGF-β) and interleukin-10 (IL-10) compared with patients with severe disease. Conversely, a reduction in the number of T-regulatory (Treg) cells, which exhibit suppressor activity, is associated with

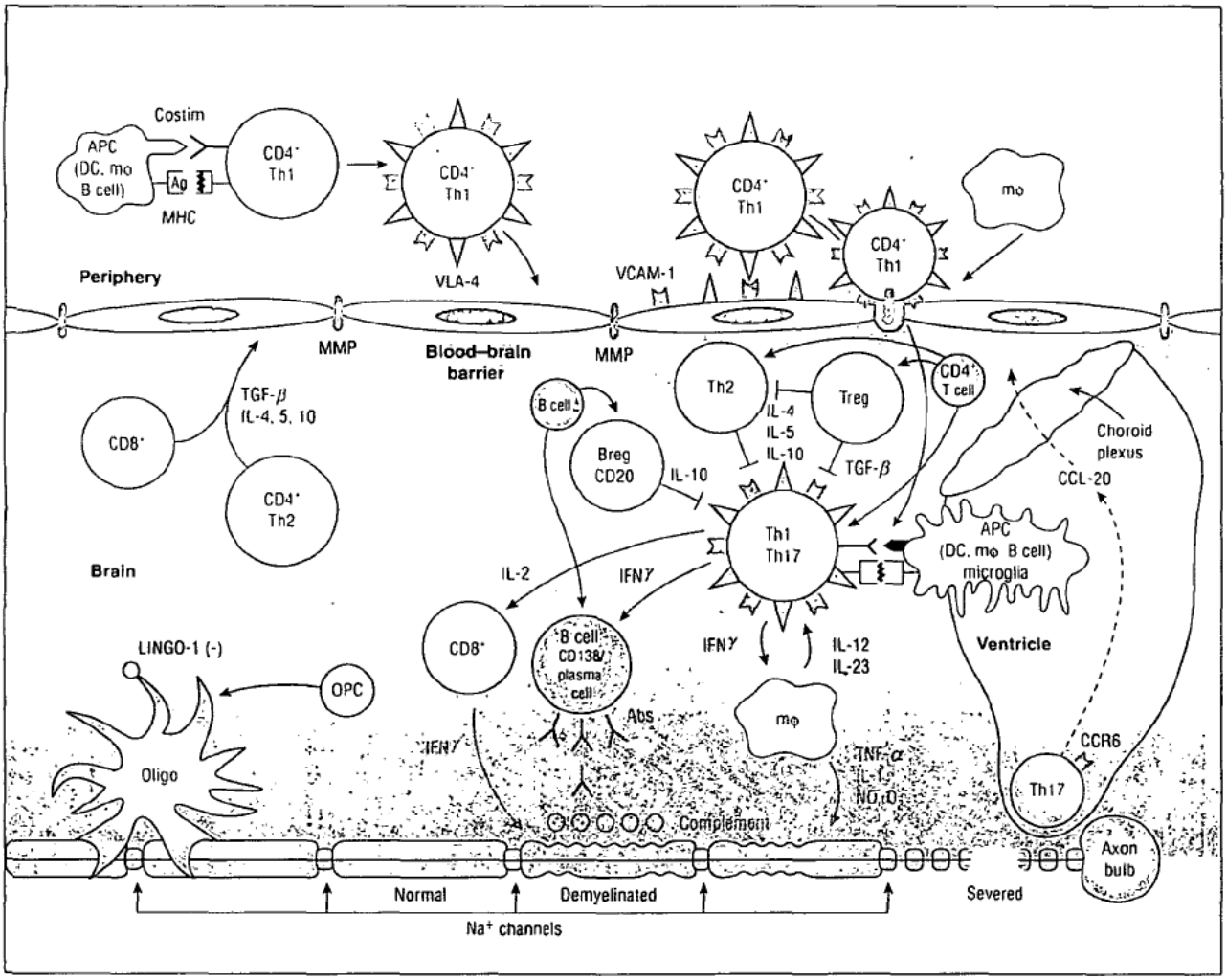

FIGURE 39 Autoimmune theory of the pathogenesis of multiple sclerosis (MS). In MS, the immunogenic cells tend to be more myelin-reactive, and these T-cells produce cytokines mimicking a Th1-mediated proinflammatory reaction. T-helper cells (CD4+) appear to be key initiators of myelin destruction in MS. These autoreactive CD4+ cells, especially of the T-helper cell type 1 (Th1) subtype, are activated in the periphery, perhaps following a viral infection. The activation of T- and B-cells requires two signals. The first signal is the interaction between MHC and APC (macrophage, dendritic cell, B-cell). The second signal consists of the binding between B7 on the APC and CD28 on the T-cell for T-cell activation. Similarly, CD40 expressed on APCs and CD40L expressed on T-cells interact to signal the proliferation of B-cells within the blood–brain barrier following the entry to T-cells. The T-cells in the periphery express adhesion molecules on their surfaces that allow them to attach and roll along the endothelial cells that constitute the blood–brain barrier. The activated T-cells also produce MMP that help to create openings in the blood–brain barrier, allowing entry of the activated T-cells past the blood–brain barrier and into the CNS. Once inside the CNS, the T-cells produce proinflammatory cytokines, especially interleukins (ILs) 1, 2, 12, 17, and 23, tumor necrosis factor-α (TNF-α), and interferon-γ(INF-γ), which further create openings in the blood–brain barrier, allowing entry of B-cells, complement, macrophages, and antibodies. The T-cells also interact within the CNS with the resident microglia, astrocytes, and macrophages, further enhancing production of proinflammatory cytokines and other potential mediators of CNS damage, including reactive oxygen intermediates and nitric oxide. The role of modulating, or downregulating, cytokines such as IL-4, IL-5, IL-10, and transforming growth factor-β (TGF-β) also has been described. These cytokines are the products of CD4+, CD8+, and Th1-cells.[10] New pathogenic mechanisms involve, but are not limited to, receptor-ligand mediated T-cell entry via choroid plexus (CCR6-CCL20 axis),[28] coupling of key receptor-ligands for inhibition of myelination/demyelination (LINGO-1/NOGO66/p75 or TROY complex, Jagged-Notch signaling).(Ag, antigens; APC, antigen presenting cell; DC, dendrite cell; IgG, immunoglobulin G; MΦ, macrophage; Na+, sodium ion; MMP, matrix metalloproteinases; MHC, major histocompatibility complex; OPC, oligodendrocyte precursor cell; VLA, very late antigen; VCAM, vascular cell adhesion molecule.)

active MS and can be found in patients with progressive disease. It should be noted, however, that Treg ratios do not always correlate with disease activity. Of note, experimental evidence associates high 25-hydroxyvitamin D levels with improved Treg function, favoring the Th2 phenotype in the Th1/Th2 balance.[31]

of MS, the intrathecal synthesis of multiple clones of immunoglobulins, remains unclear. The antigen(s) against which these immunoglobulins are directed remain unknown, but do not appear to include common CNS myelin antigens.[31] The complex interplay of a variety of cells, antibodies, and cytokines remains

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