Multiple Sclerosis in the Emergency Department

Introduction

Multiple sclerosis (MS) is an immune-mediated process causing impairment to the neurons of the optic nerve, brain, and spinal cord. This leads to central nervous system (CNS) demyelination, chronic inflammation, axonal transections, and scarring, manifesting by clinical signs and symptoms and an abnormal magnetic resonance imaging (MRI).

The signs and symptoms of MS can be nonspecific or can mimic other neurologic entities. One study showed that 26.6% of MS diagnoses were missed on presentation to the ED and took up to a year to diagnose in 18.4%. Prompt and accurate diagnosis of MS is important for early treatment, since early treatment of MS improves neurologic outcomes.

There are five subgroups of MS presentations:

• clinically isolated syndrome (CIS): A self-limited episode that most often is monophasic, lasting at least 24 hours, and most commonly involving the optic nerve or a single area of the brain or the spinal cord;

• relapsing-remitting MS (RRMS): Progressive MS symptoms with periods of improvement or resolution;

• primary progressive MS (PPMS): A continuous decline in MS from the time of an initial diagnosis of MS without relapses;

• secondary progressive MS (SPMS): This occurs only after the RRMS has been present > 10 years, manifested by a chronic decline with fewer relapses;

• progressive (or primary) relapsing MS (PRMS): A rare variant that is a continual decline in MS from the time of an initial diagnosis of MS.

Although these five subgroups are not always clinically useful, especially in the ED, the utility of citing them is to be aware of the variability of MS presentations. The forms of MS that are associated with acute episodes of disability are due to inflammation vs. degeneration in the progressive subtypes. The rate and degree to which patients develop and remain with disability are highly variable. As symptoms decline over time, age is the only predictor for disease progression. Therapies appear to be less beneficial in the older population.

Epidemiology

Approximately 23 million people are diagnosed with MS worldwide. The prevalence of MS in North America is more than 140/100,000, and it is the most common demyelinating disease. MS is more prevalent in women than men, with a 3:1 ratio, and it is most common among Caucasians. A majority of MS cases are found in North America and Europe and are less common closer to the equator. CIS typically occurs between the ages of 20 and 45...
Multiple sclerosis (MS) is an inflammatory and demyelinating disease of the central nervous system. Early diagnosis and treatment are important.

Optic neuritis and bilateral internuclear ophthalmoplegia are important eye findings that are highly correlated with a diagnosis of MS. Therefore, it is important to do a visual field and visual acuity assessment as well as test extraocular movements.

Etiology

The primary etiology of MS has not been established and it is thought to be multifactorial. Risk factors include infections, immunity, genetics, demographics, and environmental influences. The Epstein-Barr virus (EBV) is a strong risk factor for MS. Recurrent episodes of RRMS are caused by recurrent EBV infections. Roseola infantum (human herpesvirus 6) has been associated with an increased risk of MS later in life. A previous history of herpes simplex virus and human endogenous retroviruses has been shown to be associated with MS as well. Many nonviral environmental exposures have been linked to the development of MS. In adults, onset, relapse, and progression are positively affected by sun exposure and vitamin D levels and negatively by smoking. Genetic factors and their relationship to the patient’s environment affect MS risk. Autoimmune diseases share many genetic markers with those of MS, suggesting an overlap between autoimmune diseases and MS.

Pathophysiology

MS can involve the brain, sphincter, visual, pyramidal, brainstem, cerebellar, or sensory pathways. MS occurs in two stages. The first phase is caused by acute inflammatory demyelination, which leads to interruptions within axonal conduction, expressed as flares of symptoms. Six months of persistent demyelination leads to the second phase, which is disability. Disability is a manifestation of a complete loss of axons and mitochondrial dysfunction, which increases the likelihood that these changes are irreversible. This is independent of focal inflammation and can be visualized by MRI. MS signs and symptoms typically present over hours to days and gradually resolve within weeks to months. It can manifest as a lesion of the optic nerve, the brain (including the brainstem, cerebellum, or, less commonly, the cerebrum), and the spinal cord.

Clinical Features

New neurologic complaints consistent with MS develop over hours to days. The typical patient is between 15 and 50 years of age and female. The most common presentations of new-onset MS are numbness or weakness of the extremities, followed closely by visual deficits.

The differential diagnosis for numbness and weakness is broad (see Table 1), but the most specific presentation is an ophthalmologic complaint that presents as unilateral optic neuritis. Patients typically will have acute onset of ocular pain with eye movements (92% of cases), usually followed by decreased vision in the same eye, and absence of visible external eye abnormalities. Most often, symptoms will spontaneously improve over several weeks, and the patient typically will have normal vision in six to 12 months. Optic neuritis presents as diminished visual acuity and pain with extraocular movements from the loss of axonal conduction. This pain typically is unilateral and associated with loss of central vision. Flashing lights represent a hyperexcitable symptom of optic neuritis. Optic neuritis can be seen on MRI approximately six months after the onset of symptoms. When the brainstem or cerebellum is involved, MS will present most often as bilateral internuclear ophthalmoplegia (INO). MS-induced bilateral INO is caused by inflammation and plaques that cause demyelination present at the site of the medial longitudinal fasciculus (MLF) between the third and sixth cranial nerve (CN) nuclei. This leads to a diminished conjugate gaze when looking to either side. The patient senses it as double vision when looking to the right or left. When a lesion of the INO is unilateral, one should consider other diagnoses, such as a stroke. When bilateral INO is present, this is considered to be pathognomonic for MS.

Less common presentations involve the cerebrum, which manifest as deficits of language, spatial orientation, memory, and mood. Spinal cord involvement leads to gait impairment, partial myopathy, Lhermitte sign or phenomenon (electric shocks), paresthesias, erectile dysfunction or urinary urgency or incontinence, and pain of the bladder or bowel.

Although early recognition and diagnosis of a new onset of MS are important, the emergency physician will encounter and manage those with a known diagnosis of MS more often. The patient with known MS who presents with increasing or additional neurologic symptoms could represent a relapse or a pseudorelapse. Clinically, these can be indistinguishable. The difference is the underlying pathophysiology and treatments. An MS relapse, also referred to as a pseudorelapse, is often heralded by a prodrome of symptoms. MS can be treated with medication to relieve symptoms and prevent further exacerbations. It is important to refer patients with MS to their local MS clinic to administer individualized care.
to as a flare, an exacerbation, or an attack, occurs at least one month after a previous MS relapse, and the signs and symptoms will be continuous for at least 12–24 hours or longer. MS relapses are common and unpredictable. They may involve a similar presentation as prior MS episodes or different areas of the nervous system and involve a single symptom 71% of the time. An MS relapse affects an additional area in the CNS, and new lesions appear on MRI. New deficits identified that represent a true relapse should be managed by mitigation of new inflammation. In contrast, a pseudorelapse is when the signs and symptoms result from an exacerbation of an existing area of MS axonal lesions and are intermittent and/ or waxing and waning for a duration less than 24 hours. A pseudorelapse will not reveal MRI findings, and it is triggered by a form of stress. The types of stress include fatigue, exertion, infection and/ or increased body temperature, exposure to elevated external (air) temperature or humidity, and distended bowel or bladder. Treating a pseudorelapse involves treating the underlying stress. A urinary tract infection (UTI) and an upper respiratory infection (URI) are the most common causes. Spinal cord lesions often lead to urinary retention, which increases the risk of a UTI. Up to 30% of patients with MS have oropharyngeal dysphagia as well, placing them at risk for aspiration pneumonia and pneumonitis. Uhthoff’s phenomenon or Uhthoff’s sign is an exacerbation of MS signs or symptoms from exercise or exposure to heat that occurs in 60% to 80% of patients with MS. MS causes a decline in respiration as a result of weak respiratory muscles, bulbar dysfunction, impaired cough, abnormalities of the control of breathing, neurogenic pulmonary edema, and leading to hypercarbia and, less commonly, hypoxia or respiratory arrest.

If the patient has altered mental status or one of the common pain syndromes (chest pain, low back pain, etc.), it is unlikely to represent a pseudorelapse (or a relapse as well), and other non-MS conditions should be considered. If neurologic symptoms are hyperacute (seconds to minutes), non-MS conditions, such as malignancies, autoimmune disorders, fungal infections, tuberculosis, and psychiatric disorders, need to be considered, such as malignancies, autoimmune disorders, fungal infections, tuberculosis, and psychiatric disorders. In addition to the medications listed in Table 2, adjunct medications also can be used. These may include antimuscarinics for bladder dysfunction, antidepressants/ anxiolytics, amantadine for fatigue, muscle relaxants, and stimulant medications to aid with cognitive dysfunction.

<table>
<thead>
<tr>
<th>Table 1. Differential Diagnosis</th>
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<tbody>
<tr>
<td>Vascular</td>
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<tr>
<td>Ischemic stroke, hemorrhagic stroke, transient ischemic attack (TIA), cerebral aneurysm, vertebral/carotid dissection, central venous thrombosis, amaurosis fugax, anemia</td>
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<tr>
<td>Infectious/inflammatory</td>
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<tr>
<td>Severe infection (sepsis), viral encephalitis (including herpes simplex virus [HSV]), bacterial meningitis, Lemierre syndrome, human immunodeficiency virus (HIV), neurosyphilis, systemic lupus erythematosus, polyarteritis nodosa, Lyme disease</td>
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<tr>
<td>Toxicologic/trauamic</td>
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<tr>
<td>Concussion/trumatic brain injury (TBI), neuroparaxia, spinal injury, rhabdomyolysis, ciguatera poisoning, coral snake bite, bark scorpion sting, tick paralysis, botulism, organophosphates, methanol poisoning</td>
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<tr>
<td>Autoimmune</td>
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<tr>
<td>Guillain-Barré syndrome, myasthenia gravis, Lambert-Eaton syndrome, autoimmune encephalitis</td>
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<tr>
<td>Metabolic</td>
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<tr>
<td>Hypoglycemia, hypokalemia, hypocalcemia, vitamin B12 deficiency</td>
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<tr>
<td>Neoplastic</td>
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<tr>
<td>Intracranial tumors, spinal cord tumors, Schwannoma, metastatic lesions</td>
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<tr>
<td>Congenital</td>
</tr>
<tr>
<td>Arnold-Chiari malformation</td>
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<tr>
<td>Degenerative</td>
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<tr>
<td>Diabetic neuropathy, amyotrophic lateral sclerosis (ALS), Huntington’s disease</td>
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<tr>
<td>Endocrine</td>
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<td>Hypothyroidism, hyperthyroidism</td>
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</table>

(In particular, the close mimickers that have a relapsing and remitting course are: neuromyelitis optica, neurosarcoïdosis, central nervous system vasculitis, Susac’s syndrome, CADASIL [cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy], systemic lupus erythematosus, Sjögren’s syndrome, antiphospholipid syndrome, Behcet’s disease, CLIPPERS [chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids], and Leber’s hereditary optic neuropathy.)

Cognitive Effects

MS patients may have an underlying psychiatric condition that may exacerbate or cloud the clinical picture of an MS flare or pseudorelapse. This includes less emotional expression, depression, or involvement in control issues, including abuse or manipulation by family or friends. Cognitive deficits caused by MS influence the expression of disease or ability to cope. Cognition can affect multitasking, performing activities of daily living (ADLs), concentration,
<table>
<thead>
<tr>
<th>Name</th>
<th>Types of MS Treated</th>
<th>Frequency</th>
<th>Most Common Side Effects</th>
<th>Possible Clinical Syndromes</th>
<th>Possible Lab Abnormalities</th>
<th>Rare Life-Threatening Conditions</th>
</tr>
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<tbody>
<tr>
<td><strong>Injectable Medications</strong></td>
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<tr>
<td>Interferon beta-1a (Avonex, Rebif)</td>
<td>CIS, RRMS, SPMS</td>
<td>Avonex: weekly; Rebif: 3 times/week</td>
<td>Headache, flu-like symptoms, injection site symptoms, depression</td>
<td>Psychosis, CHF, TMA, seizures</td>
<td>Transaminitis, decreased cell counts, UTIs</td>
<td>Suicidality, liver failure, anaphylaxis</td>
</tr>
<tr>
<td>Interferon beta-1b (Betaseron, Extavia)</td>
<td>CIS, RRMS, SPMS</td>
<td>Every other day</td>
<td>Flu-like symptoms, headache, injection site reactions (including necrosis), hypertonia</td>
<td>Drug-induced SLE, CHF, TMA</td>
<td>Lymphopenia, transaminitis</td>
<td>Anaphylaxis, fatal capillary leak syndrome</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone, Glatopa)</td>
<td>CIS, RRMS, SPMS</td>
<td>Daily (20 mg) or 3 times/week (40 mg)</td>
<td>Injection site reactions (including lipoatrophy), infection, flushing</td>
<td>Transaminitis</td>
<td></td>
<td>Liver failure</td>
</tr>
<tr>
<td>Ofatumumab (Kesimpta)</td>
<td>CIS, RRMS, SPMS</td>
<td>Monthly</td>
<td>URIIs, flu-like symptoms, injection site reactions, UTIs</td>
<td>Immunosuppression</td>
<td>Reduction in immunoglobulins</td>
<td>PML, hepatic failure (due to hepatitis B)</td>
</tr>
<tr>
<td>Peginterferon beta-1a (Plegridy)</td>
<td>CIS, RRMS, SPMS</td>
<td>Every 2 weeks</td>
<td>Injection site symptoms, flu-like symptoms, headache, pyrexia</td>
<td>CHF, TMA, autoimmune disorders, seizures</td>
<td>Transaminitis, decreased cell counts</td>
<td>Liver failure, anaphylaxis</td>
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<tr>
<td><strong>Oral Medications</strong></td>
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<tr>
<td>Teriflunomide (Aubagio)</td>
<td>CIS, RRMS, SPMS</td>
<td>Daily</td>
<td>Headache, diarrhea, alopecia</td>
<td>Immunosuppression, DRESS, interstitial lung disease</td>
<td>Transaminitis, decreased cell counts</td>
<td>Liver failure</td>
</tr>
<tr>
<td>Monomethyl fumarate (Bafiertam)</td>
<td>CIS, RRMS, SPMS</td>
<td>Twice daily</td>
<td>Flushing, abdominal pain, nausea</td>
<td>Immunosuppression</td>
<td>Transaminitis, lymphopenia</td>
<td>Anaphylaxis, angioedema, PML, opportunistic infections (PJP, disseminated HSV, etc.)</td>
</tr>
<tr>
<td>Dimethyl fumarate (Tecfidera)</td>
<td>CIS, RRMS, SPMS</td>
<td>Twice daily</td>
<td>Flushing, abdominal pain, diarrhea</td>
<td>Immunosuppression</td>
<td>Transaminitis, lymphopenia, eosinophilia</td>
<td>Anaphylaxis, angioedema, PML, fatal opportunistic infections (PJP, disseminated HSV, etc.)</td>
</tr>
<tr>
<td>Fingolimod (Gilenya)</td>
<td>CIS, RRMS, SPMS</td>
<td>Daily</td>
<td>Infections, hypertension</td>
<td>Immunosuppression, bradycardia, AV blocks, QT prolongation, Kaposi’s sarcoma, macular edema, cutaneous malignancies, lymphoma</td>
<td>Lymphopenia, transaminitis</td>
<td>Opportunistic viral, bacteria, and fungal infections, PRES</td>
</tr>
<tr>
<td>Cladribine (Mavenclad)</td>
<td>CIS, RRMS, SPMS</td>
<td>Two separate treatment cycles</td>
<td>URIIs, headache, nausea</td>
<td>Immunosuppression, malignancy, TB, GVHD with blood transfusion, cardiac failure</td>
<td>Lymphopenia, transaminitis, pancytopenia</td>
<td>Opportunistic viral, bacteria, and fungal infections, liver failure (due to direct liver injury or hepatitis), PML (continued)</td>
</tr>
</tbody>
</table>
judgment, as well as processing and memory impairment.⁴⁰,⁴¹

When communicating with MS patients in the ED, provide enough time for the patient to verbalize understanding, allow digestible fragments of information, and provide written summaries of results and plans. MS patients are at a significantly higher risk of developing depression and anxiety.⁴² This likely is the result of a combination of the inflammatory changes of the brain parenchyma as well as the social impact of a disability.⁴³ Depression is more common in men,
which is different from the non-MS population.44 This is exacerbated by the lack of control and uncertainty of the progression of symptoms.46 Depression can reduce compliance with treatments, and many MS medications can exacerbate depression.46 (See Table 2.) There have been multiple proposed screening tools for depression in MS.47 The most practical in the ED is the PHQ-2, since it is simple and efficient. It consists of these two questions.48

1. In the last two weeks, how many days have you had little interest or pleasure in doing things?
2. In the last two weeks, how many days have you felt down, depressed, or hopeless?

The PHQ-2 has an accuracy of 0.84 and a negative predictive value of 0.96.47 This can be a rapid aid in the ED to screen for ongoing depression in MS patients to help guide management, therapy regimens, and disposition decisions.

If a patient presents with complaints of new or worsening psychiatric effects, the etiology usually is multifaceted. Changes in mood could be related to physical deficits and their impact on livelihood. Mood changes can be affected by the medications used to treat MS, as noted in Table 2. Medication reconciliation and review of recent changes in medications should be performed in detail.

Behavioral changes can be a result of frontal lobe plaques inherent to the disease process as well, resulting in a lack of normal verbal inhibitions. New psychiatric symptoms may be a sign of a relapse, even in the absence of physical deficits. Dementia is unlikely to be a contributing factor in MS patients, since MS does not increase the risk of dementia or affect intelligence.49

**Diagnostic Tools**

MS is a clinical diagnosis that requires an array of data and historical factors over time to make. In the history of present illness, elicit the historical neurologic abnormalities that are relevant to the algorithm outlined in the 2017 McDonald criteria.50 (See Table 3.) The 2017 McDonald criteria are not intended to rule out non-MS diagnoses and should not be used by the ED physician to make a final diagnosis.

Alternate diagnoses should be considered as well to ensure a separate phenomenon is not causing the new symptoms (e.g., ischemic stroke, infections, metabolic disturbances). Along with a thorough history and physical exam, obtain a visual field test. A unilateral loss of vision suggests optic neuritis with a scotoma of the central or cecocentral visual field. The monocular vision loss is associated with the presence of relative afferent pupillary defect (RAPD) on exam, otherwise known as a Marcus Gunn pupil. RAPD is elicited by shining a bright flashlight at the unaffected eye in a dark room and swinging the light to the affected eye (with visual loss). In a patient with optic neuritis, this results in a diminished or absent pupillary constriction.

The Lhermitte phenomenon is a relatively unique exam finding of MS that occurs when MS affects the spine. This also is known as the barber chair phenomenon, which is an electric shock-like sensation that occurs in the neck on flexion of the neck. Urinary retention can be seen with a bladder scan. The level of spinal cord involvement determines which symptoms will affect the patient.

MRI is the primary imaging modality that provides diagnostic information by determining a new diagnosis or an exacerbation of MS, or demonstrable progression of chronic MS, and serves to guide treatments.51-53 An MRI is positive in 80% of CIS and is abnormal in nearly 100% of patients with an established diagnosis.54 A spinal MRI is important because almost 50% of patients with a CIS and up to 90% of those with chronic forms of MS have a lesion seen in the spine, usually the cervical spine.55-58 Most commonly, there are foci of abnormalities identified within the white matter, located in the periventricular, infratentorial, or the juxtacortical areas.54

In the ED, obtain a workup that includes a complete blood count, comprehensive metabolic panel, urinalysis, and an electrocardiograph. Check for any signs of neutropenia, lymphopenia, or other signs of immunocompromise. Consider additional testing to evaluate other entities that increase the risk of MS that include a mononucleosis spot test and EBV nuclear antigen immunoglobulin G (IgG) levels.17 Send extra tubes of blood to the lab to add on further possible MS workups, such as myelin-oligodendrocyte glycoprotein (MOG-IgG) antibodies.

When the history, exam, and MRI are not able to provide a clear diagnosis of MS, a lumbar puncture (LP) may be necessary. The cerebrospinal fluid (CSF) in MS demonstrates a normal white blood cell (WBC) count or slight pleocytosis (up to 25 WBCs per cm³), increased protein (under 1 g/L), elevated IgG index, and IgG oligoclonal bands.34 CSF oligoclonal bands are present up to 90% of the time when patients are diagnosed with MS.59

Non-MS-related diagnoses need to be considered. MS is diagnosed incorrectly in up to 10% of cases.60 Common misdiagnoses include fibromyalgia, small vessel cerebrovascular disease, migraine headache, and other functional neurological conditions.60,61

The ED physician should be able to integrate history and clinical exam findings and facilitate further diagnostic studies. Ultimately, a definitive diagnosis of MS should be made by either an MS subspecialist or a neurologist who is familiar with MS diagnostic criteria and treatment.

**Management**

The most common life-threatening problem is sepsis, typically related to respiratory infections or urinary tract infections.62 Less commonly, complications of medical management listed in Table 1 can occur, including anaphylaxis, immunosuppression leading to fatal opportunistic infections, or hepatic failure. The options of treatment include intravenous (IV) steroids, oral steroids, adrenocorticotropic hormone (ACTH), plasma exchange, disease-modifying treatments (DMTs), and nonpharmacologic modalities, such as physical therapy. Treatment for an MS relapse is initially 1,000 mg of methylprednisolone IV or orally daily for three to five days.63 A three-day course has fewer side effects compared to the five-day course. Inform the patient about the side effects of methylprednisolone that include facial flushing, dysgeusia,
The dosing of oral steroids is 25
and appear to be equally as effective as
they are less cumbersome, less expensive,
steroids may be preferred over IV, since
are not inferior to IV steroids for optic
recent evidence that oral corticosteroids
the past for optic neuritis, but there is
have been the standard treatment in
to five days. Intravenous corticosteroids
dexamethasone tablets per day for three
50-mg prednisone tablets or 32 6-mg

Table 3. The 2017 McDonald Criteria for Diagnosis of Multiple Sclerosis in Patients
with an Attack at Onset

<table>
<thead>
<tr>
<th>Number of lesions with objective clinical evidence</th>
<th>Additional data needed for a diagnosis of multiple sclerosis</th>
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<tbody>
<tr>
<td>≥ 2 clinical attacks</td>
<td>None*</td>
</tr>
<tr>
<td>≥ 2 clinical attacks</td>
<td>Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡</td>
</tr>
<tr>
<td>1 clinical attack</td>
<td>Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶</td>
</tr>
<tr>
<td>1 clinical attack</td>
<td>Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶</td>
</tr>
</tbody>
</table>

If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis. An attack is defined in panel 1. *No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (eg, CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered. ‡Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed. †The MRI criteria for dissemination in space are described in panel 5. §The MRI criteria for dissemination in time are described in panel 5. ¶The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

side effects from the injections, which can happen in 17% to 46% of those in their first year of treatment. \textsuperscript{74-76} Oral treatments or parenteral treatments that are given once every two weeks have been shown to be an effective alternative to improve compliance when needle fatigue is present.\textsuperscript{7}

Nonpharmacologic modalities and patient preference of treatment should be based on acceptance and adherence by the patient. Options include exercise, nutritional counseling, psychosocial therapy, occupational therapy, physical therapy, and speech therapy, which have been demonstrated to improve outcomes in MS.\textsuperscript{77-79} This will improve the patient’s overall quality of life by improving the patient’s physical, mental, and social health.\textsuperscript{80} Recommending outdoor activity may be important also because sun exposure has protective effects against MS.\textsuperscript{81,82}

Address modifiable risk behaviors that can reduce the relapse and/or progression of MS that include cessation of cigarette smoking, increased sun exposure, increased exercise, Mediterranean diets, reduced exposure to air pollution, and weight loss in obese patients.\textsuperscript{17}

MS relapses often will improve spontaneously or resolve without medications. Therefore, after a careful discussion with the patient and his/her neurologist, patients may opt to forego initiation or alterations in medications. Shared decision-making is important to deliver good and compliant care.

\section*{Disposition}

Unless the patient otherwise meets inpatient criteria, outpatient management in a patient with an MS relapse is preferred for cost savings, patient wellness, and avoidance of overtreating.\textsuperscript{83}

Inpatient criteria can be considered in patients with suspected new-onset MS. An admission may be indicated to evaluate whether the patient is presenting with MS vs. a non-MS diagnosis, such as a stroke. An MS workup can include MRIs and neurology consultation as well as possible LP for CSF analysis and further laboratory tests. A neurologist will establish the diagnosis of MS.

Outpatient workup can be considered if the patient can follow up soon and demonstrates good compliance, and if urgent outpatient MRI testing and neurology consultation are available. Outpatient treatment of a relapse or a pseudorelapse (e.g., infection) also should include the clinical stability or functional safety of the outpatient setting. Evaluate the patient’s ability to care for himself or herself and the need for IV medications, oxygen, physical therapy, or other inpatient medical interventions that are required. If the patient is stable to be discharged, involve the consultation of a neurologist to assist with an outpatient treatment plan and ensure close outpatient follow-up. When discharging the patient from the ED, make the patient aware of the various treatment options, adverse effects, drug interactions, compliance, identification of treatment failures, evaluation of readiness to initiate treatment, and barriers to treatment, and counsel patients on fertility and reproduction-related concerns.\textsuperscript{23}

\section*{Summary}

MS is a complex disease that often is challenging to diagnose and initiate management in the ED. Patients who have been previously diagnosed with MS often will be knowledgeable about their condition, treatments, and disposition management. Many diagnostic considerations must be weighed when an MS patient presents to the ED, including differentiating between a new-onset presentation of MS, a relapse, and a pseudorelapse, which will guide the workup and disposition. Development of new neurologic signs or symptoms also may be a non-MS problem. Therefore, it is important that the emergency physician performs a careful history and physical exam and is familiar with the various presentations of MS, MS mimics, and conditions that can exacerbate the MS disease course. In addition to good communication, patient counseling and shared decision-making are important aspects of high-quality care. Each presentation will require a thorough evaluation and workup, patient involvement, neurology consultation, and a disposition and management plan that addresses the patient’s unique circumstances. As imaging technology advances, new pharmacologic and non-pharmacologic therapies are developed, and protocols evolve, high-quality outcomes in MS depend on a well-informed emergency physician.

\section*{References}


CME/CE Questions

1. Which of the following is a risk factor for multiple sclerosis (MS)?
   a. Smoking
   b. Cytomegalovirus infection
   c. Sunlight
   d. Air pollution

2. Which of the following is a first-line treatment for MS relapse?
   a. Corticosteroids
   b. Toradol
   c. Plasma exchange
   d. Rehabilitation

3. Which of the following is true regarding oral steroids to treat MS?
   a. They are contraindicated, since only intravenous (IV) steroids are indicated.
   b. They are equally as expensive as IV steroids.
   c. They are more convenient, less expensive, and no less effective in treating MS relapses.
   d. They are more likely to cause gastrointestinal bleeding in MS patients compared to other populations.

4. Patients with MS are particularly prone to which of the following infections?
   a. Urinary and respiratory tract
   b. Central nervous system
   c. Biliary tract
   d. Gastrointestinal tract

5. Patients with optic neuritis present with which type of pain?
   a. Only in the dark
   b. With extraocular movement
   c. When reading
   d. When there is light pressure applied to the eye

6. Which of the following is true of pseudorelapsing MS?
   a. It occurs when the patient imagines new symptoms.
   b. It is always caused by depression.
   c. It can be caused by exposure to hot conditions.
   d. It is brought on by bed rest.

7. Which laboratory abnormalities should be expected during treatment with disease-modifying treatments?
   a. Decreased leukocyte count
   b. Lipase elevation
   c. Creatinine elevation
   d. Proteinuria

CME/CE Objectives

Upon completion of this educational activity, participants should be able to:

- recognize specific conditions in patients presenting to the emergency department;
- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both the likely and rare complications that may be associated with the particular medical problems discussed in the publication.
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Medication Side Effects

<table>
<thead>
<tr>
<th>Name</th>
<th>Medication</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS, RlMS</td>
<td>Beta-1b (Avonex)</td>
<td>Headache, injection site reactions (including nevirosis), hypertension Drug-induced SLE, CHF, TMA</td>
</tr>
<tr>
<td>CIS, RlMS</td>
<td>Beta-1a (Plegridy)</td>
<td>Headache, injection site reactions (including nevirosis), hypertension Drug-induced SLE, CHF, TMA</td>
</tr>
<tr>
<td>CIS, RlMS</td>
<td>Fingolimod (Gilenya)</td>
<td>Headache, injection site reactions (including nevirosis), hypertension Drug-induced SLE, CHF, TMA</td>
</tr>
<tr>
<td>CIS, RlMS</td>
<td>Ofatumumab (Mavenclad)</td>
<td>Headache, injection site reactions (including nevirosis), hypertension Drug-induced SLE, CHF, TMA</td>
</tr>
</tbody>
</table>

Multiple Sclerosis in the Emergency Department

EMERGENCY MEDICINE REPORTS

The 2017 McDonald Criteria for Diagnosis of Multiple Sclerosis in Patients with an Attack at Onset

<table>
<thead>
<tr>
<th>Number of lesions with objective clinical evidence</th>
<th>Additional data needed for a diagnosis of multiple sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2 clinical attacks</td>
<td>≥ 2</td>
</tr>
<tr>
<td>≥ 2 clinical attacks</td>
<td>(as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location)</td>
</tr>
<tr>
<td>≥ 2 clinical attacks</td>
<td>≥ 2</td>
</tr>
<tr>
<td>≥ 2 clinical attacks</td>
<td>Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI</td>
</tr>
<tr>
<td>≥ 1 clinical attacks</td>
<td>≥ 2</td>
</tr>
<tr>
<td>≥ 1 clinical attacks</td>
<td>Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands</td>
</tr>
<tr>
<td>≥ 1 clinical attacks</td>
<td>≥ 2</td>
</tr>
<tr>
<td>≥ 1 clinical attacks</td>
<td>Dissemination in time demonstrated by an additional clinical attack implicating a different CNS site or by MRI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threatening</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Remote</td>
</tr>
<tr>
<td>Life-Threatening</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very Rare</td>
</tr>
<tr>
<td>Life-Threatening</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Possible Lab Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia, pancytopenia</td>
</tr>
<tr>
<td>Pneumonia, disseminated HSV</td>
</tr>
<tr>
<td>Angioedema, PLE, opportunistic infections (PSLE, disseminated HSV, etc.)</td>
</tr>
<tr>
<td>Anaphylaxis, angioedema, PLE, opportunistic infections (PSLE, disseminated HSV, etc.)</td>
</tr>
<tr>
<td>Opportunistic infections, bowel failure due to direct liver injury (or hepatitis), PNA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusive to our subscribers</th>
<th>RAPID ACCESS MANAGEMENT GUIDELINES</th>
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</table>
### Medication Side Effects (continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Types of MS Treated</th>
<th>Frequency</th>
<th>Most Common Side Effects</th>
<th>Possible Clinical Syndromes</th>
<th>Possible Lab Abnormalities</th>
<th>Rare Life-Threatening Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Medications</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Siponumod (Mayzent)</td>
<td>CS, RRMS, SPMS</td>
<td>Daily</td>
<td>Headache, hypertension</td>
<td>Immunosuppression, bradycardia, AV blocks, QT prolongation, maculopapular malar rash, PRES</td>
<td>Lymphopenia, transaminitis</td>
<td>Opportunistic viral, bacteria, and fungal infections, PML</td>
</tr>
<tr>
<td>Ponemixon (Ponvory)</td>
<td>CS, RRMS, SPMS</td>
<td>Daily</td>
<td>Headache, hypertension</td>
<td>Immunosuppression, bradycardia, AV blocks, QT prolongation, maculopapular edema, cutaneous malar rash</td>
<td>Lymphopenia, transaminitis</td>
<td>Opportunistic viral, bacteria, and fungal infections, PML</td>
</tr>
<tr>
<td>Droxemol fumarate (Tovumeta)</td>
<td>CS, RRMS, SPMS</td>
<td>Twice daily</td>
<td>Flushing, abdominal pain, diarrhea</td>
<td>Immunosuppression</td>
<td>Lymphopenia, transaminitis</td>
<td>Anaphylaxis, angioedema, PML, fatal opportunistic infections (PJP, disseminated HSV, etc.)</td>
</tr>
<tr>
<td>Ozaramol (Zeprosia)</td>
<td>CS, RRMS, SPMS</td>
<td>Daily</td>
<td>URTI, oral, alopecia, UTI, back pain</td>
<td>Bradypnea, hypotension, decreased pulmonary function, maculopapular rash</td>
<td>Transaminitis</td>
<td>Opportunistic viral, bacteria, and fungal infections, PML</td>
</tr>
<tr>
<td><strong>Intravenous Medications</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Alemtuzumab (Lemtrada)</td>
<td>RRMS, PMS</td>
<td>Twice treatment courses, each every 5 consecutive months</td>
<td>Rash, headache, pyrexia, nausea, URTI</td>
<td>Immune Thrombocytopenia, glomerulonephropathy, thyroid disorders, TTP, hemophilia</td>
<td>Transaminitis, decreased cell counts</td>
<td>Opportunistic viral, bacteria, and fungal infections, PML</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone)</td>
<td>RRMS, PMS</td>
<td>Every 3 months</td>
<td>Neutropenia, alopecia, depression</td>
<td>CHF, meninatal disorders including stroke, leukaemia</td>
<td>Leukaemia</td>
<td>Secondary AML, opportunistic infections</td>
</tr>
<tr>
<td>Ocrelizumab (Dovero)</td>
<td>PPS, CS, CS, RRMS</td>
<td>Every 6 months</td>
<td>Transfusion reaction</td>
<td>Herpetiform infections, fever, pernicious anaemia, breast cancer</td>
<td>Reduction in immunoglobulin levels</td>
<td>Disseminated herpes, herpes encephalitis, PML</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>CS, RRMS, SPMS</td>
<td>Every 4 weeks</td>
<td>Headache, fatigue, arthralgias</td>
<td>Immunosuppression, Transaminitis, thrombocytopenia, Herpes encephalitis</td>
<td>Transaminitis, liver failure, encephalitis, PML</td>
<td></td>
</tr>
</tbody>
</table>


### Differential Diagnosis

**Vascular**
- Ischemic stroke, hemorrhagic stroke, transient ischemic attack (TIA), cerebral aneurysm, vertebral/carotid dissection, central venous thrombosis, amniotic fluid embolism, amebiasis

**Infectious/inflammatory**
- Severe infection (sepsis), viral encephalitis (including herpes simplex virus [HSV]), bacterial meningitis, Lyme disease syphilis, systemic lupus erythematosus, polyarteritis nodosa, Lyme disease

**Toxicologic/traumatic**
- Concussion/traumatic brain injury (TBI), herpes zoster, herpetic encephalitis, PML, Guillain-Barre syndrome, myasthenia gravis, Lambert-Eaton syndrome

**Autoimmune**
- Guillain-Barre syndrome, myasthenia gravis, Lambert-Eaton syndrome, autoimmune encephalitis

**Metabolic**
- Hypoglycemia, hypokalemia, hypocalcemia, vitamin B12 deficiency

**Degenerative**
- Neoplastic
  - Intracranial tumors, spinal cord tumors, Schwannomas, metatropic lesions

**Congenital**
- Arnold-Chiari malformation

**Neonatal**
- Intracranial tumors, spinal cord tumors, Schwannomas, metatropic lesions

**Endocrine**
- Hypothyroidism, hyperthyroidism

*Supplement to Emergency Medicine Reports, September 15, 2021. “Multiple Sclerosis in the Emergency Department.”* Authors: Jay Bernstein, MD, MPH, MS, FACEP, Assistant Professor, Department of Emergency Medicine, Wright State University, Dayton, OH; Shannon Lyon, MD, Emergency Medicine Resident, Wright State University, Dayton, OH, and Rachel Tabibzadeh, University of Maryland, College Park.

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