Inflammatory Demyelinating Diseases of the Central Nervous System

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The CNS can be affected by several immunologically mediated diseases that manifest with demyelination and neuronal damage. Advances in the understanding of the pathophysiology of those diseases have translated into significant improvements in treatments. This article discusses the characteristic features of some of the demyelinating diseases of the CNS based on recent updates. This article reviews the basic underlying mechanisms of, key pathological findings, diagnostic approaches, and potential therapies for ADEM, AHL, neuromyelitis optica, and MS. In addition, a review of the fundamental concepts of immunology are presented.

Key Words: acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, demyelination, multiple sclerosis, neuromyelitis optica

Abbreviations Used: ADEM, acute disseminated encephalomyelitis; AHL, acute hemorrhagic leukoencephalitis; CNS, central nervous system; CSF, cerebrospinal fluid; IL, interleukin; MR, magnetic resonance; MS, multiple sclerosis; PNS, peripheral nervous system

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Demyelinating diseases can be divided into disorders that affect the CNS and disorders that cause the loss of myelin in the PNS. Depending on their origin, these diseases can be divided into two categories. The first, demyelinating conditions, are related to inflammatory, toxic, or metabolic causes. The second, dysmyelinating processes, are mostly of a genetic nature, and involve the progressive loss of myelin or its failure to form.

Although only a few CNS disorders are characterized by primary inflammatory changes, their overall incidence is relatively high (Table 1). Included are illnesses such as the vasculitides in which inflammation affects the vessel walls, causing ischemic damage to the brain parenchyma (Table 2). Conversely, some disorders are caused by immune cells that penetrate the blood-brain barrier and induce an inflammatory reaction. Localization of this reaction inside the CNS is responsible for the demyelination.

Despite many biomedical advances, the etiological mechanisms that underlie these diseases are not yet understood. The exception is infectious encephalitis whose pathogenesis is well defined. The virus localizes in the brain and determines mobilization of peripheral blood cells, resulting in perivenular clustering of inflammatory cells and areas of demyelination. This update reviews acquired conditions related to idiopathic inflammatory diseases that result in the loss of myelin.

Basics of Immunology

The immune system has evolved over millions of years, and its level of com-

Table 1. Inflammatory Diseases of the CNS

- ADEM
- AHL (rare form of severe ADEM, distinguished only by presence of hemorrhages and more aggressive course)
- Site-restricted acute inflammatory demyelinating diseases
  - Cerebellitis
  - Transverse myelitis
  - Brain stem encephalitis
  - Optic neuritis
- Multiple sclerosis
- Neuromyelitis optica or Devic's disease
- CNS sarcoidosis
- Paraneoplastic encephalitis
- Viral encephalitis

Table 2. Pathology Features of CNS Vasculitides

Primary Angiitis of CNS	Secondary Causes of CNS Vasculitis
Small and medium-sized leptomeningeal cortical arteries; less frequently, veins and venules	Infection (viral, bacterial, fungal rickettsial, mycoplasmal, protozoal)
Segmental granulomatous infiltrate of arterioles, side-by-side with polyarteritis-type necrotizing vasculitis and normal arterioles. Foreign body and Langhans' giant cells. Fibrinoid necrosis of the vessel wall, thrombosis, stenosis, and strokes	Systemic vasculitis
	Connective tissue disease
	Sarcoidosis
	Drug-associated (sympathomimetics, drugs of abuse)
Multiple microaneurysms, characteristic of vasculitis on abdominal or renal angiograms, distinctly rare in CNS	

plexity has increased in parallel with the evolution of organisms. Humans likely possess one of the most advanced forms of immune systems. As is common, however, increased complexity also increases the risk of related complications. Both autoimmune diseases and allergies represent derangements of normal immune function that manifest as the loss of regulation of extremely intricate machinery.

The immune system of mammals has two branches—the innate and the acquired. Innate immunity provides the first line of defense against infectious agents that penetrate the physical barrier of the skin or mucosa. A limited number of germline-encoded pattern-recognition receptors initiate an immune response that becomes increasingly specific as acquired immunity develops.[2] Macrophages and dendritic cells, the primary units of innate immunity, exploit several families of pattern-recognition receptors, such as toll-like receptors or nucleotide-oligomerization domain-like receptors, to discern pathogens from self-constituents. These cells have the role of instructing the acquired immune system to the type of response to be mounted (see below).

Toll-like receptors are highly conserved throughout all species. They target structural components of microorganisms, known as pathogen-associated molecular patterns, which are essential for the survival of microbes and viruses. Targeting those antigens is strategic because they cannot be changed by infectious agents; thus, selectivity is ensured. To date 12 different toll-like receptors have been identified in mammals, and distinct, relatively specific ligands have been associated with the various subtypes. Some of these receptors are extracellular while others are bound to endosomes and require internalization of the antigen for pattern recognition.[2]

Once macrophages detect and internalize a foreign antigen, they migrate away from the site of infection to the regional lymph nodes. There, the representative cells of the acquired immune system interact with antigens.[38] The antigens are processed by professional antigen-presenting cells, namely macrophages, dendritic cells, and B-lymphocytes. In the context of the major histocompatibility complex class I or II molecules, the antigens are then presented to the CD8- and CD4-positive lymphocytes, respectively.[13]

For lymphocytes to become activated, two events are required. Their T-cell receptor must engage with high-affinity antigens, and co-stimulatory molecules on the surface of the antigen-presenting cells must be expressed. At this point the immune response acquires specificity and long-lasting immune memory from the clonal expansion of both T- and B-cells. No longer naïve, the T-lymphocytes can transform into memory cells. Alternatively, they can expand and give rise to specific T-helper cells if expressing CD4 molecules or become cytotoxic effector T-cells if expressing CD8 molecules. Similarly, B-lymphocytes proliferate and mature into plasmacytes that produce circulating antibodies and eventually undergo apoptosis.

Two mutually exclusive profiles of cytokines can be induced by the dendritic cells and macrophages when they first encounter pathogens: Th1 and Th2. Th1 is characterized by the production of interferon-gamma and tumor necrosis factor-alpha. The Th2 profile follows the secretion of IL4 and IL13. The classic paradigm dictates that bacterial infections evoke a Th1 type of immune response while parasitic infections are more likely to produce the Th2 type of cytokines. Recently, a third profile, Th17, has been recognized.[32] On stimulation by IL-23, a pro-inflammatory cytokine produced by activated CD4 cells, the helper T-cells start producing IL-17, which is a critical inducer of in-

flammation in MS and equivalent animal models.[37]

Activated lymphocytes sustain the pro-inflammatory response by expressing the necessary surface adhesion molecules that allow transmigration through blood vessels, penetration of tissue, and sensitization to chemokines. Subsequently, counterbalanced anti-inflammatory and pro-apoptotic signals, mediated by regulatory cells secreting IL-10 and tumor growth factor-beta, are responsible for the termination of inflammation.

A subset of circulating lymphocytes, known as natural killer cells, has been identified as part of the innate immune system. Their contribution to the regulation of an immune response is slowly being defined.[21] They have the ability to generate a Th1 or Th2 profile. More importantly, they appear to have a role as suppressor cells. Hence, they are key players in regulating immune responses.

Another subtype of regulatory cells that is a fundamental player in any immune response has been identified. These cells are CD4+ lymphocytes that co-express high levels of CD25 (the alpha chain of the IL-2 receptor) molecules on their surface, and they are characterized by the production of the gene transcription factor FoxP3. FoxP3 is a reliable marker of regulatory T-cells. A reduction in the number of circulating FoxP3-positive cells results in uncontrolled immune responses and autoimmunity, whereas the induction of antigen-specific FoxP3-positive cells maintains peripheral tolerance.[9]

The innate immune system has the ability to mount a response to a foreign antigen or to ignore a self-antigen. The milieu of cytokines produced sets the stage for the type and intensity of the actions affected by adaptive immunity. Thus, innate immunity has been implicated in autoimmunity by virtue of its ability to initiate the misdirected immune response that will remain dysregulated at the level of the adaptive immune system.[15] Numerous mechanisms are set to control an autoreactive process. Failure at any step results in an autoimmune disease.

Acute Disseminated Encephalomyelitis

ADEM is characterized by a multifocal, monophasic involvement of the CNS in children or young adults and tends to resolve without sequelae.

Etiology

ADEM has etiological relationships to infections, and many agents have been implicated. In some series, infection has preceded the development of the neurological manifestations of the disease by days to weeks about 75% of the cases.[29] In early descriptions, ADEM was linked to rabies and smallpox vaccinations. The elimination of neural tissue from duck embryos as a contaminant in these vaccines has dramatically decreased the number of postvaccination cases. Nevertheless, naturally occurring infections predispose individuals to develop the disease as evidenced by the high prevalence of ADEM in areas where measles are endemic.

A possible mechanism leading to ADEM is molecular mimicry. The expected immune response that provides clearance of an infection is subsequently directed toward self-components with antigenic similarities to epitopes of the infecting microorganism.[3] Well after clearance of the latter when no microorganisms can be isolated from the patient, the inflammatory response localizes inside the CNS where it generates simultaneous, multifocal areas of inflammation. Both laboratory and clinical data support the concept of a postinfection immune response directed against antigens of the CNS, and many antigens have been implicated as targets.[36] That infections from a large variety of pathogens, including widespread bacteria, viruses, rickettsias, and even parasites, are potential triggering factors suggests the involvement of a common, multifaceted mechanism. In other words, many different antigens in microorganisms have the potential of inducing cross-reactivity to self-constituents.

In fact, T-cells that can react to self are part of a healthy immune system. The stochastic nature of the maturation of the T-cell receptor in T-lymphocytes and a certain degree of degeneracy ensure the ability to interact with a previously unknown antigen. However, those aspects also enable unexpected recognition of self. This principle is supported by a few cases in which acute demyelinating inflammatory polyneuropathy and ADEM have manifested simultaneously.[4] With even stronger evidence than for ADEM, acute demyelinating inflammatory polyneuropathy has been shown to derive from mechanisms of cross-immunity between a pathogen and gangliosides present in peripheral nerves.[42] Not surprisingly, multiple simultaneous antigens of the CNS and PNS may be targeted.

Pathology

The main features of ADEM can be summarized in scattered areas of inflammation involving the brain and spinal cord. It is primarily a white matter disease, but limited gray matter can be observed in both the cortex and basal ganglia. In affected areas, perivenular infiltration of mononuclear cells, consisting of abundant lymphocytes and monocytes, leads to demyelination and edema.[36] The appearance is that of active plaque-like lesions. Microscopically, larger lesions may be indistinguishable from the acute plaques associated with MS.

Clinical Presentation

A prodromal phase of several days of malaise, fever, myalgias, and skin rashes is common. In about half of the cases, fever is a presenting symptom. Other constitutional symptoms such as nausea, vomiting, headache, and a stiff neck are associated with the acute stage of the illness. The multifocal neurological signs that follow tend to develop a few days to several weeks after the acute infectious episode. Once triggered, the onset of the CNS disorder is usually within several hours. The neurological manifestations peak within a few days.

The most common neurological manifestations are motor signs (ataxia, hemiparesis), cranial nerve abnormalities (vision and gaze impairment, facial weakness), sensory problems, alteration of consciousness (varying from lethargy to

coma), and seizures. The simultaneous or closely spaced appearance of neurological signs reflects the diffuse and multifocal involvement of the CNS, including the spinal cord. The severity of the neurological manifestations varies. The diagnosis is often overlooked because the patients are young and otherwise healthy. Their ability to compensate for their neurological deficits masks the symptoms. Presentations such as coma and subsequent disability also occur.

After the acute stage, the disease gradually improves within a few weeks. Most cases resolve completely in 2 to 6 months. The outcome and rate of recovery can be influenced by therapy. Sometimes, however, the disease progresses and neurological deficits persist despite treatment. ADEM is typically monophasic; that is, once it resolves it does not recur. Whether a recurrence of ADEM should be considered progression to MS is still debated.

Diagnosis

Routine laboratory tests may demonstrate elevation of indices of inflammation such as the erythrocyte sedimentation rate and level of C-reactive protein. In peripheral blood the white cell count may be increased with lymphocytic predominance. Classically, however, no pathogen can be isolated as the neurological symptoms develop. Preceding infections with Epstein-Barr virus, herpes, cytomegalovirus, measles, varicella, mycoplasma, streptococcus, chlamydia, and rickettsia have been reported.[36]

The CSF shows more consistent abnormalities than the blood tests. Occasionally, however, the CSF is normal. The total levels of protein and cell counts in the CSF, again with lymphocytic predominance, are high. The indices of immunoglobulin intrathecal synthesis are positive. On immunoelectrophoresis, oligoclonal bands corresponding to immunoglobulins that migrate to form discrete bands, which are present only in the CSF specimen and not in the serum, are sometimes detected in ADEM. These bands are usually present in MS and also may be found in chronic viral infections. Elevation of the levels of myelin basic protein in the CSF seems to be proportional to the extent of the disease. This finding, which reflects the massive myelin destruction induced by the inflammation, is a constant in the aggressive demyelinating disease AHL.

MR imaging is instrumental to the diagnosis of ADEM. Invariably, these studies show multifocal signal alterations of the white matter and corpus callosum and often of the basal ganglia and spinal cord. The lesions have a confluent appearance, and their size varies. Typically, signals on T2-weighted and fluid-attenuated inversion recovery sequences are hyperintense, reflecting increased water content (i.e., vasogenic edema, demyelination, or both). MR imaging is a sensitive method for following the evolution of the lesions associated with ADEM. Complete resolution of the radiological picture correlates with clinical recovery of function.

Therapy

The inflammatory nature of ADEM renders it susceptible to treatment with the anti-inflammatory therapy of choice: steroids. High-doses of intravenous formulations of glucocorticosteroids are the widely accepted standard of treatment for ADEM. Besides case series supporting the beneficial effects of steroids, their efficacy has been tested in a limited number of controlled clinical trials. The consensus is that steroids speed the rate of recovery and improve outcomes.

The mechanism of action underlying the use of steroids for the treatment of acute demyelinating CNS diseases is partially elucidated. Steroids appear to help repair the blood-brain barrier, thus limiting penetration of the CNS by the circulating cells. Moreover, steroids induce apoptosis of the activated lymphocytes, thus limiting the recruitment of inflammatory cells into the CNS and shortening the perpetration of the immune response.

Plasmapheresis may be used as an adjunctive or alternative to steroids. However, this aggressive measure is associated with potential side effects and should be reserved for severe cases. In one series, patients with acute inflammatory demyelinating diseases of the CNS who failed to respond to steroids improved after undergoing plasmapheresis.[39] It is still unclear whether the clearance of antigens and immune complexes is responsible for the effectiveness of plasmapheresis. However, its established efficacy in the treatment of other antibody-mediated diseases, such as Guillain-Barré syndrome, a demyelinating diseases of the PNS, supports this view.

Acute Hemorrhagic Leukoencephalitis

AHL is considered to be at the end of the spectrum of ADEM. In fact, these two disease entities are part of a continuum with overlapping clinical and pathological features.

Pathology

Similar to ADEM, AHL is associated with multiple areas of inflammation that involve the white matter of both hemispheres.[36] As observed in cases of ADEM, demyelination, edema, and mononuclear cell infiltration are present microscopically. In AHL, however, the lesion is also contaminated by various degrees of hemorrhage. Tissue necrosis often follows in areas with the most pronounced hemorrhage. A distinctive feature of AHL is the presence of polymorphonucleate cells scattered around the lesions. The cells likely act as scavengers of the debris associated with the massive destruction of the tissues.

Clinical Features

The clinical manifestations of AHL are the same as those described for ADEM, including prodromic symptoms of an infectious disease followed by the appearance of meningismus, encephalopathy, and focal neurological signs. Large demyelinated regions are often associated with massive edema and hemorrhagic contamination. The appearance of these aggressive lesions on MR imaging is often indistinguishable from that of primary CNS tumors. A biopsy is sometimes required to confirm the diagnosis. Considering the level of dysfunction and neurological deficits characteristic of the

acute stages of AHL, the degree of recovery is usually remarkable. Again, prognostic factors are related to the extent of CNS involvement and therapeutic intervention.

Therapy

AHL is treated in the same way as ADEM. Given the severity of AHL, however, prompt initiation of steroids and early consideration of plasmapheresis are recommended.

Neuromyelitis Optica

Typically, neuromyelitis optica manifests with recurrent episodes of optic neuritis and transverse myelitis. The condition was referred to as optical-spinal MS, and this disease was long considered a variant of MS. Only recently has it been defined as a distinct entity.

Pathology

The pathogenesis of neuromyelitis optica is primarily inflammatory in response to an autoimmune attack on components of the CNS.[40] Only in the last few years has the potential role of IgG directed against the extracellular domain of the water channel in the CNS been recognized. Serum from patients with neuromyelitis optica contains a complement-fixating IgG that selectively binds to aquaporin-4, which is the most abundant water channel in the CNS. It is expressed as a transmembrane tetrameric protein in the end-feet of astrocytes that contact capillaries, interneuronal synaptic junctions, and ventricular ependyma. There, it functions as a major regulator of bidirectional water flux between brain and spinal fluid.

The pattern of lesions in patients with neuromyelitis optica tends to coincide with the normal distribution of aquaporin-4 in the CNS,[33] and there is strong evidence of the pathogenicity of the anti-aquaporin-4 antibodies. Several studies have demonstrated early loss of aquaporin-4 in lesions from neuromyelitis optica.[24] No direct attack on oligodendrocytes is thought to be part of the immune response, at least in the early stages of the process. The hypothetical mechanisms underlying demyelination are thought to include the cascade of inflammatory events that follows activation of complement as well as glutamate toxicity and neuronal death from the loss of regulation of the ionic microenvironment.[6]

Clinical Features

Neuromyelitis optica is more common in young adults of Asian and African descent than in Caucasians. It is associated with severe recurrent attacks of optic neuritis, affecting one or both eyes. The attacks unpredictably precede or follow episodes of longitudinally extended transverse myelitis. The severity of the episodes is characteristic of the disease. Invariably, disability follows the acute events. Complete blindness and quadriplegia from spinal cord disease often result from the recurrent attacks; a slow progression with gradual decline in function is not part of the disease process.[41]

Diagnosis

The diagnostic criteria for neuromyelitis optica have recently been modified to include the presence of the neuromyelitis optica-IgG in the serum as one of the key findings.[18] In case series, the sensitivity of the antibodies has ranged from 60 to 70%, while specificity has ranged from 90 to 99%.[24] Other criteria that support the diagnosis of neuromyelitis optica entail optical-spinal involvement with the presence of elongated spinal cord lesions that typically stretch beyond three contiguous vertebral bodies. Findings on MR imaging of the brain are not typical of MS.

Therapy

Until recently the conventional therapy for neuromyelitis optica was based on chemotherapy such as cyclophosphamide, azathioprine, mitoxantrone, or mycophenolate. However, these treatments fail to control the disease. Severe disability and death are common outcomes of this illness.

Expectations are high that rituximab may help prevent the attacks. This monoclonal antibody is selective for the CD-20 antigen and acts by depletion of B-cells. In an open-label study, this therapy was associated with a dramatic reduction in the relapse rate at the 1-year follow-up point.[12] When the B-cell count was restored to normal values 6 to 12 months after the first dose, a subsequent dose was administered. Given the overall rarity of the disease, a direct comparison with other therapies is unlikely to be possible. Based on the current understanding of the pathophysiology of neuromyelitis optica, the effectiveness of rituximab compared to the general immune suppression obtained with chemotherapies makes sense biologically. Experts in the field now recommend rituximab as a first-line agent for neuromyelitis optica.[24]

In terms of the management of acute relapses, plasmapheresis is the treatment of choice. To maximize the chances of recovery, it should be instituted at the earliest signs of an acute attack.

Multiple Sclerosis

MS is the prototype of the inflammatory demyelinating diseases of the CNS. Although its characteristic clinical and pathological features were first described more than a century ago, its pathology is still incompletely understood. The accepted notion is that the early stages of MS are initiated by an autoimmune attack against components of the myelin in the CNS. In most cases the attacks manifest as recurrent episodes of clinical relapses and spontaneous remissions. The ultimate common pathway for the disease is a degenerative process that leads to permanent disability.

Pathology and Pathogenesis

The literature on MS and its pathology is massive. Only an overview of recent advances follows.

The cardinal pathological features of MS reside in the progressive accumulation of areas of demyelination that tend to be distributed in the periventricular white matter and become confluent over time. Under the microscope the demyelinating plaques may show, depending on their stage, different degrees of myelin loss, more or less abundant inflammatory infiltration of lymphocytes and macrophages that are predominant-

ly clustered around the venules, and reactive gliosis that replaces the neurons as they die.

The classic description of MS as a disease of the white matter has been challenged by increasing evidence of extensive involvement of cortical and gray matter structures.[27,30] Based on series of brain biopsies and postmortem examinations from MS patients,[19] four distinct types of pathologies have been characterized: (1) a high degree of mononuclear cell infiltration, (2) elevated levels of antibodies, (3) elevated levels of complement staining, and (4) loss of oligodendrocytes without significant inflammation. These observations suggested that demyelination may result from alternative or partially coexistent mechanisms and that the triggering factors may be distinct for different cases. Findings from a recent report of brain autopsies of patients in the progressive phase of MS are consistent with this notion. Only a subset of patients was found to have germinal B-cell follicles localized in the meninges.[20] That demyelinating plaques were detected in the subpial regions near the meningeal follicles is indicative of their pathogenetic role. Characteristically, the absence of lymphocytic infiltration in the corresponding underlying areas of demyelination is suggestive of a humorally mediated insult.

For many years, the participation of B-cells in the pathogenesis of MS has been considered of secondary importance despite the established presence of immunoglobulins in the form of oligoclonal bands in the CSF. Although the definitive meaning of the oligoclonal bands is unknown, some evidence favors the significance of a humoral response to viral antigens in the pathogenesis of MS.[10] Interestingly, the same oligoclonal bands continue to be detected in MS patients at least 3 years after treatment with the monoclonal antibody anti-CD52 or after a bone marrow transplant of autologous stem cells when the inflammatory component of the disease has been shut off dramatically. The results of the clinical trial on rituximab strongly support a major role for B-cells in maintaining disease activity.[16] This finding is unexpected because in animal models MS can be transferred via the transfection of activated T-cells. Consequently, T-cells have been considered the major players in the pathogenesis of MS. Perhaps T-cells have the ability to initiate a process that proceeds through an interaction with B-cells and macrophages. An increasing body of evidence indicates that the regulatory mechanisms via CD4 and CD8 suppressor cells are deficient in MS patients.

The roles of genetic background and environmental factors in MS are slowly being elucidated. HHV-6 and more so Epstein-Barr virus, which has the ability to remain dormant in infected B-cells, have been considered potential candidates as initiators of an immune response that at later stages may evolve into a self-sustained autoimmune process.[34] Vitamin D, another environmental agent, has been implicated by epidemiological data, but conclusive evidence of its role in autoimmunity is lacking. An ongoing Phase II clinical trial on the benefits of high doses of vitamin D has thus far proven safe, and efficacy data are awaited.

That the penetration of activated inflammatory cells in the CNS is pathogenic represents a long-standing acquisition in MS. In fact, more than a century ago, pathologists noted this relationship, and it is universally accepted that MS is an immune-mediated disease. However, the link between inflammation and degeneration is only now being explored. A growing number of investigations using MR techniques have provided evidence that even at the earliest stages of disease, a much more diffuse insult to the brain can be detected. At the time that MS first manifests, oligodendrocytes, even in the normal-appearing white matter, are already affected by pathological changes.[27] In a correlation between MR imaging and postmortem histopathology, the extent of cortical and subpial demyelination was independent of the white matter burden of lesions. That is, the degree of axonal and gray matter loss was disproportionate to the amount of disease noted in the white matter. This finding suggests that gray matter damage is not a degenerative process related to the deep, subcortical pathology.[7] Rather, it represents primary damage, which remains a poorly understood part of the disease.

Clinical Features

Considering the potential for a random distribution of the demyelinating plaques in the brain and spinal cord, it is not surprising that the presentation of MS is as variable as its course. Studies on the frequency of symptoms have found that sensory complaints occur in about 30% of the cases, motor and coordination issues occur in another third of patients, and polysymptomatic presentations are most commonly encountered.[26] Optic neuritis, a characteristic manifestation of MS, occurs in about 20% of patients. However, the most frequently reported symptom is fatigue, which likely results from diffuse cerebral injury rather than from a few focal lesions. Such diffuse injuries may correlate with the abnormalities detected on MR imaging.[35]

The variability and unpredictability of the disease have spurred several investigations aimed at identifying markers that would distinguish a benign course from an aggressive one. Clinically, the number of clinical relapses in the early stages of disease correlates with later disease progression. However, the number of lesions detected on MR imaging remains the most reliable measure of long-term disability.[1] Ten to 15% of patients have a benign form of the disease and do not develop major disability, but loss of function is unrelenting in most cases. The primary progressive form of MS more frequently affects males who are 10 to 15 years older than the average patient at the onset of MS. This form is characterized by steady neurological deterioration without much inflammation.[28]

Diagnosis

To diagnose MS a combination of clinical features and laboratory and radiological criteria must be met. In 2001 new diagnostic criteria for MS were proposed to include MR imaging to demonstrate the required dissemination in space and time.[25] Barkhof et al. delineat-

ed the typical features of MS on MR imaging (Table 3).[5]

Application of the proposed criteria enhances diagnostic accuracy. Nonetheless, several neurological conditions, such as other autoimmune and infectious diseases, are difficult to distinguish from MS on the basis of MR imaging alone. Occasionally, even patients with small vessel cerebrovascular disease may have signal abnormalities on MR imaging that resemble demyelination. Consequently, only a comprehensive evaluation allows a correct diagnosis. In this context, CSF testing becomes important. It has a predictive value independent of MR imaging, particularly at the onset of the disease, for the so-called clinically isolated syndrome. This term is used to identify a clinical event that has characteristics of a demyelinating episode, such as transverse myelitis or optic neuritis, but MS cannot be formally diagnosed. Oligoclonal bands identified by immunoelectrophoresis in the CSF and not in the serum of patients with clinically isolated syndrome have a sensitivity of about 90% and a specificity of 96% for predicting conversion to clinically definite MS.[23]

The visual pathway is selectively affected in MS patients. Consequently, the characteristic delay in visual evoked potentials has made this test part of the diagnostic armamentarium. An even more reliable method, ocular coherence tomography, provides information about the integrity of the optic fibers at the level of the optic disc. This test relies on a harmless infrared laser beam projected through the dilated pupil. In less than 1 minute it measures the thickness of the nerve fibers at the optic disc. A decrease in the nerve fiber layer corresponds to axonal loss, which appears to be a sensitive reflection of optic nerve damage. Ocular coherence tomography supports ongoing, subclinical, slowly progressive loss of neural tissue in the optic nerve, even in the absence of a discrete clinical attack on the nerve. This loss appears to correlate directly with the gradual development of brain atrophy invariably observed in the advanced stages of MS.[14] For its objectivity, ocular coherence tomography is now an adjunctive method for the diagnosis of MS and is considered an important outcome measure for therapeutic clinical trials.

Table 3. Barkhof MR Imaging Criteria for MS Patients

Nine supratentorial lesions or one gadolinium-enhancing lesion
At least one infratentorial lesion
At least one juxtacortical lesion
At least three periventricular lesions

The finding of a clinically silent but progressively destructive process is paralleled by an increasing body of evidence from MR imaging that shows that signal abnormalities can be detected early in the oligodendrocytes of MS patients. Both cortical and deep gray matter are clearly affected and account for brain atrophy. Sophisticated MR imaging techniques, such as MR spectroscopy, magnetization transfer, and diffusion tensor imaging, combined with stronger magnets (7 or 8 Tesla scanners are now used for research), have helped improve the specificity of the signal from demyelinating lesions and have revealed previously unsuspected aspects of the disease. However, until these methods become available for routine practice, it remains important to screen for alternative diagnoses that mimic MS based on their appearance on MR imaging. Furthermore, evaluations to rule out vasculitides, sarcoidosis, and cerebrovascular disease remain necessary.

Therapy

In parallel with an improved understanding of the pathogenesis of MS, its treatment is also evolving rapidly. The first disease-modifying agent was introduced about 15 years ago. Since then the number of drugs available for treatment has increased steadily. More importantly, several other medications in Phase II and III clinical trials have already shown greater efficacy than currently available treatment (Table 4). The hope for a cure is promising.

Interferons and glatiramer acetate have been investigated extensively even in randomized clinical trials comparing medications. The efficacy of these preparations appears to be equivalent. The only exception is a 2-year study that showed that the interferon beta-1a administered once a week had an intermediate effect between high-dose interferon and a placebo.[43] The choice of which medication to use involves considerations of logistics and tolerability. Side effects are of primary importance when choosing among these agents. The risks and benefits favor initiating therapy at the earliest manifestations of the disease. In fact, data replicated in several studies and reviewed in a meta-analysis[11] support the view that early modulation of disease activity improves clinical and radiological outcomes to a level that cannot be reached by a placebo-control group.

The mechanisms of action of interferon have been the objective of intense investigations. Its positive effects in MS appear to be mediated by multiple actions, including repair of the blood-brain barrier and switching the cytokine profile away from Th1.[22] Of relevance to clinical practice is the difference in preparation of the various interferons. The first manufactured interferon was beta-1b. It contains a substitution of serine with cysteine at position 17. The interferon beta-1a has the same sequence as the natural product, including the glycosylated side chain, which renders the latter slightly less immunogenic. The immunogenicity has clinical implications for the production of neutralizing anti-interferon antibodies that can occur in MS patients treated with interferons. At high titers the effect of the medication is lost. Several reports indicate that the neutralizing antibodies may disappear over time despite continuation of therapy. The current recommendation is to discontinue interferon therapy when the neutralizing antibodies are detected at a titer greater than 1:100.[17]

The mechanisms of action underlying glatiramer acetate are far from understood. This compound is composed

of random combinations of four amino acids present in high concentrations in human myelin basic protein. It was developed in an attempt to induce MS in a mouse model and was found to be protective against the disease. Initially, it was hypothesized that a shift from Th1 to Th2 was the main effect of glatiramer. Newer data, however, do not support this theory. Its effect appears to be much broader, including an instructive role at the level of the innate immune system. Regardless of its mechanism of action, glatiramer remains a good first-line agent for MS. It is as effective as high-dose interferons, with an overall better safety profile, given the potential for worsening depression and liver toxicity associated with interferons.

Natalizumab, a humanized monoclonal antibody directed to the alpha 4 subunit of the integrin, has lately come to the forefront for the treatment of MS. It was voluntarily pulled from the market in 2006 by the manufacturing company after two patients developed progressive multifocal leukoencephalopathy. It was then reintroduced as a second-line agent with a policy of mandatory enrollment in a clinical registry aimed at monitoring adverse events. Since then its safety record has been acceptable, and its efficacy has been superior to other approved medications. Consequently in April 2008, it received approval for use as a first-line drug for the treatment of MS and severe Crohn's disease. Quenching the inflammation as it first manifests is one of the key messages of the most recent studies on therapy for MS. Natalizumab does so effectively given its ability to target the adhesion molecule on activated mononuclear cells. As an IgG1, it does not bind complement and does not induce apoptosis in the bound cells. It does prevent them from penetrating the blood-brain barrier, thus limiting the recruitment of pro-inflammatory cells into the CNS.[31] Data on patients exposed to the medication for more than 3 years have been collected, but no long-term outcome or safety data are available. Therefore, the question of what is the best continuous long-term management of MS patients treated with natalizumab remains. In fact, enthusiasm for this therapy has again been tempered by several additional cases of progressive multifocal leukoencephalopathy reported in patients treated with natalizumab as a single agent for MS.

Table 4. Disease-Modifying Therapies for MS

FDA-Approved Medications
- Interferon beta 1a: weekly intramuscular injections (Avonex)
- Interferon beta 1a: subcutaneous injections three times/week (Rebif)
- Interferon beta 1b: subcutaneous injections every other day (Betaseron)
- Glatiramer acetate: daily subcutaneous injections (Copaxone)
- Natalizumab: monthly endovenous infusion (Tysabri)
- Mitoxantrone: intravenous infusions every 3 to 6 months (Novantrone)

Drugs under Investigation
- Cladribine
- Fumarate
- Fingolimod
- Laquinamod
- DNA recombinant MBP vaccine
- Daclizumab
- Alemtuzumab
- Rituxan

MBP = myelin basic protein

Mitoxantrone is a chemotherapeutic agent that owes its efficacy to its cytotoxicity for T- and B-cells. With more than a decade of use in MS, considerable experience has been acquired with this medication and its safety profile is well established.[8] The maximum total lifetime dose of 140 mg is considered below the limit for an increased risk of leukemia and cardiotoxicity. These conditions, however, can still occur from idiosyncratic reactions. The evidence for stabilization of aggressive forms of MS with treatment with mitoxantrone is robust. Mitoxantrone is still the only agent recommended for the treatment of secondary progressive MS.

Numerous other medications are in Phase II or III clinical trials (Table 4). Expectations for some of these therapies are high.[8] Among the many newer drugs, oral formulations are of particular interest because they are more convenient than injectables and infusions and because their overall tolerability is better than current regimens. Monoclonal antibodies are a particularly promising class of medications. Thanks to their high selectivity, these molecules have thus far exhibited a relatively good safety profile combined with unprecedented effectiveness in the treatment of MS.

Conclusion

Recognizing and becoming familiar with some of the most commonly encountered immunological disorders that may affect the CNS are key to initiating appropriate treatment. The field of immunology is subject to constant updates as new concepts are introduced. Hence, the understanding of the mechanisms of action of the immune systems is continuously refreshed by new discoveries. Furthermore, the therapeutic options available to treat diseases caused by deregulated immune responses are expanding rapidly. These options will likely continue to grow, and practitioners will be provided with better therapies to offer patients. It is hoped that cures will become available for these sometimes devastating diseases in the not too distant future.

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