Demyelinating and Immunologic Disorders

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The nervous system may be affected by a number of autoimmune conditions. The most common of these conditions is multiple sclerosis, which is an immune-mediated disorder specific to the central nervous system (CNS) that results in demyelination and scarring of white matter pathways and occurs in more than one location over time. Other autoimmune and inflammatory disorders may also affect the nervous system, including acute disseminated encephalomyelitis, neuromyelitis optica, sarcoidosis, and vasculitis, and detection of autoantibodies is often the primary diagnostic approach to these disorders. In this section, the common demyelinating and immunologic disorders are reviewed.

Multiple Sclerosis

Multiple sclerosis (MS) is one of the most common causes of disability in young adults. The disease tends to be more common between the ages of 15 to 30 years, with decreasing prevalence with increasing age. MS is more common in women. In addition, the disorder is more prevalent with increasing distance from the equator, although the mechanism of this increased prevalence is unknown.

MS is often categorized by its clinical course, and three distinct temporal presentations are typically described: relapsing-remitting, secondary progressive and primary progressive MS.
Relapsing-Remitting Multiple Sclerosis

Relapsing-remitting MS is characterized by episodes of demyelination with either full or partial recovery between episodes. There typically is no disease progression between episodes. Relapsing-remitting MS is the most common form of MS at disease onset.

Diagnosis. The diagnosis of relapsing-remitting MS requires evidence of focal demyelination separated in space and time. In practice, this may require historical evidence of a prior attack, either based on imaging or history. Patients may present with any number of acute neurologic events, although heavily myelinated tracts are particularly susceptible. Common presentations include internuclear ophthalmoplegia, optic neuritis, transverse myelitis, or focal weakness or numbness. MRI may demonstrate demyelinating lesions suggestive of prior attacks and confirm the diagnosis (Figure 1). Other tests that may increase the likelihood of a diagnosis of MS include a CSF analysis demonstrating an elevated IgG index or the presence of oligoclonal bands. Visual evoked potentials or somatosensory evoked potentials may also indicate prior demyelination in the optic nerve or spinal cord, respectively, although these tests are less sensitive. Ultimately, the diagnosis requires evidence of at least two clinical attacks or a single clinical attack with radiologic evidence of prior demyelinating events, per the 2010 revision of the McDonald criteria.
Figure 1. Axial fluid-attenuated inversion recovery (FLAIR) images of multiple sclerosis lesions. A. Typical periventricular and juxtacortical lesions of multiple sclerosis (red arrows) are easily detectable on FLAIR. B. Comparison of FLAIR (left) and T2 (right) images, demonstrating significantly decreased detectability of demyelinating lesions in the posterior fossa on the FLAIR image. FLAIR also has poor sensitivity for demyelinating lesions in the spinal cord (not shown). Caution is thus advised in using FLAIR as the only MRI screening tool for multiple sclerosis. Reprinted with permission from Pirko I. Neuroimaging of demyelinating diseases. Continuum (Minneap Minn) 2008;14(4 Neuroimaging):125. © 2008 American Academy of Neurology.

Clinically Isolated Syndrome. Patients presenting with a single clinical attack and without a history of prior events are defined as having a clinically isolated syndrome. The demyelinating event in these patients is similar to those seen in patients diagnosed with relapsing-remitting MS. A head MRI and CSF studies obtained at the time of presentation can
assist in the evaluation of clinically isolated syndrome and may predict which patients are at risk for developing future attacks. In one study, the presence of demyelinating lesions on the initial head MRI was associated with a 90% risk of experiencing additional attacks, compared with a 20% risk in those individuals without lesions on MRI.

**Radiologically Isolated Syndrome.** The increasing utilization of MRI imaging has led to the detection of demyelinating lesions in individuals who are currently asymptomatic. These patients are labeled as having a radiologically isolated syndrome. If any lesions identified on MRI enhance with contrast, an increased risk of developing clinical symptoms exists. However, the management of such asymptomatic patients remains an area of active research.

**Treatment.** Acute demyelinating attacks should be treated with high-dose corticosteroids and a slow taper. The goal of steroid treatment is to shorten the course of the relapse. Both IVIg and plasmapheresis may be used in refractory cases.

Fourteen disease-modifying drugs for relapsing remitting MS are currently approved by the US Food and Drug Administration (Table 1). The goal of all of these therapies is to reduce the number of relapses, thereby delaying or preventing the development of secondary progressive MS. The beta interferons and glatiramer acetate were the first disease-modifying drugs approved for the treatment of MS and they have been shown to decrease the number of relapses by about one-third. In clinical trials, it appears that medications such as natalizumab may have an up to 50% higher efficacy in preventing relapses, but they carry an increased risk of progressive multifocal leukoencephalopathy (PML). More recently, the oral medications fingolimod, teriflunomide, and dimethyl fumarate have been approved as treatments for MS. The long-term safety profile of these newer medications is less clear, although a few cases of PML have been associated with use of fingolimod and dimethyl fumarate. Of the medications
approved, glatiramer acetate is the only one to be US Food and Drug Administration pregnancy Category B (no risk in animal studies, no data in humans). The remainder carry a higher pregnancy risk, with teriflunomide having a pregnancy Category X (risks in fetal development demonstrated in animal or human studies). Other medications may be considered for symptomatic treatment of fatigue (eg, amantadine, amphetamine derivatives), spasticity (eg, baclofen, tizanidine), gait impairment (eg, dalfampridine), and neurogenic bladder (eg, anticholinesterase inhibitors, alpha-1a antagonists), and erectile dysfunction (eg, sildenafil, tadalafil) (Table 2).

Table 1. Disease-Modifying Agents for Multiple Sclerosis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route</th>
<th>Mechanism of Action</th>
<th>Potential Side Effects</th>
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<tbody>
<tr>
<td>Interferon beta-1a (Avonex; Rebif)</td>
<td>Intramuscular or subcutaneous</td>
<td>Suppresses $T_H$1 cells</td>
<td>Headache, flulike symptoms, injection site reaction</td>
</tr>
<tr>
<td>Interferon beta-1b (Betaseron; Extavia)</td>
<td>Subcutaneous</td>
<td>Reduces number of inflammatory cells that cross blood-brain barrier</td>
<td>Flulike symptoms</td>
</tr>
<tr>
<td>Glatiramer Acetate (Copaxone)</td>
<td>Subcutaneous</td>
<td>Unknown, may shift $T_H$ cell response</td>
<td>Injection site reactions, flushing</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>Intravenous</td>
<td>Reduces number of inflammatory cells that cross blood-brain barrier</td>
<td>Headache, fatigue, diarrhea, rash, progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Daclizumab (Zinbryta)</td>
<td>Subcutaneous</td>
<td>Binds to CD25 to reduce inflammatory cells</td>
<td>Elevated liver enzymes, upper respiratory tract infections, flulike symptoms, rash</td>
</tr>
</tbody>
</table>
Fingolimod (Gilenya) Orally Binds to lymphocyte surface and traps in lymph glands Headache, flulike symptoms, elevated liver enzymes, abdominal pain

Teriflunomide (Aubagio) Orally Blocks pyrimidine synthesis pathway to halt peripheral B and T cell production Elevated liver enzymes, hair thinning, potential tuberculosis reactivation, diarrhea

Dimethyl fumarate (Tecfidera) Orally Unknown Flushing, dyspepsia, progressive multifocal leukoencephalopathy

Table 2. Symptomatic Management of Multiple Sclerosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Potential Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Amantadine, Modafinil</td>
</tr>
<tr>
<td>Spasticity</td>
<td>Baclofen, Tizanidine, Botulinum toxin</td>
</tr>
<tr>
<td>Depression</td>
<td>Selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor medications</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Donepezil, Rivastigmine</td>
</tr>
<tr>
<td>Tremor and ataxia</td>
<td>Carbamazepine, Topiramate</td>
</tr>
<tr>
<td>Ambulation</td>
<td>Dalfampridine</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Antispasticity agents, Antimuscarinic compounds</td>
</tr>
<tr>
<td>Bowel dysfunction</td>
<td>Laxatives</td>
</tr>
</tbody>
</table>

Secondary Progressive Multiple Sclerosis

Prior to the advent of disease-modifying therapy, nearly 85% of patients with relapsing-remitting MS would develop secondary progressive MS. Secondary progressive MS is characterized by progressive disability accumulation with or without relapses. The course may be variable, and
some patients may plateau for several years; however, many patients will have progressive weakness and cognitive decline. Currently approved disease-modifying therapies are not effective in treating the progressive component of the disease, although they may be used in patients with secondary progressive MS who continue to have relapses.

**Primary Progressive Multiple Sclerosis**

Around 10% of patients with MS present with the primary progressive form of the disease. Men and women are affected equally by this form, and patients tend to be diagnosed at an older age than those diagnosed with relapsing-remitting MS. The hallmark of this form is the lack of relapses, although some patients may have rare episodic events of demyelination. Many patients will present with slowly progressive, asymmetric leg weakness, although progressive ataxia is another common presentation. Importantly, enhancing lesions on MRI are uncommon. Diagnosis relies on findings on MRI and CSF studies similar to those in relapsing-remitting MS, along with a progressive course of neurologic injury that lasts more than one year. Currently, no treatments are available for primary progressive MS.

In all forms of MS, irreversible changes in the white matter (black holes) as well as atrophy of the gray matter may develop. Such changes lead to progressive dementia, mood changes, and seizures.

**Acute Disseminated Encephalomyelitis**

Acute disseminated encephalomyelitis (ADEM) is a monophasic multifocal demyelinating disease of the CNS that primarily affects children. Patients may report antecedent infection, which, along with evidence of antibodies to myelin basic protein, suggests molecular mimicry as
the cause. Patients will often present with an acute multifocal demyelinating event. Alterations of consciousness or seizures are common (rare in MS), along with focal weakness, numbness, or visual field deficits. A wide spectrum of severity exists in ADEM, although many patients may have residual disability from the attack. Patients are treated with immunotherapies, such as corticosteroids, IVIg, or plasmapheresis.

**Neuromyelitis Optica**

Neuromyelitis optica (NMO) is a demyelinating disorder of the CNS characterized by the presence of optic neuritis and transverse myelitis in the same patient with little, if any, evidence for demyelination elsewhere in the CNS. NMO is less common than MS, with an estimated 4000 individuals diagnosed with NMO in the United States versus 400,000 individuals diagnosed with MS. Relapsing NMO is significantly more common in women. Patients with NMO present with optic neuritis, which may be bilateral, and longitudinally extensive transverse myelitis (LETM) that spans more than two segments on spinal MRI (Figure 2). These demyelinating attacks may occur together or may be separated in time. NMO is thought to be an autoimmune disorder associated with antibodies against aquaporin-4. The occurrence of these antibodies in serum is diagnostic for this condition. MRI imaging characteristically does not show a large number of CNS lesions in the brain. More recently, NMO spectrum disorder has been defined as the occurrence of either optic neuritis or LETM in isolation along with the presence of the antibodies against aquaporin-4, or two classic clinical presentations (optic neuritis, LETM, area postrema syndrome) and dissemination in space in the absence of aquaporin-4 antibodies.
Although NMO may be monophasic, most patients follow a relapsing-remitting course.

For acute attacks, IV methylprednisolone or plasmapheresis may be used. For chronic
immunosuppression, there has been success with rituximab, azathioprine, and mycophenolate.
**Granulomatous Disorders**

The granulomatous disorders of the nervous system include sarcoidosis as well as chronic infections such as tuberculosis and leprosy.

**Sarcoidosis**

Sarcoidosis is a systemic granulomatous disorder of unknown etiology. Around 10% of patients with systemic sarcoidosis will develop neurologic complications of the disorder. Of those with neurologic complications, 50% will have a neurologic lesion as their presenting symptom.

Sarcoidosis may affect any part of the nervous system. Common presentations include bilateral facial palsy, other cranial neuropathies, mononeuritis multiplex, or a myopathy. Patients may also present with a myelopathy related to a spinal cord lesion or with symptoms that may be indistinguishable from common neurologic conditions, such as a distal symmetric polyneuropathy, unilateral facial palsy, or median neuropathy. Rarely, patients may present with encephalopathy, chronic meningitis or seizures. The diagnosis of sarcoidosis typically requires a biopsy demonstrating noncaseating granulomas; since the lungs are typically involved in systemic sarcoidosis, the hilar lymph nodes are typically biopsied. Serum angiotensin-converting enzyme levels may also be elevated, but the utility of this test is limited because of poor sensitivity and insufficient specificity. Neurologic evaluation includes lumbar puncture with CSF analysis, which may disclose a mononuclear cell pleocytosis, elevated protein, low glucose, elevated IgG index, and, on occasion, an elevated angiotensin-converting enzyme concentration. Biopsy of the meninges, brain, or spinal cord may occasionally be indicated and may reveal noncaseating granulomas, which establishes the diagnosis of CNS sarcoidosis. Corticosteroids
are the mainstay of treatment, although other steroid-sparing immunosuppressants are usually required.

**Infectious Causes of Granulomas**

Other causes of infectious granulomas, such as tuberculosis will be discussed in the Infectious Disease section of this syllabus.

**Central Nervous System Vasculitis**

Vasculitis of the CNS may present with a wide range of symptoms and signs, depending on which components of the nervous system are involved (Table 3). The underlying pathologic process for this group of disorders is inflammation and destruction of the blood vessels in brain, spinal cord, and peripheral nerves. CNS vasculitis can be divided into two main groups: primary CNS vasculitis, in which CNS blood vessel involvement is a main feature of the disorder; and secondary disorders, in which nervous system involvement is a byproduct of inflammation involving other organ systems. Evaluation of patients with presumed CNS vasculitis typically begins with a search for systemic vasculitis; however, lumbar puncture, head and spine MRI, and potentially a biopsy of the affected tissue may be required to establish a definitive diagnosis.

**Table 3. Classification of Vasculitis Syndromes**

<table>
<thead>
<tr>
<th>Vasculitis</th>
<th>Blood Vessel Involved</th>
<th>Common Neurologic Symptoms</th>
<th>Diagnostic Approach</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary causes of CNS vasculitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>Large and medium vessels</td>
<td>Headaches, vision loss</td>
<td>Temporal artery biopsy</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Disorder</td>
<td>Size of Arteries</td>
<td>Symptoms</td>
<td>Diagnostic Procedures</td>
<td>Treatment</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-----------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-----------------------</td>
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</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Medium-sized</td>
<td>Mononeuritis multiplex, myopathy</td>
<td>Biopsy of affected tissue, ANCA</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Wegener granulomatosis</td>
<td>Small-sized</td>
<td>Mononeuritis multiplex, cranial neuropathies, meningitis</td>
<td>Biopsy of affected tissue, ANCA</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Takayasu arteritis</td>
<td>Large vessel</td>
<td>Vertigo, syncope, headaches, dementia</td>
<td>Angiography</td>
<td>None</td>
</tr>
<tr>
<td>Primary angiitis of the CNS</td>
<td>Small- and medium-sized arteries</td>
<td>Cranial neuropathies, seizures, coma, stroke</td>
<td>Angiography, tissue biopsy</td>
<td>Immunosuppression</td>
</tr>
</tbody>
</table>

**Secondary causes of CNS vasculitis**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Size of Arteries</th>
<th>Symptoms</th>
<th>Diagnostic Procedures</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Small- and medium-sized arteries</td>
<td>Peripheral neuropathy, seizures, cognitive dysfunction, headache, strokes</td>
<td>Clinical pattern, ANA</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>Small- and medium-sized arteries</td>
<td>Sensory neuropathy, optic neuritis, transverse myelitis</td>
<td>Anti-SSA/SSB antibodies, Schirmer test, lip biopsy</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Behçet disease</td>
<td>Small- and medium-sized arteries</td>
<td>Myelopathy, encephalopathy, seizures, cognitive dysfunction</td>
<td>Clinical pattern</td>
<td>Immunosuppression</td>
</tr>
</tbody>
</table>

ANCA = antineutrophil cytoplasmic antibodies; ANA = antinuclear antibodies; CNS = central nervous system; SSA = Sjögren syndrome A; SSB = Sjögren syndrome B.

**Primary Central Nervous System Vasculitis**

The primary CNS vasculitides include giant cell arteritis, polyarteritis nodosa, Wegener granulomatosis, Takayasu arteritis, and primary angiitis of the CNS.
**Giant Cell Arteritis.** Giant cell arteritis is a chronic vasculitis of large and medium vessels. This disorder typically affects individuals over the age of 50 years. The disorder typically presents with visual system disturbances, headaches, or symptoms of polymyalgia rheumatica. Diagnosis is often based on a temporal artery biopsy demonstrating a necrotizing vasculitis in the setting of an elevated erythrocyte sedimentation rate. The temporal artery biopsy has an 85% sensitivity. Corticosteroids are the mainstay of treatment.

**Polyarteritis Nodosa.** Polyarteritis nodosa is a systemic vasculitis affecting medium-sized arteries. It may be associated with hepatitis B and C virus infections. Patients typically exhibit other systemic symptoms, including kidney, skin, joint, and gastrointestinal tract involvement. Neurologically, patients will often present with mononeuritis multiplex; patients may also present with a myopathy. Laboratory investigation includes a positive antinuclear antibodies test as well as a positive assay for antineutrophil cytoplasmic antibodies. A biopsy of affected tissue demonstrating a necrotizing vasculitis is typically required to establish the diagnosis. Treatment relies on immunosuppression.

**Wegener Granulomatosis.** Wegener granulomatosis, or granulomatosis with polyangiitis, is characterized by oral ulceration, pulmonary infiltrates and cavitations, and microscopic hematuria. Neurologic involvement includes mononeuritis multiplex, focal cranial neuropathies, sensorineural hearing loss, and meningitis. This disorder is also associated with antineutrophil cytoplasmic antibodies. Often, a biopsy demonstrating a leukocytoclastic vasculitis is required to diagnosis the disorder. Treatment relies on immunosuppression.

**Takayasu Arteritis.** Takayasu arteritis is a chronic large vessel vasculitis that affects the aorta and its primary branches. It typically affects women between the ages of 10 and 40 years and is more common in those of Asian descent. Patients may have symptoms of fatigue, weight
loss, and fever initially and may develop subclavian steal. Neurologic complications are due to involvement of the carotid and vertebral arteries, resulting in vertigo, syncope, headaches, seizures, and dementia. Angiography can be helpful in diagnosis.

**Primary Angiitis of the Central Nervous System.** Primary angiitis of the CNS is a disorder that primarily affects the small- and medium-sized arteries of the brain. Clinical manifestations can be quite nonspecific and may include cranial neuropathies, seizures, ataxia, and even coma or stroke. Headache is common but nonspecific. The vasculitis is confined to the CNS, and features of a systemic vasculitis are lacking. While this disorder may be variable in presentation, recurrent strokes, cognitive dysfunction with headaches, and abnormal imaging all raise the possibility of primary angiitis of the CNS. CSF studies may show an aseptic meningitis pattern. Conventional catheter angiography demonstrates segmental narrowing of small- and medium-sized blood vessels, referred to as “beading.” A tissue biopsy is often required for diagnosis. Immunosuppressive therapy is the preferred treatment, including glucocorticoids and cyclophosphamide.

**Secondary Causes of Central Nervous System Vasculitis**

The secondary causes of CNS vasculitis include systemic lupus erythematosus, Sjögren syndrome, and Behçet disease.

**Systemic Lupus Erythematous.** Systemic lupus erythematosus is a chronic inflammatory disorder that can affect any organ system. Systemically, patients may have a characteristic rash, arthralgia, or vascular disease. Neurologically, patients may have a peripheral neuropathy, seizures, cognitive dysfunction, headache, or psychosis. Patients are at increased risk
for strokes. Diagnosis requires recognition of the clinical pattern of systemic lupus erythematosus as well as appropriate antibody testing. Treatment requires immunosuppression.

**Sjögren Syndrome.** Sjögren syndrome is an autoimmune condition characterized by dry eyes and mouth. Neurologic complications may be varied. Patients may present with a painful sensory neuropathy that may not be length dependent. In addition, patients may develop optic neuritis, transverse myelitis, or subacute meningitis. Diagnosis includes assaying for antibodies to Ro/SSA and La/SSB. In patients who are seronegative, a Schirmer test to diagnosis dry eyes or a lip biopsy looking for lymphocytic foci may be necessary. A variety of immunosuppressive therapies have been used.

**Behçet Disease.** Behçet disease is a vasculitis that causes oral and genital ulcers. Uveitis is also a common presentation. Neurologic disease occurs in fewer than 10% of patients. Patients may develop focal parenchymal lesions in the brainstem, cerebrum, or spinal cord, which may result in myelopathy, encephalopathy, hemiparesis, seizures, or cognitive dysfunction. Patients may also develop arterial or venous thrombosis, an acute meningeal syndrome, or aneurysms. Diagnosis often relies on recognition of the clinical syndrome. Patients require immunosuppressive therapy.

**Annotated Bibliography**


This review provides additional information regarding neurologic complications of systemic autoimmune diseases. This is an appropriate review for secondary causes of central nervous system vasculitis.

This review focuses on the specific issues encountered during pregnancy with multiple sclerosis and includes information on the risk of relapse both during and after pregnancy as well as the use of disease-modifying therapies during pregnancy.


This review summarizes the available therapies in multiple sclerosis and covers the risks and benefits of each. This is a good overview of the newer disease-modifying therapies.


A number of treatment trials in primary and secondary progressive multiple sclerosis have been conducted. This review nicely summarizes available trial data, including data on symptomatic therapies, exercise, and disease-modifying therapies.

It can be challenging to know what to do when a patient presents with an isolated MRI finding. This study examines the risk of developing multiple sclerosis in the five years following a concerning MRI.


This study includes patients with neuromyelitis optica treated with azathioprine, mycophenolate mofetil, and rituximab and compares the relative efficacy of each drug.


It can be difficult to know how aggressively to treat those patients who present with an isolated clinical syndrome (eg, optic neuritis). This study evaluates what tests may inform the risk of developing multiple sclerosis.


This is a comprehensive review of acute disseminated encephalomyelitis, including diagnosis and management. It also includes information on other acute demyelinating events.

This paper is an excellent review of the diagnostic approach and treatment of neurosarcoïdosis.


This is a consensus article that defines the appropriate diagnostic approach to neuromyelitis optica spectrum disorders and is a good overview of the disease.