

20. Immunologic neuromuscular disorders

Tanuja Chitnis, MD, and Samia J. Khoury, MD *Boston, Mass*

Immune-mediated disorders of each of the structural subdivisions of the nervous and neuromuscular system have been described. Despite the immune privilege of the central nervous system, and to a lesser extent the peripheral nervous system, immune dysregulation is not uncommon. Environmental, genetic, and immunologic factors have been postulated to be involved in the development of these disorders. Major immune-mediated neurologic diseases of the central nervous system include multiple sclerosis and acute disseminated encephalomyelitis. Immune-mediated diseases of the peripheral nervous system include myasthenia gravis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, idiopathic polymyositis, dermatomyositis, and inclusion body myositis. Some of these disorders, such as myasthenia gravis and certain forms of acute inflammatory demyelinating polyneuropathy, are clearly autoimmune in nature, whereas the immune system plays an important role in pathogenesis in others. Understanding the immune mechanisms of disease and uncovering potential therapeutic targets are essential for the design of new treatments. The epidemiology, pathogenesis, diagnostic criteria, and current therapeutic approaches to the major neuroimmunologic diseases are reviewed. (*J Allergy Clin Immunol* 2003;111:S659-68.)

Key words: *Acute inflammatory demyelinating polyneuropathy, antibody, autoimmunity, chronic inflammatory demyelinating polyneuropathy, dermatomyositis, Guillain-Barré syndrome, inclusion body myositis, multiple sclerosis, myasthenia gravis, neuroimmunology*

Immune-mediated disorders occur at all levels of the nervous system. Disorders of the central nervous system (CNS) and the peripheral nervous system, including the peripheral nerve, neuromuscular junction, and muscle, have been described (Table I). Some of these disorders are clearly autoimmune, in that a clear autoantigen has been identified, whereas others are immune mediated. Many disorders are listed in Table I; we describe here the most common of these diseases in detail, outlining their epidemiology, pathogenesis, clinical features, and therapeutic approaches.

MULTIPLE SCLEROSIS

Background

Multiple sclerosis (MS) is a heterogeneous disease that is characterized by neurologic deficits disseminated

Abbreviations used

AchR: Acetylcholine receptor
ADEM: Acute disseminated encephalomyelitis
AIDP: Acute inflammatory demyelinating polyneuropathy
CIDP: Chronic inflammatory demyelinating polyneuropathy
CNS: Central nervous system
CSF: Cerebrospinal fluid
DM: Dermatomyositis
EAE: Experimental autoimmune encephalomyelitis
EMG: Electromyography
GBS: Guillain-Barré syndrome
IBM: Inclusion body myositis
IVIG: Intravenous immunoglobulin
MBP: Myelin basic protein
MG: Myasthenia gravis
MRI: Magnetic resonance imaging
MS: Multiple sclerosis
PM: Polymyositis

in time and space. It is a major cause of disability in the adult population in North America. Women are predominantly affected in a ratio of 2:1. The disease is characterized by a varying array of neurologic deficits. There are four main disease types, classified on the basis of the clinical disease course: relapsing-remitting, secondary progressive, primary progressive, and progressive relapsing.¹ Relapsing-remitting disease affects 65% of patients and is characterized by onset of neurologic deficits that remit over a period of weeks to months. After 15 years most patients with relapsing-remitting go on to have a secondary progressive form of disease in which neurologic deficits become fixed and accumulate. Patients with the primary progressive type accumulate permanent neurologic deficits from the onset of disease, whereas patients with the progressive relapsing type have a combination of progressive and stepwise deficits. Disease onset generally occurs in the early 20s for relapsing-remitting disease and in the mid 30s for primary progressive disease. There is a diminishing north to south gradient in MS prevalence in the northern hemisphere, with an opposite trend in the southern hemisphere.²

Pathogenesis

Pathologically, MS is characterized by inflammatory infiltrates in the CNS white matter, with resultant demyelination and axonal transactions,³ producing sclerotic plaques. Inflammation is generally perivenular, and lesions typically occur in the periventricular subcortical white matter, corpus callosum, brainstem, cerebellum, and spinal cord. Recently, the pathologic description of MS lesions has been classified into four distinct subtypes

From the Center for Neurologic Disease, Brigham and Women's Hospital, Harvard Medical School, Boston.

Reprint requests: Tanuja Chitnis, MD, Brigham and Women's Hospital, Center for Neurologic Disease, 77 Louis Pasteur Ave, LMRC 1st Floor, Boston, MA 02115.

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TABLE I. Immune-mediated disorders of the CNS and peripheral nervous system

Tissue	Disorder
CNS	
Gray matter	Paraneoplastic limbic encephalitis Paraneoplastic opsoclonus-myoclonus Paraneoplastic brainstem encephalitis Subacute sclerosing panencephalitis
Gray and white matter	Primary CNS angiitis
White matter	ADEM Location specific Parainfectious cerebellitis Transverse myelitis Optic neuritis Acute hemorrhagic leukoencephalitis MS CNS lupus Neurosarcoidosis Neuroborreliosis HTLV-1 associated myelopathy Stiff man syndrome
Peripheral nervous system	
Peripheral nerve	GBS AIDP CIDP Miller-Fisher syndrome Mononeuritis multiplex Paraneoplastic neuropathies Monoclonal gammopathy of unknown significance Neuropathy associated with connective tissue disorders Neuroborreliosis
Neuromuscular junction	Autoimmune MG Lambert-Eaton syndrome
Muscle	PM DM IBM Eosinophilic myositis

with the following predominant features: (1) cellular infiltration, (2) antibody deposition, (3) oligodendrocyte apoptosis, and (4) oligodendrocyte death.⁴ Combinations of these subtypes may exist in the same patient; however, the observations to date have been limited to a single subtype of lesion observed in each patient.

It is clear that the immune system plays a central role in mediating CNS damage in MS. Distinct bands seen on electrophoresis of cerebrospinal fluid (CSF), termed *oligoclonal bands*, indicate an increased production of antibody from one or more plasma cell clones. Absence of these bands in the serum indicates that antibody production is restricted to the CNS. Oligoclonal bands restricted to the CSF are commonly observed in patients with MS; however, the target of these antibodies has yet to be elucidated. Cell-mediated immunity primarily

involving T-helper cells is believed to play an important role in initiating the disease, and immunologic studies have substantiated the presence of activated T cells in MS. Most of the therapies for MS also target T cells. No clear autoantigen has been described in MS, and it therefore remains an immune-mediated disease rather than an autoimmune disease. Reactivities to various myelin antigens, including myelin basic protein (MBP), proteolipid protein, and myelin oligodendrocyte protein, have been investigated. MBP-reactive T cells are present in normal individuals,⁵ but patients with MS have a higher frequency of activated MBP-reactive T cells in the peripheral blood and the CSF.⁶

MS is thought to be a T_H1-mediated disease. T_H1 cells predominantly secrete the T_H1 cytokine IFN- γ . Increased levels of T_H1 cytokines have been observed in MS lesions,⁷ and a clinical trial of IFN- γ worsened MS.⁸ In addition, there is increased production of IL-12 (the major inducer of T_H1 cytokines) by antigen-presenting cells in the peripheral blood of patients with MS, especially those with active disease.^{9,10} Experimental autoimmune encephalomyelitis (EAE), the animal model of MS, has been helpful in dissecting the pathogenic mechanisms of the disease. Various EAE models have demonstrated that mice with a T_H1 cytokine profile are more susceptible to EAE than are wild-type mice,¹¹ whereas animals with a T_H2 (IL-4, IL-10) cytokine profile are resistant to disease development. This is far from being a universal finding, however, because EAE can be induced by transfer of T_H2 cells.¹²

The postulated immunopathogenesis of MS involves activation of myelin-specific T cells through molecular mimicry or by a superantigen. The cells cross the blood-brain barrier and get reactivated in the CNS when they are presented with their cognate antigen. Recruitment of inflammatory cells to the CNS is facilitated by production and interaction with chemokines and adhesion molecules. Reactivation within the CNS initiates an inflammatory cascade, with recruitment of other cells, secretion of cytokines and chemokines, and injury to myelin (Fig 1).¹³ Each of these steps in the pathogenesis may be targeted for therapeutic intervention. Clinical trials are underway to test the effectiveness of blocking T-cell co-stimulation. Other trials target T-cell activation, and there are ongoing trials to block the passage of activated T cells into the blood-brain barrier.

MS is a complex polygenic disease. Monozygotic twins have a concordance rate of 27%, whereas dizygotic twins of the same sex display a 2.3% concordance rate.¹⁴ The incidence for first-degree relatives of patients with MS is 2% to 5%, whereas the incidence for the general population is 0.2%. Genetic linkage studies have been performed, and several regions of interest have been found, but the most robust association remains with the HLA region. There is an increased incidence of MS among patients with the HLA-DR2 (DR1501) haplotype.¹⁵ Therefore, although genetic factors play an important role in pathogenesis, migration and other studies have demonstrated that environment also plays a critical role.

Diagnosis

MS is extremely heterogeneous in its clinical presentation. Symptoms include limb weakness or paraplegia, optic neuritis, ophthalmoplegia, sensory symptoms, tic douloureux, urinary urgency, gait disorders, vertigo, and cerebellar disorders. The most common presenting symptoms are motor and sensory symptoms. The diagnosis of MS is based on the occurrence of neurologic deficits disseminated in time and space. Ancillary tests, especially magnetic resonance imaging (MRI), allow earlier diagnosis without waiting for clinical dissemination criteria. A recent consortium has defined criteria necessary for the diagnosis of MS. Two neurologic events separated in time and MRI with lesions characteristic of MS are required for diagnosis.¹⁶ Accepted variations in presentation are one clinical event, and sequential MRIs showing new lesions separated temporally. Ancillary tests, such as CSF examination for oligoclonal bands or an increased IgG index (CSF IgG $\times$ serum albumin/serum IgG $\times$ CSF albumin) or visual evoked responses, may provide additional information in borderline cases. Primary progressive cases are defined by progressive clinical symptoms associated with demyelinating lesions on MRI. In all cases, other causes of demyelinating disease must be ruled out. The differential diagnosis of MS includes CNS Lyme disease (neuroborreliosis), syphilis, hypothyroidism, vitamin B₁₂ deficiency, sarcoidosis, CNS lupus, and other connective tissue disorders that may affect the CNS. Spinocerebellar degeneration and human T-lymphotropic virus 1 are important differential diagnoses of primary progressive MS.

MRI is an extremely valuable tool in the diagnosis of MS. Lesions are characteristically present in the deep white matter in a periventricular distribution, with involvement of the corpus callosum and occasionally the brainstem, cerebellum, or spinal cord white matter. Gadolinium enhancement on T1-weighted images represents areas in which the blood-brain barrier is leaky, a characteristic of recent lesions. T2 lesion load represents demyelination, gliosis, and axonal loss and is a nonspecific measure of disease burden. Atrophy, thought to be due to tissue destruction, may be measured by quantifying the brain parenchymal fraction.¹⁷ Black holes on T1 MRI images reflect tissue loss.

Treatment

Clinical relapses may be treated with a pulse of methylprednisolone administered intravenously for 3 to 5 days. Steroids reduce the number of gadolinium-enhancing lesions and may shorten the duration of the attack. Therapies to reduce the rate of exacerbations in relapsing-remitting disease include beta interferons and copolymer 1 (glatiramer acetate; Copaxone, Teva Pharmaceutical Industries Ltd, Petach, Israel). Interferon beta therapy is available in three different forms: subcutaneous interferon beta-1b (Betaseron, Berlex Laboratories, Inc, Montville, NY), subcutaneous interferon beta-1a (Rebif, Serono, Inc, Rockland, Mass), and intra-muscular interferon beta-1a

(Avonex, Biogen, Inc, Cambridge, Mass). Betaseron is given every other day, Rebif is given three times per week, and Avonex is given once a week. Efficacies of the three drugs are similar, with studies showing a 30% to 35% decrease in new relapses¹⁸⁻²⁰ and a significant decrease in progression in MRI lesion load. Side effects include injection site reactions and flu-like symptoms (myalgia and fever) at the time of injection. Complete blood cell counts and liver function tests must be monitored during treatment. The mechanism of beta interferon action has been attributed to IL-10-dependent mechanisms,²¹ resulting in a decreased number of T_H1 cells²² and modulation of adhesion molecule expression,²³ resulting in decreased migration of inflammatory cells through the blood-brain barrier.

Copaxone is a synthetic peptide that was designed to mimic MBP. It has been shown to cause a deviation in MBP-reactive T-helper cells from a T_H1 phenotype to a T_H2 phenotype in patients with MS²⁴; however, this may not be its only mechanism of action. Like the interferons, Copaxone has also been shown to decrease the number of relapses by 29%.²⁵ Copaxone may also cause skin reactions at injection sites, and an anxiety-type of reaction is present in a small proportion of patients. None of these medications has proven to be unequivocally effective in secondary progressive MS. A large European trial of interferon beta-1b demonstrated a 6-month delay in progression in patients with early secondary progressive disease; however, a similar North American study found no effect. This dichotomy may be related to the different patient populations involved in the two studies, with the European study including patients with more relapses. A recent study with the alkylating agent mitoxantrone demonstrated a delay in progression in secondary progressive MS. Cyclophosphamide, another alkylating agent, has been used extensively to delay progression in secondary progressive MS.²⁶

Long-term management of MS involves treatment of spasticity, which is often responsive to tizanidine or baclofen but in some cases requires the use of an intrathecal baclofen pump. Bladder symptoms are treated with anticholinergic agents, such as oxybutinin, or with intermittent catheterization and occasionally diversion procedures. Depression is a common symptom of MS and must be treated vigilantly, especially because interferons may exacerbate the symptoms of depression. Fatigue may be the most disabling symptom of MS; even in early cases, it is treated with amantadine and, more recently, with modafinil.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Background

Acute disseminated encephalomyelitis (ADEM) is defined as a monophasic demyelinating episode associated with vaccination or a systemic viral infection. It may affect both adults and children; however, it occurs more frequently in children. It was originally described in association

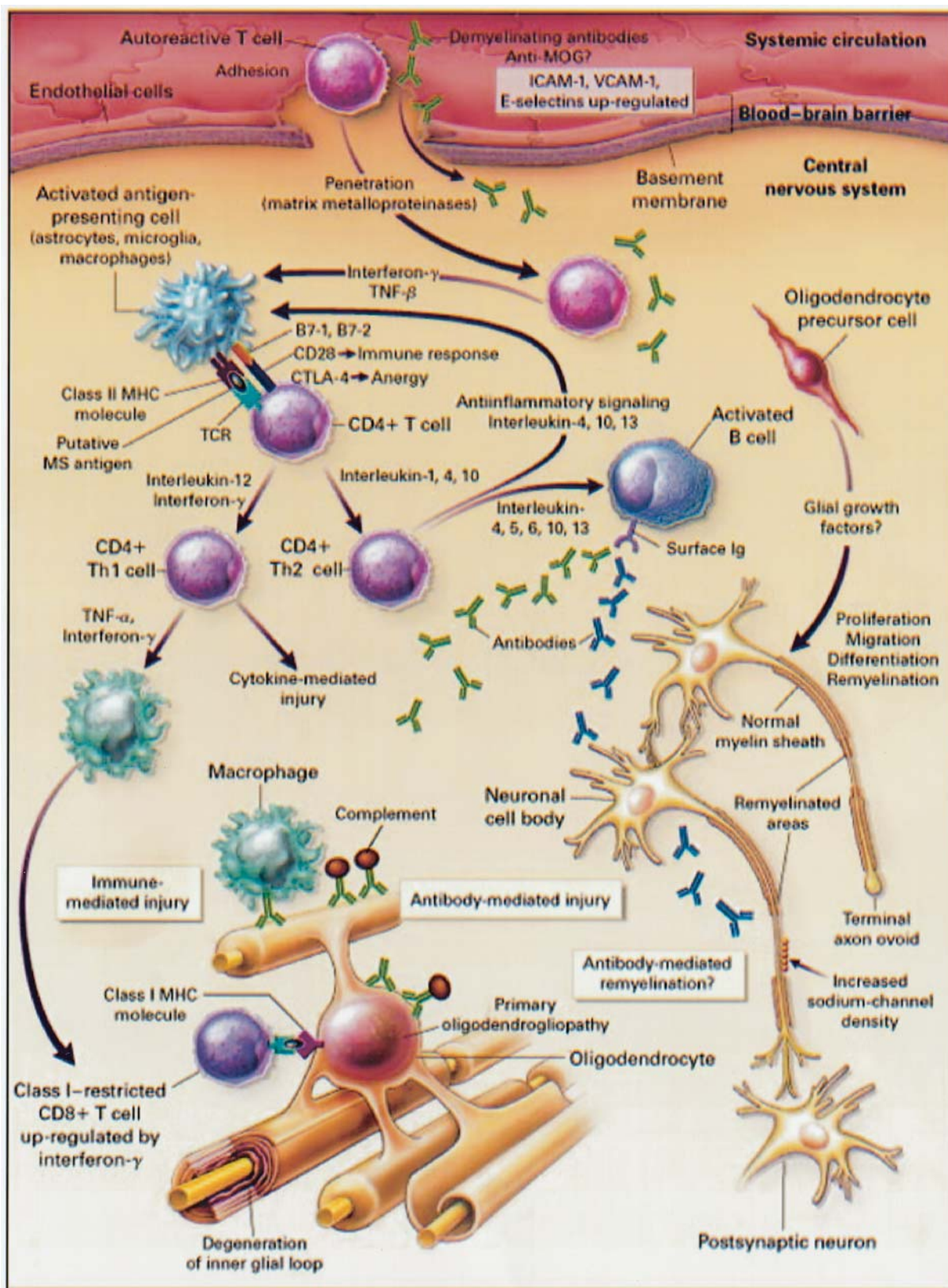


FIG 1. Legend on following page.

with rabies and smallpox vaccines, both of which were prepared with neural tissues, suggesting a parallel with EAE, the animal model of MS. These vaccines have since been modified to use nonneural human diploid cell lines. ADEM has not been associated with any vaccines that are currently administered in the United States. The parainfectious variant of ADEM has been associated with measles infection, rubella, mumps, and several other viruses.

Pathogenesis

The lesions in ADEM resemble those of MS. The CNS white matter contains perivascular inflammatory infiltrates, as well as demyelination. The most likely mechanism by which this disease occurs is molecular mimicry. Experimental evidence has shown that T cells isolated from patients with ADEM are 10 times more likely to react with MBP than are control cells, likening this disease to EAE in animal models.²⁷ Because of the monophasic nature of the illness, it appears that the immunologic response occurs acutely but further reaction is abrogated.

Diagnosis

ADEM generally is seen with a monophasic episode of focal or multifocal neurologic symptoms, and in most cases it occurs after a viral infection. Symptoms may include weakness, numbness, ataxia, and cranial nerve palsies, as well as lethargy, seizures, and coma. Diagnosis is made on the basis of a combination of clinical fea-

tures, CSF examination, and MRI appearance. Presentation resembles some aspects of initial demyelinating events seen in MS; however, several features differentiate ADEM from the initial presentation of MS. Distinguishing between these two disease entities is critical for long-term prognosis and treatment management. Clinical features that are common in ADEM but not in MS include simultaneous bilateral optic neuritis, loss of consciousness, meningismus, raised body temperature, and severe shooting limb pains. Mortality ranges between 10% and 30%, with 50% of patients experiencing a full recovery within weeks to months. Relapses have been observed within 3 to 6 months after the initial onset of symptoms; relapses beyond this time point, however, suggest a diagnosis of MS.

MRI in a patient with ADEM typically demonstrates multifocal white matter lesions involving the cerebrum, brainstem, cerebellum, and spinal cord, which may or may not enhance with gadolinium. Involvement of the gray matter is more common in ADEM than in MS. Resolution of lesions on follow-up MRI, with the appearance of no new lesions, helps to confirm the monophasic nature of ADEM. CSF is characterized by normal pressure, moderately elevated cell count (5-100 cells/ μ L), moderately elevated protein level (40-100 mg/dL), and normal glucose level. The presence of red blood cells may indicate a diagnosis of hemorrhagic leukoencephalitis. Oligoclonal bands are seen less frequently in ADEM than in MS.

FIG 1. Possible mechanisms of injury and repair in MS. Genetic and environmental factors (including viral infection, bacterial lipopolysaccharides, superantigens, reactive metabolites, and metabolic stress) may facilitate the movement of autoreactive T cells and demyelinating antibodies from the systemic circulation into the CNS through disruption of the blood-brain barrier. In the CNS, local factors (including viral infection and metabolic stress) may upregulate the expression of endothelial adhesion molecules, such as intercellular adhesion molecule 1 (*ICAM-1*), vascular cell adhesion molecule 1 (*VCAM-1*), and E-selectin, further facilitating the entry of T cells into the CNS. Proteases, including matrix metalloproteinases, may further enhance the migration of autoreactive immune cells by degrading extracellular matrix macromolecules. Pro-inflammatory cytokines released by activated T cells, such as IFN- γ and TNF- α , may upregulate the expression of cell-surface molecules on neighboring lymphocytes and antigen-presenting cells. Binding of putative MS antigens, such as MBP, myelin-associated glycoprotein, myelin oligodendrocyte glycoprotein (*MOG*), proteolipid protein, B-crystallin, phosphodiesterases, and S-100 protein, by the trimolecular complex—the T-cell receptor (*TCR*) and class II MHC molecules on antigen-presenting cells—may trigger either an enhanced immune response against the bound antigen or anergy, depending on the type of signaling that results from interactions with surface costimulatory molecules (eg, CD28 and cytotoxic lymphocyte antigen-4 [*CTLA-4*]) and their ligands (eg, B7-1 and B7-2). Downregulation of the immune response (anergy) may result in the release of anti-inflammatory cytokines (IL-1, IL-4, and IL-10) from CD4⁺ T cells, leading to the proliferation of anti-inflammatory CD4⁺ T_H2 cells. T_H2 cells may send anti-inflammatory signals to the activated antigen-presenting cells and stimulate pathologic or repair-enhancing antibody-producing B cells. Alternatively, if antigen processing results in an enhanced immune response, pro-inflammatory cytokines (eg, IL-12 and IFN- γ) may trigger a cascade of events, resulting in the proliferation of pro-inflammatory CD4⁺ T_H1 cells and ultimately in immune-mediated injury to myelin and oligodendrocytes. Multiple mechanisms of immune-mediated injury of myelin have been postulated: cytokine-mediated injury of oligodendrocytes and myelin; digestion of surface myelin antigens by macrophages, including binding of antibodies against myelin and oligodendrocytes (antibody-dependent cytotoxicity); complement-mediated injury; and direct injury of oligodendrocytes by CD4⁺ and CD8⁺ T cells. This injury to the myelin membrane results in denuded axons that are no longer able to transmit action potentials efficiently within the CNS (loss of saltatory conduction). This slowing or blocking of the action potential results in the production of neurologic symptoms. The exposed axonal segments may be susceptible to further injury from soluble mediators of injury (including cytokines, chemokines, complement, and proteases), resulting in irreversible axonal injury (such as axonal transection and terminal axon ovoids). There are several possible mechanisms of repair of the myelin membrane, including resolution of the inflammatory response followed by spontaneous remyelination, spread of sodium channels from the nodes of Ranvier to cover denuded axon segments and restore conduction, antibody-mediated remyelination, and remyelination resulting from the proliferation, migration, and differentiation of resident oligodendrocyte precursor cells. Adapted from a drawing by the Mayo Foundation, and originally in the *New England Journal of Medicine* 2000;353:938-52 (reproduced with permission of the Massachusetts Medical Society).

Treatment

Acute episodes of ADEM should be treated with intravenous steroid administration. The usual dose is 1 g methylprednisolone sodium succinate for 5 days in adults. Refractory cases have been treated with plasmapheresis or cyclophosphamide. Patients whose findings are suggestive of MS should be followed up with MRI.

IMMUNE-MEDIATED NEUROPATHIES

Background

The immune-mediated peripheral neuropathies are a large and heterogeneous group of diseases. We focus here on acute inflammatory demyelinating polyneuropathy (AIDP) and chronic inflammatory demyelinating polyneuropathy (CIDP), which may be defined by the time to peak disability, 4 weeks for the former and 2 months for the latter. Although AIDP and CIDP share many characteristics, the question of whether one is a continuum of the other is still under debate. AIDP or Guillain-Barré syndrome (GBS) presents usually with symmetric ascending weakness and may be associated with autonomic dysfunction and respiratory depression. Sensory systems may be involved and may present with paresthesia or numbness. Demyelination and axonal damage may be involved to varying degrees. If the patient's symptoms continue to progress beyond 4 weeks, the illness is considered to be CIDP.

AIDP is the most common acute paralytic disease in the Western world, with a mean annual incidence of 1.8 cases/100,000 persons. There is an increasing incidence with age. In the past, mortality was generally due to respiratory failure, but this has been significantly reduced by the introduction of positive-pressure ventilation. Epidemics have been identified, most notably in northern China, where a high incidence of AIDP has been associated with *Campylobacter jejuni* infection.²⁸

Pathogenesis

AIDP or GBS is characterized pathologically by a perineural lymphocytic, monocytic macrophage infiltrate. Several autoantibodies to myelin glycolipids have been identified, including GM1, Gd1a, and Gd1b. Antibody-mediated demyelination as a result of complement activation has been identified in pathologic specimens.²⁹ In some cases, axonal damage is present and is believed to be a result of bystander damage. GBS is primarily an antibody-mediated disease, as evidenced by the fact that many patients have improvement after treatment with plasmapheresis and that serum from patients with GBS causes demyelination after transfer into experimental animals and peripheral nerve cultures.

The occurrence of AIDP has been linked with many infectious diseases, including *C jejuni*, *Mycoplasma pneumoniae*, and many other bacterial and viral infections, as well as with vaccinations. The incidence of infection in the 30 days prior to occurrence of GBS has been reported to be 10% to 60%.³⁰ *C jejuni* is one of the

most commonly identifiable agents, and large outbreaks in China have been associated with a form of GBS primarily involving motor axons. Molecular mimicry and host susceptibility are believed to play a role in disease pathogenesis in general and in *C jejuni*-associated cases in particular. Autoantibodies not present in control specimens have been identified in serum samples from patients with GBS associated with *C jejuni*, including GM1, Gd1a, Gd1b, and Gq1b.³¹

In CIDP the histopathologic picture is similar to that in AIDP; however, most studies reveal fewer inflammatory infiltrates. Nerve biopsy specimens reveal mixed demyelination and axonal changes. Onion bulbs may be present, indicating repeated demyelination and remyelination. There is little laboratory evidence that this disease is antibody mediated; paradoxically, however, patients do have improvement with plasmapheresis. There is indirect evidence that CIDP is T-cell mediated; however, this area is still under investigation. Although CIDP is characterized by a lack of antiganglioside antibodies, multifocal motor neuropathy may represent a variant of CIDP and is characterized by high titers of anti-GM1 IgM antibodies. Identification of this subtype is important, because treatment with intravenous immunoglobulin (IVIG) and oral cyclophosphamide have been shown to be effective.

Diagnosis

The typical clinical presentation of AIDP is a subacute onset of paresthesia, sensory symptoms, and ascending weakness. Symptoms are generally symmetric and may progress to involve respiratory, facial, and oropharyngeal muscles. Autonomic features, such as orthostatic hypotension or bradycardia, occur in most patients.³² Hyporeflexia or areflexia is an invariable feature. Diagnosis is made on the basis of clinical presentation and examination and may be confirmed with CSF examination and serial electrophysiologic studies. The typical CSF pattern consists of elevated protein in the absence of an elevated white blood cell count. Oligoclonal bands may also be present. Ninety percent of patients exhibit abnormalities on electrophysiologic testing, including prolonged distal motor and F-wave latencies, reduction in distal compound muscle action potential amplitudes with or without temporal dispersion, and slowing of motor conduction velocities.³³ Electromyography (EMG) may show decreased motor unit recruitment.

If there is sustained progression of symptoms beyond 4 weeks or relapses occur, then the disease is considered to be CIDP. Electrophysiologic studies in CIDP are similar to those in AIDP and in most cases reflect patterns of acquired multifocal demyelination. CSF exhibits an albuminocytologic dissociation, and nerve biopsy may be useful to differentiate CIDP from other causes of chronic neuropathy.

Treatment

Treatment of AIDP involves supportive care and cardiac and respiratory monitoring. Plasmapheresis and IVIG have been used for acute treatment of AIDP and have been shown to be equally effective in shortening

recovery time.³⁴ High-dose steroids have not been found to be effective in AIDP.³⁵

In contrast to AIDP, CIDP responds well to high-dose oral steroids. Both plasmapheresis and IVIG³⁶ have been used with success. Immunosuppressants, such as cyclosporine, cyclophosphamide, and azathioprine have had positive outcomes in refractory cases; however, these agents require further testing in controlled studies. Multifocal motor neuropathy, a variant of CIDP, responds well to IVIG with oral cyclophosphamide.

AUTOIMMUNE MYASTHENIA GRAVIS

Background

Myasthenia gravis (MG) is a disorder of the neuromuscular junction. It is an autoimmune disorder, and 80% to 90% of patients have detectable autoantibodies to the α subunit of the acetylcholine receptor (AChR). MG is characterized by fluctuating weakness and fatigability, primarily in muscles innervated by the cranial nerves, but may occur in skeletal and respiratory muscles. MG has a biphasic age distribution. Most cases occur in women aged 20 to 40 years, and the remainder occur in older patients with an equal sex distribution. Thymomas occur in 10% to 15% of cases, mainly in the older age group. Seventy-five percent of patients have some thymic abnormality, with 85% of these abnormalities being thymic hyperplasia. MG is often associated with other autoimmune diseases, thyroid disorders, rheumatoid arthritis, pernicious anemia, and systemic lupus erythematosus (SLE).³⁷ A similar syndrome, Lambert-Eaton syndrome, is associated with antibodies against the presynaptic, voltage-gated calcium channel.

Pathogenesis

Autoimmune MG is caused by the presence of anti-AChR antibodies and is a B-cell-mediated disease. From 80% to 90% of patients have detectable autoantibodies. These are polyclonal and may be of any IgG subtype. Transfer of serum from patients with MG to experimental animals results in neuromuscular blockade. The mechanism by which antibody mediates neurologic symptoms is controversial. Possible mechanisms include neuromuscular blockade and from complement-mediated damage to the AChR after attachment of the IgG antibody. There is, however, poor correlation between serum antibody titers and disease course and severity.

Although the B cell is the effector cell producing antibodies, experimental evidence has shown that autoreactive T cells are necessary for the disease to occur.³⁸ Removal of the thymus results in improvement of disease in 80% to 90% of patients with MG. The role of thymic abnormalities remains unclear, and patients with thymomas may display antibodies to additional skeletal muscle proteins, such as the ryanodine receptor and titin³⁹; however, the clinical significance of these antibodies is unclear.

Investigations are currently underway to determine the cause of the failure of T-cell tolerance and subsequent

failure of B-cell tolerance. Both normal and myasthenic thymus glands contain myoid cells and epithelial cells that express the AChR. T cells expressing the Vb 5.1+ T-cell receptor are overrepresented, both in the core of germinal centers and in perifollicular areas of hyperplastic thymuses, suggesting a role in the autoimmune response.³⁹ Failure of central or thymic tolerance may play an important role in disease pathogenesis.

Genetic factors play a role in the pathogenesis of autoimmune MG, but monozygotic twins demonstrate a concordance rate of less than 50%. There is a moderate association with HLA antigens B8 and DRw3 in young women. The stronger association with HLA-DQw2 remains controversial. There is an unusually high incidence of other autoimmune diseases, such as SLE, rheumatoid arthritis, and thyroid diseases, in first-degree relatives of patients with MG, suggesting the presence of shared autoimmune genes.

Diagnosis

MG is characterized by progressive fatigability of particular muscle groups. Common presenting symptoms include diplopia, ptosis, dysarthria, dysphagia, and weakness in the shoulder and neck muscles, as well as weakness in other muscle groups. Respiratory muscle fatigue and failure may also occur. Common complaints include difficulty talking, chewing, or swallowing and blurred vision. Symptoms are often worse at the end of the day or after prolonged use of a particular muscle group or during systemic illness, including viral infections.

Diagnosis is made on the basis of clinical symptoms, testing with anticholinesterase inhibitors, and EMG. Serum antibodies to the AChR may be present in as many as 80% to 90% of patients; however, seronegativity does not rule out MG.⁴⁰ Reversibility of clinical symptoms with anticholinesterase inhibitors is another hallmark of diagnosis. Treatment with the short-acting edrophonium chloride improves clinical symptoms in as many as 90% of patients with MG; however, reversibility is not specific to MG alone. EMG provides ancillary evidence for MG. Repetitive nerve stimulation demonstrates a decremental response in the compound muscle action potential in 61% of patients with MG. Single-fiber EMG may demonstrate jitter, a phenomenon seen in disorders with abnormal neuromuscular transmission.⁴¹

Treatment

Therapies in MG are targeted toward alleviating symptoms with acetylcholinesterase inhibitors and strategies to abrogate the disease target, the immune system. Thymectomy is recommended for patients 15 to 65 years old, with an 80% to 90% remission rate.⁴² The thymus plays an important role in T-cell education in the developing human being, so prepubertal thymectomy is discouraged. A variety of anticholinesterase inhibitors, including pyridostigmine bromide (Mestinon, ICN Pharmaceuticals, Inc, Costa Mesa, Calif) and neostigmine bromide (Prostigmin, ICN Pharmaceuticals, Inc, Costa Mesa, Calif), are the most commonly used agents. These

provide temporary symptomatic relief in most cases and must be taken as frequently as three to four times daily.

MG is an antibody-mediated disease and therefore responds to therapies that nonspecifically target antibodies. Both plasmapheresis and treatment with IVIG are used for acute MG exacerbations or in preparation for surgery.⁴³ Plasmapheresis is a short-term immunotherapy that nonspecifically removes antibodies from the circulation. IVIG is an immunomodulating agent commonly used in the treatment of allergic and autoimmune diseases. Because the autoantigen in MG is known, investigational therapies may target specific molecules, such as the B-cell surface immunoglobulin or the T-cell receptor, and deliver immunotoxins.

Immunosuppressive agents, such as cyclosporine and azathioprine, are used to augment treatment when symptoms are not adequately controlled by the previously described methods, but the decision to use such agents must balance the need against the side effects. Corticosteroids are used at various stages of treatment and have multiple effects on the immune system, including reducing AchR antibody levels.

INFLAMMATORY MUSCLE DISEASES

Background

Polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM) are all immune-mediated diseases of the muscle and the surrounding connective tissue. Each has its own unique clinical and immunohistologic features. Both PM and DM are more common in female patients, whereas IBM is more common in male patients. IBM occurs less frequently than either PM or DM. DM is associated with an increased risk of cancer, and a full cancer screening should therefore be part of patient management.

Pathogenesis

PM is thought to result from a multitude of causes, including systemic autoimmune disorders, connective tissue disorders, and viral and bacterial infections. PM is characterized histopathologically by an endomysial inflammatory infiltrate containing predominantly CD8⁺ T cells. There is relative sparing of blood vessels. In one subtype of PM, T cells with $\gamma\delta$ receptors have been identified surrounding nonnecrotic muscle fibers.⁴⁴ In contrast, DM is characterized by perifascicular atrophy. There is hypoperfusion and subsequent degeneration of the muscle fibers in the periphery of the fascicle secondary to microvascular damage. Damage to capillaries resulting in microinfarcts is mediated by complement.⁴⁵ Immunofluorescence studies have revealed immune complex deposition within the endothelium, indicating that this is an antibody-mediated disease and thus different from PM.

Various autoantibodies directed against nuclear and cytoplasmic cell components are found in as many as 30% of inflammatory myopathies. Most are nonspecific for connective tissue disease. Viruses including coxsackievirus B

are implicated in the pathogenesis of disease, and patients with either PM or DM may have anti-Jo-1 antibodies to the viral enzyme histidyl transfer RNA synthetase.⁴⁶

As with PM, IBM is mediated by CD8⁺ T cells. However, a muscle biopsy specimen may also demonstrate the presence of characteristic autophagic "rimmed" vacuoles. Amyloid deposits may be demonstrated in the muscle, similar to those seen in Alzheimer disease, suggesting similarities in pathogenesis.⁴⁷

Diagnosis

PM is characterized by onset of fluctuating muscle weakness and tenderness in the distribution of the proximal upper and lower extremities. Severe pain in the muscles makes the diagnosis of PM less likely. Respiratory and oropharyngeal muscles may also be involved, causing dysphagia and respiratory difficulties. Associated symptoms include Raynaud phenomenon, cardiac involvement, arthralgia, and fevers. DM is characterized by a heliotrope erythematous rash around the eyelids or on the extensor joint surfaces in addition to the typical symptoms of PM. Both PM and DM are associated with other rheumatologic diseases, most commonly scleroderma, and both, but particularly DM, are associated with malignancies. All age groups may be affected, and there is a slight preponderance in female patients.

IBM is seen with a painless, progressive atrophy in both proximal and distal muscles that is asymmetric. Facial weakness and dysphagia are also common symptoms. This disease usually occurs in adults older than 50 years, and men are affected more frequently than are women.⁴⁸

Diagnosis of all the inflammatory myopathies is based on an elevated serum creatine kinase level, EMG findings, clinical presentation, and results of muscle biopsy. EMG should demonstrate insertion irritability and short-duration, low-amplitude, polyphasic potentials. Muscle biopsy is the criterion standard for diagnosis and in most cases clearly distinguishes the subtypes of inflammatory myopathy. Anti-Jo antibodies may be present in as many as 20% of patients with PM and DM.⁴⁹

Treatment

The mainstay of treatment of PM and DM is steroids. Dosages may vary from 60 to 100 mg/d of prednisone, and duration is determined by clinical outcome. Alternative treatment options for the inflammatory myositis diseases include IVIG, methotrexate, azathioprine, cyclophosphamide, cyclosporine, and, in extreme cases, whole-body irradiation.^{50,51} Mortality rates vary between 15% and 35%, and death is generally due to cardiac or respiratory failure.⁵² Because there is a higher incidence of malignancy with PM and DM, screening for breast, lung, hematologic, ovary, stomach, and colon carcinoma should be performed on each patient with the diagnosis.⁵³

IBM may be more resistant to steroid therapy and is often diagnosed after a case of presumed PM fails to respond to treatment. There is currently no effective treatment for IBM; however, IVIG may provide some benefit.

PARANEOPLASTIC SYNDROMES

Neurologic paraneoplastic disorders are defined as neurologic syndromes arising in association with a cancer. These disorders are mediated by antibodies that are produced by the immune system in reaction to a tumor antigen and cross-react with neural tissue. Because many autoantibodies have been identified, the mechanism of action of paraneoplastic syndromes is autoimmune. It is likely that aberrant, primitive, or hamartomatous antigens are expressed by the tumor cells.

We discuss here several of the many examples of neurologic paraneoplastic disorders. The anti-Hu antibody arises in association with small cell cancer of the lung and cross-reacts with neurons to produce a syndrome of encephalomyelitis or sensory neuropathy. The Lambert-Eaton myasthenic syndrome is associated with P/Q-type voltage-gated calcium-channel antibodies, and some patients have anti-Hu antibodies. Paraneoplastic cerebellar degeneration may occur in association with the Lambert-Eaton myasthenic syndrome.⁵⁴ Anti-Yo antibody produces cerebellar degeneration as a result of cross-reactivity with Purkinje cell cytoplasm and is associated with breast and ovarian cancer. Opsoclonus-myoclonus syndrome is due to anti-Ri antibody and has been associated with cancer of the ovary and breast.

There is evidence of a more active cellular infiltrate in tumors associated with paraneoplastic syndrome than in those not associated with a paraneoplastic syndrome. Therefore, one might postulate that the immune system is more active in these situations. In the case of small cell lung cancer, cases with anti-Hu antibody positivity are generally associated with a better outcome.⁵⁵

CONCLUSION

The field of immunology has progressed significantly in the past 20 years. This knowledge is currently being applied to immune-mediated diseases in neurology. In this rich environment, we can expect many advances in the field of neuroimmunology including new therapies and better strategies for inducing remission.

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