Multiple Sclerosis

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INTRODUCTION

Multiple sclerosis (MS) is a T-cell mediated autoimmune disease triggered by unknown exogenous agents (e.g., viruses, bacteria) in individuals with a specific genetic background. The disease can produce various combinations of symptoms and neurologic signs that reflect the location of a lesion or lesions in different areas of the brain, spinal cord, and optic nerves. Historically, MS was considered to be a disease of the brain white matter, but recent data suggest that primary involvement of gray matter is also quite prevalent in the disease.1

MS is the most common neurologic condition affecting young adults in their most productive years. Onset typically is in the third or fourth decade of life but in 5% of patients can be as early as 8 or as late as 70 years of age. As with most autoimmune illnesses, females are affected more often than males. Between 8000 and 10,000 new cases of MS are diagnosed each year in the United States, with an incidence ranging from 1 in 1500 people in the Southwest to 1 in 750 in the Pacific Northwest. The overall prevalence of MS in the United States is considered to be 400,000 to 500,000 patients; worldwide, MS prevalence is estimated to be close to 2.5 million people.2 Prevalence varies between areas of high, medium, and low risk, with MS being more prevalent in populations located further north from the equator in the Northern Hemisphere and further south from the equator in the Southern Hemisphere. Reasons for this distribution are unknown, although there are data supporting variable geographic distribution of genetically susceptible populations and possible environmental factors.3

MS is the most common of several demyelinating disorders. The others include acute disseminated encephalomyelitis (ADEM), neuromyelitis optica (NMO, or Devic’s disease), Marburg variant of MS, Schilder’s disease, and Balo’s concentric sclerosis. ADEM often responds to high-dose steroid treatment and tends to be monophasic, with good resolution of the neurologic deficit.

NMO/Devic’s disease is a recurrent or monophasic inflammatory demyelinating illness affecting the optic nerves (bilateral optic neuritis) and spinal cord (myelitis).4,5 Resolution of the neurologic deficit tends to be incomplete, clinical response to MS treatment (immunomodulatory medications) ineffective, and progression of disability rapid. Immunosuppressive agents and plasma exchange are sometimes effective in treatment of Devic’s disease. A recently discovered serum antibody, NMO-IgG, is 70% sensitive but nearly 100% specific for Devic’s disease diagnosis.6

Marburg variant of MS is an acute, aggressive, and rapidly progressive form of MS, which is poorly responsive to treatment. Schilder’s disease is a rare, progressive demyelinating disorder that begins in childhood and is characterized by dementia, aphasia, seizures, personality changes, poor attention, tremors, balance instability, incontinence, and muscle weakness. Schilder’s disease responds poorly to treatment and is generally characterized by a progressive, disabling course.7

Balo’s concentric sclerosis is a rare variant of MS pathologically characterized by alternating rings of demyelination and spared myelin. The clinical course of Balo’s concentric sclerosis was considered similar to that of Marburg variant of MS, and most reported cases have involved young adults and resulted in death within weeks to months. Recently, an increasing number of cases have been described as having prolonged survival or spontaneous remission. The most commonly reported clinical manifestations are headache, aphasia, cognitive or behavioral dysfunction, and/or seizures. Cerebrospinal fluid (CSF) studies often reveal a mononuclear inflammatory reaction and occasionally oligoclonal bands.8

This review presents 6 cases encompassing a range of clinical presentations of MS, MS subtypes, differential diagnosis, treatment options, and prognosis. We will also consider an algorithm for clinical decision making in cases of patients who present with MS.
CASE 1 PRESENTATION

A 32-year-old previously healthy man presents for evaluation of acute numbness that began in both feet, ascended up the legs over 4 days, and by the end of the week involved the trunk to the level of the nipples. The patient reports that he has also experienced mild urinary urgency. He denies any abnormality of bowel function, arm symptoms, or headache. The history is negative for preceding systemic infection or pertinent travel. Neurologic examination reveals normal strength in all 4 extremities. There is hyperreflexia in the left patellar and left Achilles tendons to 3+/4+. Babinski sign is positive bilaterally. There is decreased vibratory sense in both feet. There is spinal sensory level at T4 to temperature and pain.

- What is the differential diagnosis for this patient’s symptoms?

The differential diagnosis for the symptoms described in this case includes idiopathic autoimmune transverse myelitis, ADEM (postinfectious or postimmunization), viral myelitis, MS, vasculitis from systemic autoimmune disease, spinal cord infarction, paraneoplastic myelopathy, other infections (eg, Lyme disease, syphilis, human T-cell lymphotropic virus type 1 [HTLV-1] infection), vitamin B₁₂ deficiency (subacute combined degeneration of the spinal cord), other metabolic abnormalities, sarcoidosis, vascular malformations, and spinal cord compression due to tumor or trauma. In particular, this patient’s clinical history fits very well with the diagnosis of transverse myelitis. Transverse myelitis is a syndrome of acute inflammation of the spinal cord that can affect any age-group and both sexes. It typically produces weakness, numbness, and bowel or bladder dysfunction. Most cases are related to inflammation and demyelination in the spinal cord, but some can be a direct result of viral infection, a direct or indirect effect of cancer, or due to other causes. Typical clinical features include subacute onset of ascending sensory symptoms, often followed by paraparesis or paraplegia with variable loss of bowel or bladder control. The midthoracic region is the most common site of involvement; therefore, arms are usually spared. In 20% of patients, the cervical spinal cord is affected, resulting in symptoms in both upper and lower extremities. Back pain may be variably present.

Table 1. Predicting Risk of Conversion from CIS to MS

<table>
<thead>
<tr>
<th>No. of MRI Lesions</th>
<th>Patients, n</th>
<th>Progression to CDMS, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>27</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>2–3</td>
<td>16</td>
<td>14 (87%)</td>
</tr>
<tr>
<td>4–10</td>
<td>15</td>
<td>13 (87%)</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>20</td>
<td>17 (85%)</td>
</tr>
</tbody>
</table>

NOTE: Brain magnetic resonance imaging (MRI) in clinically isolated syndrome (CIS) predicts long-term risk of clinically definite MS (CDMS). In this study, only 11% of patients with normal brain MRI scans at the time of CIS developed CDMS at 5 to 10 years of follow-up, whereas more than 80% of patients with 2 or more brain lesions developed CDMS within the same time interval. (Adapted with permission from O’Riordan JI. Thompson AJ. Kingsley DP, et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS: a 10-year follow-up. Brain 1998;121:498.)

- Is it common for MS to present as transverse myelitis?
- What is the risk of developing MS after an episode of transverse myelitis?

MS often presents for the first time as an episode of neurologic dysfunction indicating an inflammatory/demyelinating lesion in the optic nerve (optic neuritis), brain stem/cerebellum (acute brain stem syndrome), or spinal cord (transverse myelitis). Characteristically, spinal cord involvement that is due to demyelination is partial, affecting less than two thirds of the diameter of the cord. This initial episode of neurologic dysfunction is known as clinically isolated syndrome (CIS). However, not all patients who present with CIS as described in the case patient go on to develop clinically definite MS (CDMS). The risk of conversion to CDMS is lower after acute complete transverse myelitis and greater in individuals with partial myelitis. In 1 study, 85% of MS patients experienced at least 1 attack of partial transverse myelitis during the course of their illness. Studies suggest that the risk of conversion to MS after an episode of complete motor and sensory loss below the level of the lesion is less than 5% over 5 to 40 years of follow-up. The rate of developing CDMS following partial myelitis is much greater and was reported to be between 25% and 80%.

The presence and number of characteristic brain lesions on magnetic resonance imaging (MRI) suggestive of inflammatory disease at the time of CIS appears to be predictive of future development of CDMS (Table 1, Figure 1). The most important finding is the presence of clinically silent T2 hyperintense lesions on brain MRI following an episode of transverse myelitis, with the higher number of brain MRI lesions...
Multiple Sclerosis

Initial presentation/CIS diagnosis/work-up initiated

- Somatosensory, visual, brainstem evoked potentials
- MRI of brain and cervical/thoracic spine
- CSF analysis for oligoclonal bands, IgG index, IgG synthesis rate, MBP degradation products
- Blood work to rule out MS mimic syndromes

Does patient satisfy diagnosis of MS by McDonald criteria?

Yes

- PPMS
  - No therapy
  - Monthly steroids
  - Consider immunosuppressants (oral or IV)

- RRMS
  - Immunomodulators

- CIS
  - New MRI lesions, change on neurologic exam, new exacerbation
  - 6 mo

  - Low probability for converting to MS or no change

  - Follow-up with CNS and clinical exams (every 6 mo for 1 yr, then every yr); no treatment unless patient converts to MS

No

- Another diagnosis?
  - SLE
  - Sarcoidosis
  - Sjogren’s
  - Lyme
  - B12 deficiency

- No therapy
- Monthly steroids
- Consider immunosuppressants (oral or IV)

Figure 1. Clinical decision making in multiple sclerosis (MS). When a patient initially presents with a neurologic complaint (optic neuritis, myelitis, brainstem syndrome, hemiparesis) and a diagnosis of clinically isolated syndrome (CIS) is made, a formal diagnosis of MS must be sought. If a patient fulfills McDonald criteria for the diagnosis of MS following appropriate work-up, treatment considerations are important. For relapsing-remitting MS (RRMS), immunomodulatory therapy should be discussed with the patient. For patients presenting with chronic progression of neurologic symptoms who receive a diagnosis of primary progressive MS (PPMS), supportive and symptomatic therapy can be of value. Alternatively, chemotherapeutic options can also be discussed and tried in selected cases. If a patient does not fit the diagnostic criteria for MS and does not have an alternative diagnosis to explain neurologic symptoms, frequent follow-up with clinical neurologic examinations and magnetic resonance imaging (MRI) is warranted until the patient demonstrates changes consistent with clinically definite MS (CDMS). In selected cases, treatment with immunomodulatory agents can be initiated for patients with CIS if the index of suspicion for impending conversion to CDMS is high. Patients initially seen in secondary progressive disease stage (SPMS) or who convert to this stage with time should be offered chemotherapy as a treatment option. This is best administered via specialized MS centers or oncology offices under the supervision of an MS specialist. CNS = central nervous system; IV = intravenous MBP = myelin basic protein; SLE = systemic lupus erythematosus.

signifying the greater risk of conversion to CDMS. Early treatment with immunomodulatory agents (interferon beta-1a, interferon beta-1b, glatiramer acetate) has been shown to delay conversion from CIS to CDMS in patients presenting with transverse myelitis, optic neuritis, or a brain stem syndrome as their first event.

- What additional tests are important to perform in this patient?

CSF analysis may help to differentiate an acutely inflammatory or infectious condition from MS. If oligoclonal bands are present in the spinal fluid and myelin basic protein degradation products and IgG index are increased, this indicates a higher likelihood of demyelinating disease in the appropriate clinical setting. In a prospective study of 183 patients with monosymptomatic suspected MS, the presence of oligoclonal bands in the CSF was associated with a 24% conversion rate to MS within the follow-up period of 34 months, while only 9% of patients without oligoclonal bands in the CSF developed MS during the same period

Visual evoked responses help to assess for possible previous damage to the optic nerves. A battery of blood tests is generally sent on each new patient presenting with CIS to rule out alternative conditions in the differential diagnosis. Although no standardized blood test panels exist, tests performed at our MS center for new patients presenting with partial transverse myelitis include vitamin B12 levels, angiotensin-converting enzyme levels, antinuclear antibody titers, Lyme titer, and HTLV-I serology.

MRI of the brain and a full MRI of the spine should be performed. In a study by Brex et al, patients with CIS and a single lesion on MRI had a 98% risk of MS at 14 years, with 88% going on to have a second attack and 10% having another new lesion on MRI characteristic of MS, thus satisfying the McDonald criteria for the diagnosis of CDMS (Table 2).
CASE 1 CONTINUED

MRI of the spine shows 2 well-defined lesions at the C5 and T4 segments involving less than 50% of the cord diameter. The lesions do not extend beyond 1 spinal segment each. The T4 lesion shows gadolinium contrast enhancement on T1 sequences. CSF analysis is unremarkable.

- What further information about MS is provided by various neuroimaging techniques and different MRI sequences?

T1 gadolinium-enhancing lesions demonstrate blood-brain barrier leakage, inflammatory disturbances, and recent (<8 weeks) activity with new lesion formation. The histopathologic correlate of a T1 gadolinium-enhancing lesion is a breakdown of the blood-brain barrier, edema, and infiltration of macrophages and lymphocytes into the tissue with active myelin stripping and axonal transection. T1 hypointense lesions (black holes) reflect more severe tissue pathology; they correlate with axonal loss and clinical disability. T2 hyperintense lesions and FLAIR (fluid-attenuated inversion recovery) lesions provide information regarding total disease burden, including reversible and irreversible pathology. In early MS and in CIS, these are most predictive of subsequent disease course.

Adequate assessment of atrophy is possible via several MRI sequences. Atrophy is detectable in both the brain and spinal cord of MS patients. It correlates with axonal loss, neuronal loss, and neurologic disability.\(^1,2\) Central atrophy (estimated by measuring the third ventricular width) correlates well with cognitive impairment and physical disability.\(^21,22\)

N-acetyl aspartate (NAA), a marker of neuronal and axonal metabolism, can be reliably and noninvasively measured via MR spectroscopy. NAA is decreased in MS lesions and in normal-appearing white matter in brains of MS patients.\(^23\) Demyelinating lesions in the gray matter of cerebral cortex have also been described in MS.\(^24\)

Magnetization transfer imaging (or ratio) indicates more severe lesions with tissue destruction.\(^25\) It is also abnormal within lesions and normal-appearing central nervous system (CNS) tissue. Functional MRI (fMRI), a research technique that uses changes in blood oxygenation level–dependent MR signals during performance of tasks as a surrogate for changes in neuronal and synaptic activity, may potentially improve delineation of critical brain systems involved in response to injury and loss and recovery of functions.\(^26\)

Table 2. McDonald Diagnostic Criteria for MS

<table>
<thead>
<tr>
<th>Disease Episodes</th>
<th>Objective Lesions</th>
<th>Additional Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or more</td>
<td>2 or more</td>
<td>None; additional evidence must be consistent with MS</td>
</tr>
<tr>
<td>2 or more</td>
<td>1</td>
<td>Dissemination in space by MRI OR +CSF AND 2 or more MRI lesions consistent with MS, OR another attack involving different site</td>
</tr>
<tr>
<td>1</td>
<td>2 or more</td>
<td>Dissemination in time by MRI OR another clinical attack</td>
</tr>
<tr>
<td>1 (CIS)</td>
<td>1</td>
<td>Dissemination in space AND time by MRI, OR another attack, OR MRI space dissemination AND +CSF</td>
</tr>
<tr>
<td>0 (progressive from onset)</td>
<td>1</td>
<td>+CSF AND specific MRI dissemination in space criteria AND MRI dissemination in time OR continuous progression for 1 year</td>
</tr>
</tbody>
</table>

NOTE: The McDonald criteria were established with a cohort of patients with clinically isolated syndrome (CIS) and showed a sensitivity of 83% at 1 year and a specificity of 83% at 3 years. CSF = cerebrospinal fluid; MRI = magnetic resonance imaging. (Adapted from McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:124, with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

CLINICALLY DEFINITE MULTIPLE SCLEROSIS/OPTIC NEURITIS

CASE 2 PRESENTATION

A 27-year-old previously healthy woman presents for neurologic evaluation. She reports that 3 days ago she awoke with right-sided head pain and a sensation of cloudy vision in her right eye. She also experienced mild pain on moving her right eye. Visual blurring progressed over the course of 3 days. At the time of this visit, the patient reports being able to see shapes of large objects only. She cannot distinguish colors on the right side.

Upon further questioning, the patient admits to an episode of left leg numbness 2 years prior to this visit. The numbness was fairly pronounced, started distally in the left foot, and ascended up to the level of the umbilicus on the left side. She may have had a mild limp on the left side as well. There was no associated bladder or bowel dysfunction. Symptoms lasted less than 1 week and subsided completely. The patient attributed the symptoms to a sports injury and did not seek medical attention. There is no family history of neurologic disease. No other significant pertinent historic information is available.
On neurologic examination, there is an afferent pupillary defect on the right. The remainder of the neurologic examination is significant only for mildly increased muscle tone and an up-going planter response in the left leg.

MRI shows 3 T2 sequence hyperintense lesions in the brain and a small intramedullary lesion in the thoracic spinal cord, at the T3–T4 segment.

- **What is the differential diagnosis for unilateral loss of vision in a young patient?**

Various disorders may cause unilateral loss of vision with or without eye pain. In a patient younger than 45 years without previous medical history or with a previous history of another neurologic event, optic neuritis is the primary diagnostic consideration.

Optic neuritis is a group of disorders that have in common inflammation and, often, demyelination of the optic nerve, resulting in a unilateral decrease or loss of vision. It can occur as an isolated event (idiopathic or monosymptomatic optic neuritis) or as a manifestation of MS. A feature that is typical for optic neuritis is a sudden or subacute (< 2 weeks) unilateral loss of vision; patients complain of dimness, decreased brightness of colors on the affected side, and patchy areas of complete loss of vision (particularly common in the center of the visual field [scotomas]), associated with variably dull or achy pain on eye movements with or without a headache. Clinical features that are less typical include positive visual phenomena and absence of color changes (possible retinal disease), macropsia or micropsia (possible macular disease), and progression of visual loss beyond 2 weeks without clinical improvement after 2 months (compressive or infiltrative optic neuropathy such as granulomatous disease [sarcoidosis], tumors [glioma, lymphoma], or chronic infection [fungal]). Mitochondrial disease (Leber’s hereditary optic neuropathy) and vascular disease also need to be considered.

Of note in this case, the patient presents with an afferent pupillary defect, which is identified by shining a direct beam of light sequentially into each eye and observing pupillary dilation instead of expected constriction on the affected side. Afferent pupillary defect is often seen after optic neuritis and may persist for many years, even after complete visual recovery.

- **What diagnostic tests can be performed to support the diagnosis of optic neuritis?**

 Neuro-ophthalmologic evaluation including a dilated eye examination, visual acuity testing, red color desaturation test, and visual fields testing are most helpful in acute disease. MRI of the brain or a dedicated MRI of the orbits with gadolinium contrast should be performed. Frequently, acute inflammatory optic neuritis is associated with gadolinium contrast uptake by an optic nerve on T1 post-contrast sequences. Evaluating the orbits for possible infiltrative or neoplastic disease is important in cases of unusual clinical presentations. In addition, brain MRI and cervical spine MRI are important tools in assessing a patient’s risk for a CNS inflammatory demyelinating disease such as MS.

- **Does this patient have MS? What criteria are used to diagnose MS?**

This patient fulfills the McDonald criteria for the diagnosis of MS (Table 2). She has a history of 2 episodes of neurologic dysfunction, separated in time (years) and space (spinal cord and optic nerve). She has evidence of physical impairment of at least 2 neurologic subsystems (pyramidal tract and visual pathway). Under these circumstances, the diagnosis of MS is established based on clinical grounds (Table 3) and characteristic MRI scan appearance (Figure 2), assuming that the remaining work-up fails to provide an alternative explanation for her symptoms.

Prior to 2001, the Poser criteria for diagnosis of MS were used. These criteria relied on clinical evidence of 2 relapses, with or without objective evidence of CNS disease, with or without supportive laboratory evidence. MRI data were not included in the criteria but could provide paraclinical evidence of disease.

The McDonald criteria were established in 2001. They preserve the traditional clinical diagnostic criterion of 2 episodes of disease separated in space and time. They also state that there must be no better explanation for the patient’s symptoms and add specific MRI criteria, including MRI hyperintensities to support the clinical diagnosis of MS.
CSF findings, and analysis of visual evoked potentials as a means of identifying the second episode. In 2005, revised McDonald criteria were published, which rely more heavily on MRI. Only 2 MRI scans are now required to evaluate disease progression; detection of a new gadolinium-enhancing lesion within 3 months of the baseline scan or detection of a new T2 lesion at any time beyond 30 days of the baseline scan now qualifies for dissemination in time criterion.

- What is the rationale for intravenous steroid treatment in patients with optic neuritis?

The Optic Neuritis Treatment Trial (ONTT) was a prospective study designed to address visual outcomes in patients with optic neuritis treated with corticosteroids. Study participants were randomized to either 1 g/day of intravenous methylprednisolone (IVMP) for 3 days followed by oral prednisolone for 11 days or to 1 mg/kg/day of oral prednisolone for 14 days or to placebo for 14 days. IVMP treatment resulted in hastened visual recovery but had no significant effect on the degree of improvement of visual function. In addition, the group of patients receiving IVMP showed delayed
occurrence of a second clinical event, diagnostic of MS; only 7.5% of IVMP-treated patients converted to CDMS over 2 years compared with 15% of oral prednisolone-treated patients and 17% of patients receiving placebo. This beneficial effect of IVMP treatment was lost within 5 years of the acute optic neuritis episode, when approximately one third of all patients from the original ONTT converted to MS. The risk of developing MS after optic neuritis, as after any other CIS, seems to be related to the number of T2 hyperintense lesions in the white matter of the brain at the time of the diagnosis; a higher number of lesions indicates greater probability of CDMS over time (Table 1).

• What are the possible clinical courses for MS?

Four distinct disease subtypes are defined within MS. Relapsing-remitting MS, characterized by clearly defined relapses of neurologic deficit, is the most common variant of MS and is diagnosed in approximately two thirds of patients on initial presentation. Either complete recovery or residual disability may be observed after each relapse.

Less than 10% of patients present with primary progressive MS, a disease subtype characterized by disease progression from the onset, with occasional plateaus and minor improvements possible. There are no exacerbations. Primary progressive MS does not respond to immunomodulatory medications used to treat relapsing-remitting disease type.

Over time (10–25 years), 75% to 89% of patients with relapsing-remitting disease convert to secondary progressive MS. While rare exacerbations of neurologic deficit remain possible in this disease type, it is characterized in most patients by chronic and relentless progression of disability, over time leading to the need for assistive ambulation devices and eventually a wheelchair. Muscle weakness, spasticity, ataxia, and loss of sensory modalities are typical at this stage. Few patients, however, may remain ambulatory for extended periods of time.

Finally, progressive relapsing MS is characterized by disease progression from the onset but with superimposed occasional relapses. It differs from relapsing-remitting disease type with incomplete recovery by manifesting as clearly identifiable disability progression from the onset.

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### RELAPSING-REMITTING MULTIPLE SCLEROSIS

#### CASE 3 PRESENTATION

A 32-year-old woman with a recent diagnosis of relapsing-remitting MS presents for discussion of treatment options. She has had 3 relapses over the last 12 months. Her MRI scan and CSF examination are consistent with inflammatory/demyelinating CNS disease. She wants to know what drugs are available for her and how they work. She also wants to know whether taking these drugs will be beneficial for her over the duration of her illness.

• What treatments are available for MS, and what are the goals of therapy?

There are 2 classes of disease-modifying medications for treatment of MS: immunomodulators and immunosuppressants. The treatment goal is to alter the natural course of the disease by decreasing relapses, decreasing MRI disease burden, and delaying disability progression. Immunomodulators currently available for treatment of relapsing-remitting MS are shown in Table 4. Interferons are believed to exert their actions through several mechanisms. These include an

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### Table 4. Immunomodulatory Agents Available for Treatment of Relapsing-Remitting MS

<table>
<thead>
<tr>
<th>Type/Agent</th>
<th>Indication(s)</th>
<th>Relapse Rate Reduction</th>
<th>Side Effects</th>
<th>MRI Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recombinant protein</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INF beta-1a</td>
<td>Reduce relapse frequency Slow accumulation of disability</td>
<td>20% annualized</td>
<td>Flu-like symptoms, liver function test elevation, anemia, neurogenic injection-site reactions</td>
<td>Reduce new T2 lesion formation, new enhancing lesions, and rate of atrophy</td>
</tr>
<tr>
<td>INF beta-1a, high dose</td>
<td>Same as INF beta-1a</td>
<td>27%–33% over 2 yr</td>
<td>Same as INF beta-1a</td>
<td>Same as INF beta-1a</td>
</tr>
<tr>
<td>INF beta-1b</td>
<td>Same as INF beta-1a</td>
<td>30% over 3 yr</td>
<td>Same as INF beta-1a</td>
<td>Same as INF beta-1a</td>
</tr>
<tr>
<td><strong>Polypeptide mixture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Same as INF beta-1a</td>
<td>32% over 2 yr</td>
<td>Injection-site reactions, flushing</td>
<td>Same as INF beta-1a</td>
</tr>
</tbody>
</table>

INF = interferon; MRI = magnetic resonance imaging.
antiproliferative effect, blocking of T-cell activation, apoptosis of autoreactive T cells, interferon gamma antagonism, cytokine shifts, an antiviral effect, and indirect effects on the CNS. Glatiramer acetate is believed to act by blocking autoimmune T cells, induction of anergy, induction of anti-inflammatory Th2 cells, bystander suppression, and, possibly, neuroprotection.

Natalizumab, a recombinant monoclonal antibody, is the first selective immunomodulator in the treatment of MS. Natalizumab blocks the molecular interaction of alpha-4-beta-1 integrin with vascular cell adhesion molecule-1 on vascular endothelial cells. Therefore, it prevents adhesion of activated T cells to endothelium and prevents transmigration of lymphocytes to the CNS. In the 2-year AFFIRM study involving nearly 1000 patients, natalizumab demonstrated significant efficacy in the treatment of relapsing-remitting MS; the annualized rate of clinical relapse was reduced by 68% (from 0.75 to 0.24), and the number of new or enlarging brain lesions on MRI was reduced by 83%. Clinical disease progression over the 2-year period was also decreased in patients receiving natalizumab (17% versus 29% in those receiving placebo). The 2-year SENTINEL trial demonstrated results that were very similar to the AFFIRM trial, indicating that a combination treatment is nearly as effective as treatment with natalizumab alone. In March 2005, natalizumab marketing was voluntarily suspended by the manufacturer due to reports of 2 cases of progressive multifocal leukoencephalopathy (PML). Both cases occurred in patients who concomitantly received weekly intramuscular injections of natalizumab and interferon beta-1a. However, no additional cases of PML were confirmed, and the clinical hold on natalizumab was lifted in February 2006. Natalizumab will be resumed in patients who had previously been receiving the drug within an investigational new drug study and will likely re-enter clinical practice before the end of 2006.

**CASE 3 CONTINUED**

Available treatment options are discussed with the patient, and she decides to start treatment with interferon beta-1a. She also wants to discuss several symptoms that she has been having over the past few weeks. She has noticed that her legs are stiff at night, and she has developed mild urinary urgency.

- **How often will this patient’s blood work, clinical course, and MRI disease activity need to be monitored?**
- **How is treatment failure defined in relapsing-remitting MS?**

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**Table 5. Expanded Disability Status Scale for Rating Impairment in MS**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal neurologic examination</td>
</tr>
<tr>
<td>1.0–1.5</td>
<td>No disability</td>
</tr>
<tr>
<td>2.0–2.5</td>
<td>Minimal disability</td>
</tr>
<tr>
<td>3.0–3.5</td>
<td>Mild to moderate disability</td>
</tr>
<tr>
<td>4.0–4.5</td>
<td>Moderate disability</td>
</tr>
<tr>
<td>5.0–5.5</td>
<td>Increasing limitations in ability to walk</td>
</tr>
<tr>
<td>6.0–6.5</td>
<td>Walking assistance needed</td>
</tr>
<tr>
<td>7.0–7.5</td>
<td>Confined to wheelchair</td>
</tr>
<tr>
<td>8.0–8.5</td>
<td>Confined to bed/chair; self-care with assistance</td>
</tr>
<tr>
<td>9.0–9.5</td>
<td>Completely dependent</td>
</tr>
<tr>
<td>10.0</td>
<td>Death due to MS</td>
</tr>
</tbody>
</table>


Upon starting therapy with interferons, liver function tests and complete blood counts will need to be monitored monthly. Patients cannot be pregnant or nursing while on treatment with immunomodulatory agents. Subsequent blood work should be done at 3-month intervals for a period of 1 year and then biannually. If the patient is clinically stable, she will need to be seen twice yearly for a complete neurologic examination. Expanded disability status scale (EDSS) score needs to be computed at each follow-up visit (Table 5). At our MS center, it is our practice to repeat brain MRI 6 months after starting treatment and then annually, unless there is a clinical reason to suspect medication failure (increasing relapses, accumulating disability due to incomplete recovery from the relapses.) Other MS centers may follow different scanning protocols.

An increase in the number of relapses and/or new or gadolinium-enhancing MRI lesions in a patient with a history of prior adequate response to immunomodulatory therapy should raise a question about treatment failure. Disease activity might be related to development of neutralizing antibodies against interferon medications. Alternatively, it may be related to inherent properties of the disease in an individual patient. Changing therapy to a different primary agent or to combination therapy with injectable medicines and oral immunosuppressants and/or intravenous corticosteroids must be considered. Typically, a 6-month trial of an interferon and a 6- to 9-month trial of glatiramer acetate are adequate to assess a favorable therapeutic response. If a patient does not respond
to a particular immunomodulatory agent, a different agent from the same class (interferon) or a medication from a different class (glatiramer acetate) can be tried as an alternative. Some data indicate that switching poorly responding patients from interferon beta-Ib to glatiramer acetate improves therapeutic outcomes. However, no clear practice guidelines or randomized trials exist to support this approach, and a change of therapy should be considered on a case-by-case basis by an MS specialist.

- What gives rise to symptomatic complaints in MS?

In MS, the mechanism of nerve signal transmission along the nodes of Ranvier is no longer perfect because parts of the myelin and, indeed, axons themselves are destroyed by inflammation and demyelination. When this process of signal conduction is altered, several problems may occur. First, the speed of conduction decreases because the signal can no longer travel rapidly along an intact and insulated axon. This translates into decreased muscle strength or inability to sustain muscular effort for a long period of time (muscle fatigue). Second, demyelinated axons can send “spontaneous discharges,” resulting in abnormal shock-like sensations traveling up and down the spine (Lhermitte’s sign), producing flashes of light on eye movements, or causing tingling sensation arising without cause in an arm or a leg. Third, axons may not be able to conduct reliably with increased temperatures and, as the body temperature rises with systemic infections or in a hot environment, signal conduction in a nerve may slow down to a crawl or stop altogether. This explains exceptional heat sensitivity in MS patients. Sometimes a hot bath alone may be enough to produce recurrence of weakness or numbness (Uhthoff’s phenomenon). Finally, a so-called “cross-talk” or ephaptic transmission can arise between neighboring compromised axons, resulting in intermittent or paroxysmal symptoms, such as trigeminal neuralgia, transient loss of balance, or painful spasms triggered by touch or movement of the extremity. Although only 1 set of nerve fibers may need to respond to a specific stimulus, many additional nerve fibers become stimulated at the same time, resulting in neurologic complaints.

- What symptoms are common in MS patients, and are there any medications to help with them?

Multiple symptoms and complaints can be seen in MS patients. Some symptoms are directly related to the locations of lesions, while others likely result from global cerebral dysfunction. Involvement of pyramidal tracts results in weakness and spasticity, while lesions in the sensory system result in numbness, paresthesias, and sensory ataxia. Bladder and bowel dysfunction (urgency and frequency of urination, urinary retention, constipation, bowel incontinence) are often seen with spinal cord, pontine, or significant frontal lobe lesion burden. However, there rarely is one-to-one correlation between specific lesion location and a symptom or a complaint that the patient experiences. The symptoms of extreme fatigue, cognitive difficulties, and sleep disorder are likely related to diffuse cerebral dysfunction, although their exact mechanisms have not been elucidated. Pharmacologic and nonpharmacologic treatments are available for most of the symptoms and result in improved quality of life for MS patients.

Depression in MS is substantially undertreated, while effective therapies are readily available. A short list of commonly used medications includes serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, dopamine/norepinephrine reuptake inhibitors, serotonin modulators, and tricyclic and tetracyclic antidepressants.

Spasticity is a common symptom that negatively affects ambulation, causes painful muscle spasms and cramps, and impacts normal sleep. Baclofen, an agonist of gamma-aminobutyric acid, reduces presynaptic release of excitatory neurotransmitters and, in higher doses, antagonizes their actions postsynaptically. Baclofen is used orally and can also be administered intrathecally via subcutaneous pump. Tizanidine stimulates α2-adrenergic receptors in the spinal cord, invoking presynaptic excitatory inhibition. Both medications reduce painful spasms and are generally well tolerated. Intramuscular injections of botulinum toxin are used in patients with severe localized spasms for painful contractures.

Bladder and bowel dysfunction is a common and disabling complaint. Several patterns of bladder problems are recognized most commonly in MS. Detrusor muscle hyperreflexia leads to increased contractility and decreased capacity of the bladder, causing urinary urgency and frequency and even urge urinary incontinence. Detrusor sphincter dyssynergia leads to impaired voiding mechanism, with both urgency and hesitancy of urination. Oxybutynin chloride relaxes the detrusor smooth muscle, increases bladder capacity, and delays the initial desire to void. Tolterodine tartrate is a competitive muscarinic receptor agonist in the bladder, which acts to increase bladder capacity and voiding control. Tricyclic antidepressants are sometimes helpful for fecal and urinary incontinence due to their moderate anticholinergic effects.

Fatigue is experienced by 75% to 92% of MS patients and is reported by some as the most disabling symptom. Modafinil has a wake-promoting effect...
similar to amphetamines, although the precise mecha-
nism of action of this CNS stimulant is not known. It is
used in doses of 200 mg/day for effective fatigue control
in MS patients. Amantadine is an antiviral agent that
exhibits a mild psychoactive effect; it is used in MS and
other neurologic illness in doses of 100 mg to 200 mg
daily for treatment of fatigue, with variable success.
Amphetamine-based CNS stimulants need to be used
with caution in MS patients due to common side effects
of nervousness, dizziness, emotional lability, and urinary
retention that may worsen other MS-related symptoms.

Pain is common in MS patients. Much of the pain
syndromes relate to musculoskeletal abnormalities.
This pain is often secondary to the disease process
(e.g., resulting from poor posture due to loss of muscle
strength in lower extremities or to overuse of upper ex-
tremities in wheelchair-bound patients). The primary
MS pain is often dyesthetic, most commonly in the
lower extremities, but can be felt in any location. This
pain can be controlled with carbamazepine, phenytoin,
gabapentin, or tricyclic antidepressants.

SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

CASE 4 PRESENTATION

A 56-year-old woman comes to you seeking another
opinion about management of her MS. She was initially
diagnosed with MS 12 years ago, following an episode of
horizontal double vision followed by another episode of
urinary retention and bilateral leg weakness. The patient
had no relapses of her illness for the 3 years following her
diagnosis. Thereafter, she started having 2 to 3 relapses
per year, manifesting as bilateral leg weakness, ataxia,
or painful paresthesias in the right arm and right leg.
She responded well to intravenous steroid treatments
and was started on interferon beta-1a, with a decrease in
the number of yearly relapses. However, her symptoms
have progressed over the last year, with declining ability
to walk resulting in a need for walking assistance with
a cane and a walker, decreasing energy level, and occa-
sional urinary incontinence. You review her original MRI
scan as well as a series of scans obtained by her treating
neurologist throughout the course of her illness.

• What stage of MS does this patient have at this
time?

• How does this stage differ from relapsing-remitting
MS in terms of pathophysiology, clinical symptoms,
MRI appearance, and treatment options?

This patient has secondary progressive MS. From 70%
to 89% of patients who start with relapsing-remitting
MS eventually convert to secondary progressive MS
within 10 to 25 years, on average. Secondary progres-
sive MS is characterized by a steady progression of
neurologic disability, with or without superimposed
minor relapses. Although the pathophysiology is ex-
ceedingly complex, it is thought that the secondary
progressive phase of MS is related to failure of remy-
elination, gliosis, and irreversible axonal injury and axo-
nal degeneration.34 In contrast to relapsing-remitting
MS, an inflammatory component plays a relatively
minor role in progressive accumulation of disability at
this juncture. MRI appearance changes; there is rela-
tively little increase in new T2 and FLAIR hyperintense
lesions and minimal accumulation of new gadolinium-
enhancing lesions on T1 sequences. There is prominent
and progressive brain atrophy, both central and periph-
eral, as well as an increase in T1 hypointense lesions
corresponding to areas of axonal destruction and loss.
Interestingly, some patients continue to exhibit signs of
an inflammatory process with continuous formation of
gadolinium-enhancing lesions, and these patients tend
to respond best to immunosuppressive therapy.

Immunomodulatory agents are not specifically rec-
commended for secondary progressive MS, although
some studies suggest possible efficacy of these medica-
tions in cases of relapses superimposed on a progressive
course. Treatment with high-dose interferon has been
shown to decrease the rate of transition from relapsing-
remitting to secondary progressive MS by 50% over
4 years in the PRISMS study55 and by 90% in a 3-year
study by Li et al.56

Mitoxantrone is the only chemotherapeutic agent
approved by the US Food and Drug Administration
(FDA) for use in secondary progressive MS.57,58 In a
pivotal trial, combination treatment with mitoxantron
and methylprednisolone was associated with significant
decreases in the progression of disability and appear-
ance of new MRI lesions.58 Cyclophosphamide is also
widely used as an alternative chemotherapeutic agent
for treatment of secondary progressive MS or refrac-
tory relapsing-remitting MS. Pulse monthly cyclophos-
phamide treatments were associated with a small but
significant reduction in progression in more than 30%
of treated patients.59,60

CASE 4 CONTINUED

You discuss chemotherapeutic treatment options
you feel are appropriate considerations, but the patient
does declines, saying she would like to try something “less
aggressive.”


- What other treatment options does this patient have?

Data on the use of other immunosuppressants in MS patients is limited. Sometimes, monthly boosts of intravenous corticosteroids, alone or in combination with oral immunosuppressive medications (mycophenolate mofetil, methotrexate, azathioprine), are used as treatment regimens for aggressive relapsing-remitting MS or secondary progressive MS. Success of these treatments is variable.

**COGNITIVE DYSFUNCTION IN MULTIPLE SCLEROSIS**

**CASE 5 PRESENTATION**

A woman with a known diagnosis of relapsing-remitting MS is brought to the neurology clinic by her husband. During the evaluation, it becomes apparent that the patient has significant cognitive impairment. She finds it difficult to focus, often loses her train of thought, and complains of poor memory. The patient is having difficulty keeping up with her work and her family obligations. The husband also reports that his wife has been depressed and had frequent spells of crying alternating with laughter.

- **How common is cognitive dysfunction in patients with MS? What are possible pathologic mechanisms for this dysfunction?**

Cognitive impairment is present in many etiologically diverse neurologic diseases that primarily affect the white matter of the brain, including leukodystrophies, neurofibromatosis, lupus, vitamin B<sub>12</sub> deficiency, and postradiation encephalopathy. Approximately 50% of patients with MS demonstrate some degree of cognitive dysfunction, including impairments in attention, speed of information processing, and memory.<sup>61</sup> Cognitive deficits can be a cause of significant disability in MS patients, disproportionately impacting patients’ social and professional environment, burdening interpersonal interactions, decreasing productivity, and impairing quality of life.

It is becoming increasingly recognized that MS involves both white matter tracts (myelin and axons) as well as gray matter (neurons) of the CNS.<sup>62,63</sup> This widespread involvement produces a variety of signs and symptoms that reflect damage to sensory pathways, motor circuits, cerebellum, brain stem structures, and the autonomic system as well as higher cerebral functions such as memory, attention, information processing speed, and others.

- **How is neurocognitive function assessed in MS patients?**

Neurocognitive function encompasses several domains, including language, memory, attention, executive function, and visuospatial abilities.<sup>64,65</sup> Neuropsychological performance can also be influenced by personality, mood, and behavioral patterns.

A significant proportion of MS patients perform poorly on a variety of neuropsychological paradigms—especially those involving frontal systems functions—both early and later in the course of the illness. Patients with MS make 40% more errors on the Wisconsin Card Sorting Test, which measures problem-solving and executive function, than do healthy, age-matched controls. Attention, as assessed by the Paced Auditory Serial Addition Test (PASAT), where subjects are presented with a series of numbers and are required to add them together sequentially, is also often impaired in MS patients who, on average, commit 30% more errors than comparable control subjects. The Selective Reminding Test assesses short- and long-term memory and also shows deficits in MS patients, although to a lesser extent than do the previous 2 tests. Visuospatial function, as tested by the Benton Judgment of Line Orientation Test, is usually spared in MS patients. However, MS does not generally cause a primary language disturbance, such as aphasia or dysphasia (unless a large destructive lesion undercuts cortical area directly responsible for language function), or a severe amnestic dementia.

- **What are some research tools used to monitor cognitive function in MS patients?**

In the 1980s, the Brief Repeatable Battery of Neuropsychological Tests, which contains some of the tests previously noted, was designed and validated by Stephen Rao, a neuropsychologist now credited with first recognizing cognitive impairment in MS as a prevalent and disabling symptom. This battery was used in clinical trials throughout the 1990s and early 2000s but has been supplanted by the more comprehensive MACFIMS (Minimal Assessment of Cognitive Function in Multiple Sclerosis) battery,<sup>65</sup> which is now the gold standard in studies that require assessment of cognitive function in patients with MS. This battery is quite long, however, and must be administered by a trained neuropsychologist. Currently, there are no widely accepted tests that rapidly and sensitively assess the cognitive status of MS patients at the time of a clinical visit with a neurologist, although computer-based tools are being developed for this purpose.
- **What psychiatric diseases are more prevalent in MS patients than in the general population?**

In addition to specific neuropsychological deficits, primary psychiatric diseases are more prevalent in MS patients than in the general population. These include major depressive disorder and bipolar affective disorder. Patients with these diseases and MS may have even more compromised cognitive function.

Cognitive dysfunction in MS is quite difficult to treat. There is limited evidence on the efficacy of immunomodulatory agents for treatment of cognitive dysfunction in MS. In a small, 2-year trial of patients with relapsing-remitting MS, those treated with interferon beta-1a worsened less rapidly (by 47%) on PASAT performance compared with patients receiving placebo. Another small trial was carried out in 17 nursing home residents with secondary progressive MS, who received 5 mg of donepezil for 4 weeks followed by 10 mg of donepezil for 8 weeks. Statistically significant improvement was observed in several cognitive domains, including attention, memory, and executive function, as well as different aspects of behavior.

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**ACUTE DISSEMINATED ENCEPHALOMYELITIS**

**CASE 6 PRESENTATION**

You are seeing a 19-year-old woman in the emergency department who presented with a 2-day history of generalized malaise, moderate diffuse headache, and progressive left-sided arm and leg weakness. She also gives a history of upper respiratory infection 10 days prior to the onset of these symptoms. After performing the neurologic examination and appropriate laboratory and imaging studies, you suspect an acute intracranial process. ADEM is high on your list of possibilities.

- **What is the differential diagnosis for this patient’s acute neurologic presentation?**

The differential diagnosis for the clinical history and neurologic findings described in this case includes meningitis, viral encephalitis, cerebrovascular disease (stroke), endocarditis with cerebral embolization, intracranial abscess, intracranial hemorrhage, CNS vasculitis, CNS sarcoidosis, and Marburg variant of MS.

- **What is ADEM? Is it easy to distinguish between ADEM and CIS?**

ADEM is an acute demyelinating disease of the CNS that tends to follow a monophasic course. It is sometimes referred to as acute postinfectious or postvaccinal encephalomyelitis. Specific viral and bacterial infections or the vaccines against these infections have a known association with ADEM, including herpesviruses, coxsackieviruses, influenza, measles, mumps, rubella, *Borrelia burgdorferi* (Lyme disease), *Legionella pneumophila*, *Mycoplasma*, and *Leptospira*. It may be very difficult to distinguish prospectively between ADEM and a first attack of MS (CIS). While there is no single feature that allows one to reliably distinguish between the 2 entities, the combination of polysymptomatic neurologic illness, encephalopathy, preceding systemic illness within 1 month of neurologic illness, headache, and pyramidal signs on presentation has a highly significant chance of being due to ADEM rather than MS.

CSF examination is generally not helpful in making a distinction between ADEM and MS, although higher lymphocytosis and protein elevation in CSF tend to be associated more frequently with ADEM, and oligoclonal bands tend to be seen mostly in MS patients. In addition, patients with ADEM are more likely to have sparing of periventricular white matter on brain MRI scans. They also tend to have lesions of greater size (> 1 cm) and more frequent involvement of the basal ganglia and cerebral cortex than is typically seen in MS. Contrast enhancement, if present, often affects all lesions equally, and susceptibility artifacts within lesions indicating microhemorrhage are more likely to be seen in ADEM.

**CASE 6 CONTINUED**

You make a diagnosis of ADEM and recommend admitting the patient to the hospital for observation and treatment. The patient wants to know her treatment options.

- **What are options for treatment of ADEM?**

There are no controlled therapy trials in patients with ADEM. Intravenous steroids have been used most commonly. A typical treatment strategy is to initiate a course of IVMP at a dose of 1 g/day for 5 days, followed by a gradual oral prednisolone taper over 1 to 2 weeks. Often, clinical improvement is seen within 2 to 3 days of starting steroid treatment. If no improvement is seen or clinical worsening is observed within the first week despite steroid treatment, alternative treatment options should be considered. Plasma exchange and intravenous immunoglobulin (IVlg) have been used successfully in various case reports and series, but no controlled trials with either modality are available at the time of this review. IVlg is used at a dose of 0.4 g/kg/day for 5 days. Plasma exchange may be
performed daily for a period of 5 days; if there is a positive therapeutic response, an additional course or courses may be considered. A combination of all 3 treatment modalities can be used in succession in patients with incomplete response to any of the single treatments.

Chemotherapy has been used as a last resort treatment in patients with severe, fulminant ADEM unresponsive to other therapies. However, there is no rigorous evidence of chemotherapeutic efficacy in these patients, and its use is based on anecdotal evidence.

**CONCLUSION**

MS is a prevalent neurodegenerative disease characterized by inflammation and demyelination in the brain, spinal cord, and optic nerves. Clinical manifestations can be variable and often include extremity weakness, numbness, ataxia, decrease in vision, and bowel and bladder dysfunction. Partially effective treatments are available in the form of injectable medications (formulations of interferon beta and glatiramer acetate) for the relapsing disease subtype and chemotherapy for the progressive disease subtype. MS is an area of active scientific and clinical research. This research serves to improve our understanding of pathologic mechanisms underlying the disease process and to ensure emergence of new and more effective MS therapies.75

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