MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES

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MULTIPLE SCLEROSIS

Background

1. Multiple sclerosis (MS) is the most common disabling neurologic condition of young adults in European and North American populations. It was first recognized as a disease entity in the latter part of the 19th century. The first description of "disseminated sclerosis" dates back to 1835 and is credited to French neurologist Cruvellhier. Jean Martin Charcot, at the Salpetriere Hospital in Paris, France, described the ataxia and oculomotor abnormalities that are often observed in younger patients. The pathologic features at autopsy, described in the first few decades of the 20th century, are now well known.
2. The cause of MS remains unknown. Theories of the cause have reflected concepts that were popular in different eras. Lesions of MS are often found close to small venules, and thrombosis of these veins was at one time thought to be important. Stress was believed by some to play a role, reflecting ideas of the psychosomatic movement of several decades ago. A search for viruses, as intact infective agents or as DNA fragments, has unsuccessfully continued for many decades. Epstein-Barr Virus (EBV) may play a particular role in MS: The studies have found that antibodies to the viral proteins, Epstein-Barr nuclear antigens, viral capsid antigens, and diffuse early antigens are significantly raised in people with MS. One study found that people with the highest levels of antibodies to EBV were 33 times more likely to develop MS than people with the lowest levels. It is not clear whether there is a causative or temporal association between infection with a specific pathogen and MS onset. In the last few decades, genetic predisposition was determined to clearly pay a role. We now define MS as a *T cell–mediated autoimmune central nervous system (CNS) disease triggered by unknown exogenous agents, such as viruses or bacteria, in subjects with a specific genetic background.*
3. In most patients, MS is a chronic disease. In 85% of patients, it begins with a focal inflammatory lesion of the nervous system, developing over days and recovering after months. Further lesions develop and cause clinical relapses, usually at a rate of one or two relapses per year. Magnetic resonance imaging (MRI) data have shown us that in actuality lesions occur in the brain and spinal cord at a far more rapid pace, often 10 times as frequently as relapses that are clinically recognized. After a number of years, or even decades, most patients enter a slowly progressive phase of the illness, with increasing disability. Impairment of gait, reduced visual acuity, paresthesias and pain, loss of bladder control, and cognitive deficits dominate the clinical picture after the progressive phase has advanced further. In large registries of patients, for example, from France and from Denmark, it is found that reduction in life span due to MS is not common, but that most (75% to 80%) of the patients are disabled and unable to work by age 65.
4. Other variants of MS occur. About 10% of patients have primary progressive MS (PPMS) (i.e., no relapses are recognized and the patient steadily worsens from

the onset). Another 10% have so-called benign MS, with few relapses and no disability even though they have been known to have the disease for many decades. A small number of patients have acute MS, with frequent and large lesions and poor recovery, and it is among this group that a fatal outcome is occasionally seen.

5. Most of the data regarding treatment of MS are derived from studies that exclude variant forms of MS and instead use the more common version of the disease, with relapses followed in time by a secondary progressive phase. Since the variant forms have not been tested, it is often difficult clinically to decide whether a particular form of treatment is appropriate for an individual patient. Wide variations in the course of the disease make it imperative that carefully designed clinical trials furnish the evidence for treatment.

Epidemiology

1. MS is the most common neurologic disease among young adults.
2. Incidence is the highest from ages 20 to 40, but the disease can start even in childhood or after age 60.
3. In the United States alone, there are about 500,000 MS patients and about 10,000 new cases are diagnosed yearly.
4. There is 7:3 female-to-male ratio.
5. There are zones of high incidence and medium incidence, and there are places in the world where the disease is almost unknown.
   a. Prevalence decreases with proximity to equator creating a so-called "North-South Gradient" of MS distribution.
   b. High incidence includes all of Europe, North America, New Zealand, and southern Australia. In these areas, the prevalence is about 60/100,000. In Minnesota and many of the northeastern states of the United States, one person of every 500 has MS (i.e., a prevalence of 200/100,000). In general, MS is more than twice as common in the northern tier of the United States as in the southern states.
   c. Race plays an important role: U.S. residents who are of Japanese, Native American, or Sub-Saharan African descent have a much lower incidence of MS than do people of Irish, British, or Scandinavian background under equal geographic circumstances.
   d. Incidence of MS in African Americans is 25% of that of persons with Caucasian background. However, the disease tends to be more rapidly disabling and resistant to therapies in this patient population.
6. If persons with ethnically and geographically low risk develop MS, the disease may be atypical in clinical manifestations and imaging findings.

Pathophysiology

1. *The pathologic hallmarks* of MS are demyelination and predominantly perivenular inflammation. Severe or advanced disease causes axonal disruption and loss and cortical atrophy leading to a process of neurodegeneration.
2. Historically, MS was considered a disease of cerebral white matter. Recent data provide evidence for primary involvement and neurodegeneration of central and cortical gray matter.
3. The immunologic mechanism involves activation of autoreactive CD4+ cells in the peripheral immune system followed by their migration into the CNS via a disrupted blood–brain barrier (BBB). This is followed by reactivation of the cells by in situ myelin antigens, activation of B cells and macrophages, and secretion of proinflammatory cytokines and antibodies.
4. The typical lesion of MS is a few millimeters to a centimeter in size. Viewed three-dimensionally, a lesion is often ovoid or linear rather than circular. This is a

feature of the MRI appearance. Activated T cells and macrophages are present. The cells express T helper 1 (T_H1) cytokines such as interferon gamma (IFN-γ), tumor necrosis factor (TNF), and interleukin-2 (IL-2). Cytokines of the T_H2 series such as IL-4, IL-10, and IL-13 are reduced. Many kinds of proinflammatory molecules, such as integrins and other adhesion molecules, are upregulated.

   a. *Microscopically*, lesions show destruction, swelling or fragmentation of myelin sheaths, proliferation of glial cells, variable axonal destruction (new and old plaques), and variable damage to neurons, but relatively good preservation of background structure, and cystic lesions are rare.
   b. Early/acute lesions (days to weeks) show marked hypercellularity, macrophage infiltration, astrocytosis, perivenous inflammation with plasma cells and lymphocytes, and disintegration of myelin.
   c. Active/non-acute lesions (weeks to months) show lipid-laden phagocytes with minimal inflammatory response at the center of lesions but prominent at the edges of lesions with increased numbers of macrophages, lymphocytes, and plasma cells.
   d. Chronic inactive plaques (months to years) show prominent demyelination (almost complete loss of oligodendrocytes), extensive gliosis, and hypocellularity.
   e. Remyelinating plaques may result from differentiation of precursor cells common to type II astrocytes and oligodendrocytes. They show uniform areas of aberrant and incomplete myelination (shadow plaques).

5. Chronic lesions with poor recovery have the appearance on biopsy, at autopsy, or on MRI of an empty astroglial scar. The term *multiple sclerosis* refers to these late-stage discolored plaques or scars.
6. In demyelinated areas, transmission of nerve impulses is blocked and signals fail to arrive at their destination.

Genetics

1. If a mother has MS, her children also have a 3% to 5% chance of having MS—at least a 20-fold increase.
2. If a father has MS, his son has a 1% chance, and his daughter a 2% chance, of having MS.
3. A sibling of an affected person, including a nonidentical twin, has a 3% to 4% chance of having MS.
4. An identical twin has a 30% chance of having MS if one includes asymptomatic twins with only MRI or spinal fluid findings.
5. MS is associated with major histocompatibility complex II (MHC-II) and three specific alleles in the DR2 haplotype.
6. Full-scale genome screens have shown no convincing locus for an "MS gene." It is likely that a number of genes contribute liability by increasing immune reactivity to common viruses or to antigenic components of myelin to which other persons are nonreactive.

Diagnosis

1. *Clinically isolated syndrome (CIS),* that is, optic neuritis (ON), transverse myelitis (TM), or a brainstem syndrome as the first ever episode of neurologic dysfunction. The patient does not meet criteria for MS diagnosis. Specific clinical syndrome depends on location of lesion(s) within brain, spinal cord, or optic nerves. The attack typically progresses for several days, plateaus, and then improves over days, weeks, or rarely months. Improvement can be complete, or partial.
2. *Most common presenting symptoms of MS* include visual/oculomotor problems (49%), leg paresis/paresthesias (42%), cerebellar ataxia (24%). Other symptoms may include progressive or abrupt cognitive changes, Lhermitte's phenomenon (electrical painful paresthesias induced by neck flexion), Uthoff phenomenon (worsening symptoms with increased body temperature), neuropathic pain, and fatigue.

3. Clinically definite MS (CDMS): Patient meets McDonald criteria for MS diagnosis.
4. *McDonald MS criteria* for MS diagnosis (2001–2006)
   One attack with objective evidence of neurologic disease, plus a second attack, which can be defined by MRI criteria, positive spinal fluid findings, or abnormal evoked potentials. Eighty-three percent sensitive at 1 year and 83% specific at 3 years for diagnosis of MS.

   McDonald MRI criteria:

   Must have at least three of the following to count as dissemination in space:
   - One Gd-enhancing lesion or nine T2/FLAIR hyperintensities
   - One or more infratentorial lesions
   - One or more juxtacortical lesions
   - Three or more periventricular lesions

   Dissemination in time

   - Three-month follow-up MRI shows enhancement at a new site.

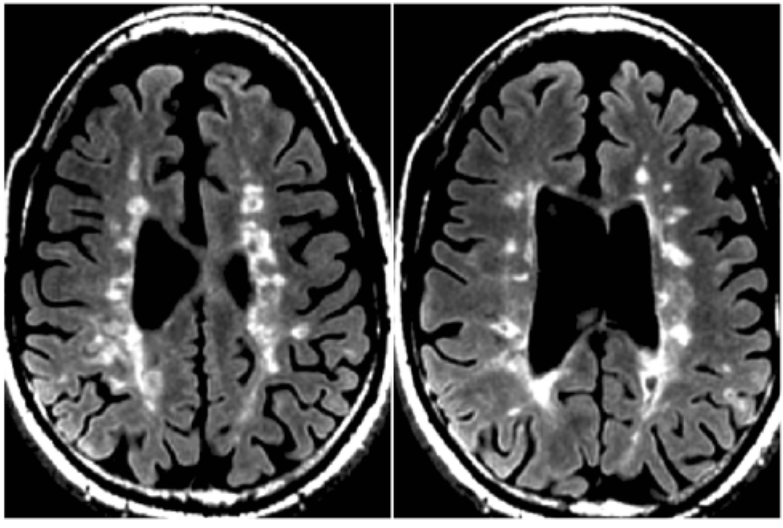
   OR

   - Six-month follow-up MRI shows new enhancing lesion or a new T-2 lesion.
5. Over the course of the disease, each attack may leave some residual deficits. Accumulation of such deficits results in increasing disability. After several attacks of various types, a patient may present with common "fixed" problems:
   a. Mild reduction in vision in one eye
   b. Dysconjugate eye movements, with diplopia
   c. Extensor plantar responses and inability to walk heel-and-toe
   d. Reduced vibration sense in the legs
   e. Urgency of bladder function
   f. Cognitive impairment
6. Common late-stage deficits include dementia, inability to stand or walk, slurred speech, ataxia, incontinence, and marked sensory loss in hands and legs.

Diagnostic Testing

Magnetic Resonance Imaging

1. MRI is now the dominant laboratory method for diagnosis of MS. MS lesions are usually easily detected and often are characteristic. Conventional MRI techniques are now widely accessible to community and academic neurologists. By scan:
   a. Lesions are bright on T2-weighted and fluid-attenuation inversion recovery (FLAIR) images, indicating a higher than normal water content. These MRI sequences reflect the total burden of disease (Fig. 7-1A).
   b. Lesions are usually isodense on T1-weighted images, indicating that the tissue itself is intact.
   c. Lesions may be hypodense on T1-weighted images, indicating underlying axonal disruption (black holes) (Fig. 7-1B).
   d. Lesions may be present in many areas of the brain, but most typically they are found adjacent to the lateral ventricles, oriented perpendicular to them, and in the corpus callosum (best seen on midline sagittal FLAIR images [Fig. 7-2]), and in the cerebellar peduncles. MS plaques directly touch the ventricular wall following the location of the small venules. In contrast, small vascular lesions are usually seen several millimeters away from the ventricular wall.
   e. Acute and subacute lesions (<8 weeks since formation) often show enhancement on T1 postgadolinium contrast sequences indicating inflammation, BBB disruption, and recent disease activity (Fig. 7-3).
   f. Size of cerebral lesions varies from 5–10 to 100 mm or greater.



(A) (B)

Figure 7-1. A: Axial FLAIR. This MRI was performed in a patient with secondary progressive MS. There are innumerable ovoid hyperintense lesions abutting lateral ventricles, involving the U-fibers and subcortical white matter. Cerebral atrophy is apparent: lateral ventricles are enlarged, and cortical ribbon is thinned. **B:** "Black holes." T1 sequence shows hypointense lesions corresponding to some hyperintense lesions on FLAIR sequence. These are areas where severe axonal damage is seen pathologically. There is a correlation between axonal damage and neurologic disability.

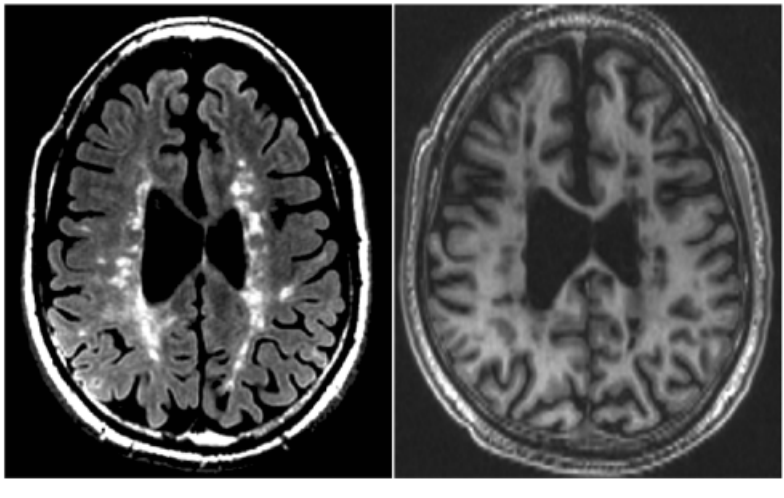


Figure 7-2. Sagittal FLAIR and T1. Typical "Dawson fingers" corresponding to areas of demyelination and inflammation are seen on sagittal FLAIR image. Atrophy of the corpus callosum is best appreciated on sagittal T1 precontrast sequence.

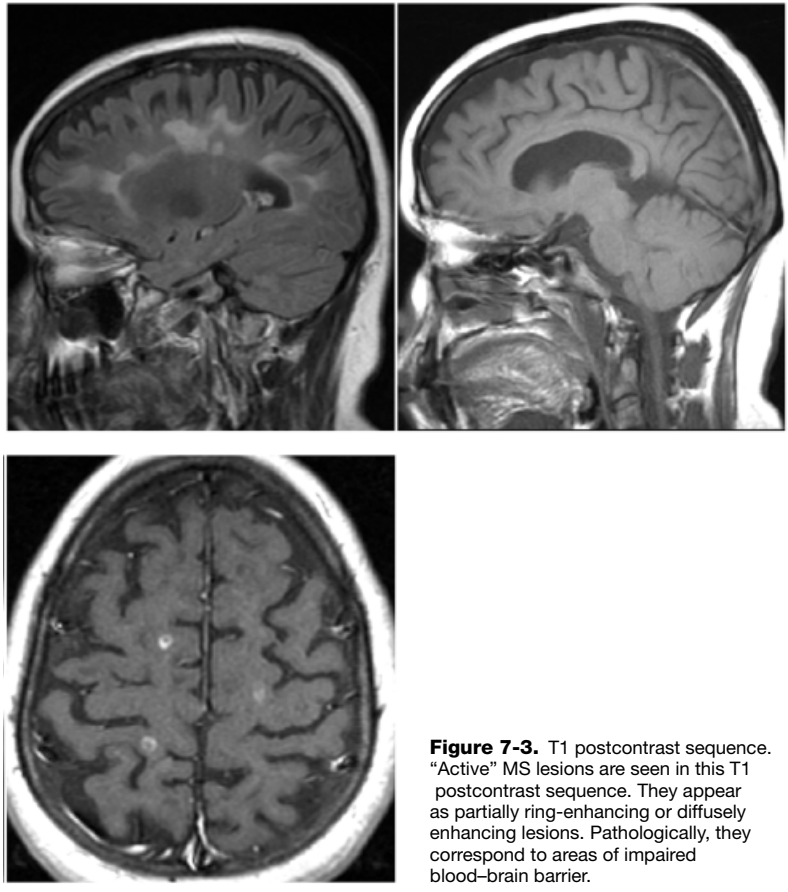


Figure 7-3. T1 postcontrast sequence. "Active" MS lesions are seen in this T1 postcontrast sequence. They appear as partially ring-enhancing or diffusely enhancing lesions. Pathologically, they correspond to areas of impaired blood–brain barrier.

   g. Lesions are common in the spinal cord, especially the cervical cord opposite the C-2 or C-3 vertebrae. They typically involve less than two contiguous segments of the spinal cord and less than half of the transverse diameter of the cord.

2. Most patients with MS have MRI scan findings that are characteristic of MS. Some may have atypical or nonspecific patterns of lesions. Only extremely rarely do patients with a typical clinical course suggestive of MS have normal MRI scans. Such patients present great diagnostic difficulty, and repeated scanning and other examinations may be required.

3. Nonconventional MRI techniques are employed in clinical trials and can be used in specialized MS centers for research or disease monitoring purposes.

   a. Global and focal cerebral atrophy measures in brain and spinal cord: Atrophy correlates with axonal and neuronal loss, and physical and cognitive impairment.

   b. NAA (*N*-acetylaspartate) levels measured with MR spectroscopy: A marker of neuronal and axonal metabolism, NAA is decreased in MS lesions and in normal-appearing white matter in brains of MS patients.

c. Magnetization transfer imaging or ratio: Abnormal in more severe lesions with greater tissue destruction, it can be abnormal despite normal routine MRI sequences.
d. Functional MRI (fMRI) measures critical circuitry involved in response to injury, activation, loss of function, and recovery of function in MS.

Other Tests

1. Lumbar puncture is needed in some patients with MS, but is not performed routinely in cases of diagnostic certainty. Characteristic findings in the cerebrospinal fluid (CSF) in MS are a modest number of lymphocytes (fewer than 50/mm^3), total protein less than 0.8 g/L, elevated immunoglobulin G (IgG) synthesis levels (3.3 mg/day in 90% of patients), and high IgG index (0.7 or greater in 90% of patients). Myelin basic protein (MBP) is normally <1 ng/mL but increases in 80% of acute MS relapses. Presence of oligoclonal banding (OCB) on electrophoresis is the most sensitive of the CSF tests, being present in 75% to 80% of patients with established MS, and in 50% to 60% of patients with CIS. OCB may also be present in other infectious/autoimmune conditions such as Lyme disease, neurosarcoidosis, neurosyphilis, and human immunodeficiency virus (HIV).
2. Evoked potentials testing—especially testing of visual evoked potentials—will occasionally help. It can establish evidence of prior damage to optic nerves in the absence of a clear clinical history by showing unilateral prolongation of P100 wave.

Differential Diagnosis

Many other neurologic conditions may be confused with MS (Table 7-1). They fall into two categories:

1. Diseases that look like MS clinically, including other CNS inflammatory diseases such as lupus, sarcoidosis, and chronic meningitis, and degenerative processes such as hereditary ataxia, adrenoleukodystrophy, and motor neuron disease
2. Diseases that look like MS by MRI findings, including other causes of "white spots"
   a. Vascular disease: Small-vessel disease in hypertension, migraine, CADASIL (cerebral autosomal dominant anteriopathy with subcortical infarcts and leukoencephalopathy).
   b. Infections: Lyme disease, HIV.

TABLE 7-1 Diagnoses That Mimic Multiple Sclerosis

Infectious	Toxic-metabolic	Inflammatory	Other
Lyme disease	B12 deficiency	SLE	CADASIL
Neurosyphilis	Vitamin E deficiency	Sjögren disease	CNS lymphoma
HIV		Neuro-Behçet disease	Cerebrovascular disease
HTLV-1		Sarcoidosis	Leukodystrophies
PML		CNS vasculitis	Motor neuron disease
			Cervical spondylosis

HIV, human immunodeficiency virus; HTLV, human T-lymphocyte virus; PML, leukoencephalopathy; SLE, systemic lupus erythematosus; CADASIL, cerebral autosomal dominant anteriopathy with subcortical infarcts and leukoencephalopathy; CNS, central nervous system.

c. Granulomatous disease: Sarcoidosis, Behçet disease
d. Monosymptomatic demyelinating disease: TM and acute disseminated encephalomyelitis (ADEM)

Classification and Clinical Considerations

1. Several MS classifications are used.
a. Based on disability accumulation: Benign MS (5% of all patients)—no or minimal neurologic disability after 10 to 15 years. Malignant MS (5% to 7% of all patients)—neurologic disability requiring ambulation assistance after ≤5 years.
b. Based on clinical course: Relapsing–remitting MS (RRMS). This subtype is the most common (85% of all patients fit into this disease category at diagnosis). It is characterized by relapses and remissions of neurologic disability over years to decades. Incomplete recovery from relapses often leads to disability accumulation. Secondary progressive MS (SPMS) follows RRMS in 10 to 25 years after the diagnosis in 60% to 80% of patients. This subtype is characterized by absence of relapses and progressive worsening of neurologic function involving the pyramidal system, cerebellar connections, dorsal columns, and cortical association fibers. Patients exhibit paraparesis or hemiparesis, ataxia of gait, sensory ataxia, neuropathic pain symptoms, and cognitive decline. Ambulation assistance is often required at this stage. PPMS often presents with indolent or rapid evolution of neurologic symptoms and usually involves progressive leg weakness with difficulty walking as the initial feature of the disease. Careful history taking confirms absence of exacerbations of neurologic deficits. This disease category is more common in men, in the fourth and fifth decades of life. Prognosis is worse for this group of patients. They do not respond to currently available MS therapies.
c. Based on predominant clinical subtype: In recent years, specific clinical phenotypes of MS are identified based on the most affected neurologic subsystem. These include "spinal MS variant," "cerebellar MS variant," and "cognitive MS variant."
2. The combination of several epidemiologic, clinical, and imaging factors carry better prognosis for stable disease course. Positive prognostic factors include
a. Younger age of onset
b. Female sex
c. Monosymptomatic onset
d. Sensory symptoms or ON at onset
e. Few T2 of FLAIR lesions on original MRI
f. Long interval between first and second attacks
g. Low attack frequency in the first 2 years
h. Full recovery of function after the first attack
3. There is no consistent evidence that the postpartum state, anesthesia, surgical procedures, stress, or intercurrent illnesses worsen clinical outcome in MS patients. However, the above factors may temporarily aggravate preexisting neurologic deficit creating a "pseudo-exacerbation." These are not considered true relapses, and it is important to screen patients for infections in presence of transient or fluctuating neurologic worsening.
4. Expanded Disability Status Scale (EDSS): Ordinal 0 to 10 scale; most widely accepted measure of disability in MS.
a. EDSS 0: No disability
b. EDSS 6: Needs unilateral ambulation assistance (cane)
c. EDSS 10: Death due to MS
5. Fifty to seventy percent of patients with MS are not able to work in prior occupation 10 to 15 years after disease onset.

TABLE 7-2 Medications for Depression in Multiple Sclerosis

Medication	Initial dose	Final dose range
Fluoxetine (Prozac)	10 mg	10–80 mg
Paroxetine (Paxil)	10 mg	10–50 mg
Sertraline (Zoloft)	25 mg	25–200 mg
Citalopram (Celexa)	10 mg	20–60 mg
Venlafaxine (Effexor)	37.5 mg	75–300, given twice a day

Treatment

Treating Symptoms

Depression Approximately half the patients with MS at some time undergo an episode of clinical depression. Symptoms of irritability, altered sleep pattern, and low self-esteem occur. Women are twice as likely as men to become depressed. There is little correlation with disability; in fact, depression may be more common in the earlier stages, with less disability. There is a causative connection in that some of the frontal lobe and limbic connections may be damaged by MS lesions.

1. Selective serotonin reuptake inhibitors (SSRIs) are the mainstay of treatment of depression: fluoxietine (Prozac), sertraline (Zoloft), paroxetine (Paxil), or second-generation drugs such as bupropion (Wellbutrin), citalopram (Celexa), or escitalopram (Lexapro) (Table 7-2). Care should be taken that the dose is sufficient. Most SSRIs reduce libido. In young adults, there is a higher risk of suicide on SSRIs. The involvement of a psychopharmacologist should be considered in difficult cases.
2. In addition to drug therapy, counseling or some other form of supportive psychotherapy is often beneficial. Ideal treatment is a combination of the two.
3. Tricyclic antidepressants are helpful but have many side effects, such as weight gain, dry mouth, and drowsiness. On the other hand, they may help insomnia or urinary urgency. Examples are amitriptyline, desipramine, or nortriptyline.
4. Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs) are useful in treatment of depression, such as venlafaxine (Effexor) and duloxetine (Cymbalta). Some (duloxetine) are also helpful in treating pain in MS patients.
5. Fatigue can be a compounding issue and may be hard to distinguish from depression. Use of a stimulant such as modafinil (Provigil) or methylphenidate on a trial basis may be helpful (see the section on Fatigue).
6. If there is a history of manic disorder, psychiatric consultation is advisable because bipolar disease requires a separate set of long-term preventive drugs such as lithium carbonate, carbamazepine, or valproate.
7. Depressed patients need to be followed, the success of treatment assessed, and risk of suicide should be considered at all times. In apathetic patients, thyroid deficiency, sleep apnea, and adverse effects of other medications should be considered.

Fatigue The fatigue experienced by many MS patients may be disabling, pervasive, and not relieved by rest. Careful planning, avoidance of exhausting exercise, short rest periods, and other coping strategies may help. The following medications are in use:

1. Amantadine (Symmetrel) 100 mg, two or three times a day. This medication has been in use for more than 20 years for MS. About a third of patients find it useful. Hallucinations, ankle swelling, and skin mottling may be seen, especially in older patients.

2. Modafinil (Provigil), 100 or 200 mg twice a day. This agent was approved for producing wakefulness in patients with narcolepsy. Some insurance plans will cover its cost only for this approved use. Data supporting its use for MS fatigue are scant. Large numbers of patients find this compound helpful and some patients have been able to be reemployed.
3. Methylphenidate (Ritalin), 5 to 10 mg/d, up to a maximum of 40 mg/d. A long-acting version (Concerta), at a dose of 18 mg once or twice a day, may be preferable. Other amphetamine-based preparations can be tried. They can exacerbate anxiety disorders and cause insomnia.

Cognitive or Memory Problems In some patients with MS, the lesions of the central white matter destroy nerve fibers and their coverings. The results of this axon loss are gradual atrophy of the white matter, enlargement of the ventricular system, and behavioral and cognitive deficits. Primary gray matter pathology is also known to play a role in this process. In minor form, cognitive dysfunction may be common and occur early in the disease course. Many patients with MS will note memory and recall problems, difficulty handling complex or multiple stimuli, or inability to concentrate well. When more severe, emotional lability, poor judgment, and personality change may occur.

1. Structuring of the environment may help: avoidance of complexity, doing "one thing at a time," asking for help.
2. Recognizing and treating fatigue or depression (see above) may provide a therapeutic option.
3. Small non-blinded trials have assessed the possible efficacy of acetyl-cholinesterase inhibitors in treatment of MS-related dementia. While results are mixed, these medications may be tried on an individual basis.
4. Cognitive-behavioral therapy is helpful for some patients.

Spasticity

1. Several kinds of symptoms are a consequence of an increase in spinal cord reflexes leading to spasticity of the extremities. Walking may become slower and labored, with adduction of the hips and difficulty lifting the toes and ankles (foot drop). Spontaneous spasms may occur, especially at night, and may be painful. Usually these flexor spasms affect both legs. Spasticity is accompanied by varying degrees of weakness and clumsiness.
   a. Physiotherapy and exercise have a limited but important role. Maintenance of joint flexibility by stretching and range of motion can be accomplished by many techniques. Aerobic training may be detrimental.
   b. Baclofen (Lioresal) blocks γ-aminobutyric acid (GABA), one of the major spinal cord inhibitory transmitters. The dose is gradually increased from 20 to 100 mg/d. Side effects include drowsiness and hypotonicity with reduced muscle stretch reflexes. The drug has its best effects on flexor spasms and often affects walking speed only slightly.
   c. Tizanidine (Zanaflex), an α-2 adrenergic agonist, is used for the same indications. The drug is available as a 4 mg tablet. It must be increased very slowly from a starting dose of 2 mg at bedtime to a maximum of 16 to 20 mg/d. It can cause drowsiness, but not hypotonicity.
   d. Benzodiazepines, such as clonazepam (Klonopin) 0.5 to 2.0 mg at bedtime, have some usefulness but tachyphylaxis and dependency limit their value.
   e. Dantrolene (Dantrium) is used only rarely because of liver toxicity. However, it has a role for acute spasticity or muscle contracture.
   f. Gabapentin (Neurontin) has been tried at doses of 900 to 1,800 mg/d, but the data supporting its use for spasticity are fragmentary.
2. For severe spasticity, an intrathecal pump system is available, consisting of a subcutaneous programmable reservoir and a tiny catheter into the spinal subarachnoid space, which delivers baclofen.

3. Botulinum toxin injections in isolated muscles may provide spasticity relief. The range of doses can be used to either improve ambulation quality or to relieve contracture-related pain.

Urinary Urgency Many patients with MS have impairment of bladder function. The most common pattern is one of a small-capacity bladder, with urgent and involuntary contractions but incomplete emptying. Less commonly, MS patients may have a hypotonic bladder, with difficulty initiating urination and a large postvoiding urinary residual.

1. Oxybutynin (Ditropan), an anti-muscarinic drug, may be used empirically. It is effective in patients with hypertonic bladders in whom involuntary contractions and dyssynergy of sphincter function are the main problems. Dosages range from 2.5 mg to 10–15 mg/d. A long-acting version may be more convenient. Dry mouth and constipation are encountered at high dose levels.
2. Tolterodine (Detrol), another anti-muscarinic agent, is used in the same manner, and may be substituted for oxybutynin. Dry mouth is less of a problem. Dosage is 2 mg, once or twice a day.
3. Other anticholinergic drugs, including tricyclic antidepressants, are sometimes useful.
4. For severe hypotonicity with retention, and especially with frequent urinary tract infections (UTIs), self-catheterization is indicated. For men, external drainage systems may be used, but they will not empty the bladder well. Referral to a urologist for assessment and training is usually required.

Pain

1. Pain is a common component of MS, particularly in mid-stage disease. Pain may be dull or burning and is often located in a large region, such as an arm, a leg, one side of the body, a band-like sensation over the trunk, or in the face. Sharp lancinating pain in the face may be very reminiscent of idiopathic trigeminal neuralgia.
2. Consideration should always be given to the possibility of non-MS pain, including various forms of nerve root compression, visceral pain, and psychogenic causes including depression. Various medications may be helpful:
   a. Gabapentin (Neurontin) may be used at dosages up to 3,600 mg/d. Above that dose level, little further medication is absorbed by active intestinal transport. Some patients are drowsy or lethargic at dosages of 600 to 900 mg/d and are unlikely to achieve much benefit.
   b. Tricyclic antidepressants, such as amitriptyline 50 to 75 mg/d or nortriptyline at 100 to 150 mg/d, are helpful, but dry mouth, urinary retention, drowsiness, confusion, and other symptoms due to anticholinergic side effects may occur.
   c. Carbamazepine (Tegretol) at dosages of 400 to 1,000 mg/d is helpful. The long-acting form of the medication is preferable. Other antiepileptic drugs may be tried as well, including valproate (500 to 1,500 mg/d) or topiramate (Topamax) (50 to 150 mg/d).
   d. Referral to a pain specialist is indicated if a patient is not achieving benefit from multimodality medical therapy. Sometimes interventional procedures, such as nerve blocks, can help.

Alternative or Complementary Medicine

1. In the United States about half the patients with MS are involved in some type of nontraditional treatment in addition to conventional medical therapies. These nontraditional treatments may be classified as follows:
   a. Biologically based therapies, such as herbs, diet, bee venom, or bee stings
   b. Non-Western medical systems, such as Chinese, Tibetan, or homeopathic approaches
   c. Mind–body intervention, including meditation, yoga, and prayer

TABLE 7-3 Six Principles of Management in Multiple Sclerosis

1. Relapses with significant impairment of function should be treated with high-dose intravenous corticosteroids.
2. All relapsing–remitting patients should be receiving long-term immunomodulatory treatment.
3. Secondary progressive patients need aggressive treatment early. Late treatment (more than a few years after the onset of the progressive phase) accomplishes little.
4. Primary progressive patients cannot be expected to respond to any disease-altering treatment.
5. Multiple sclerosis is a lifelong illness, and there is no current paradigm for discontinuation of therapy once started. If one treatment is not tolerated, or fails, another should be sought.
6. Patients need to be watched for signs of disease activity by clinical and/or magnetic resonance imaging monitoring. Changes or additions in treatment need to be started before there is irreversible loss of function.

   d. Manipulative or body-based treatments including chiropractic manipulation or massage
   e. Energy therapies, such as magnets, Reiki, and therapeutic touch
2. Most of these treatments are complementary to standard conventional approaches and should not replace them. A nonconfrontational approach can lessen the risk that patients will abandon or avoid important avenues of treatment. Some of these treatments are helpful, a few may be promising, and most are unproven.

Treatments that Alter the Course of the Disease

1. The six principles of treatment are listed in Table 7-3 and discussed in detail below. Drug safety during pregnancy is considered in Table 7-4.
2. Disease-modifying therapy in MS aims to alter the natural course of the disease and maximize the quality of life by decreasing:
   - Frequency of relapses
   - New brain and spinal cord lesions (overall lesion burden and active lesions)
   - Progression of brain atrophy
   - Disability progression: Physical and cognitive
3. There are two classes of drugs used in treatment of MS: immunomodulatory agents and immunosuppressive agents.
4. Six medications are now approved in the United States for use in patients with MS to affect the course of the disease. Five of them are in the category of immunomodulators specifically used for RRMS patients. Doses, frequency, and mode of administration are outlined in Table 7-5. They reduce the number of relapses and the activity of the disease as visualized on MRI scans. All five are only partially effective in providing reduction in, but not a complete abatement of, relapses. Three of these five are beta-interferons, one is a monoclonal antibody, and the other is a synthetic polypeptide designed to resemble MBP.
5. One drug, mitoxantrone, is approved for SPMS. It is a chemotherapy agent administered at relatively low dose.
6. The precise mechanism of action of IFNs or glatiramer acetate is not known. IFNs are recombinant proteins. They do not cross BBB and exert their effects in the periphery, in the lymphoid organs, and not in the CNS. It is hypothesized from laboratory studies that they block T-cell activation, have antiproliferative

TABLE 7-4 Safety of Multiple Sclerosis Drugs When Used During Pregnancy

Category B: Animal data show no fetal harm; no human data available
- Glatiramer (Copaxone)
- Oxybutynin (Ditropan)
- Antidepressants such as SSRIs

Category C: Animal data show fetal harm; no human data available
- Corticosteroids
- Interferon-β 1α
- Interferon-β 1β
- Baclofen
- Amantadine (Symmetrel)
- Tizanidine (Zanaflex)
- Carbamazepine (Tegretol) and other antiepileptic drugs

Category D: Known to cause fetal harm when administered to humans
- Mitoxantrone (Novantrone)
- Cyclophosphamide (Cytoxan)
- Methotrexate

SSRIs, selective serotonin reuptake inhibitors.
From Damke EM, Shuster EA. Pregnancy and multiple sclerosis, *Mayo Clin Proc*. 1997;72:977–989, with permission.

effects on T cells and anti-viral effects, and induce apoptosis of autoreactive T cells.

7. Glatiramier acetate is a polypeptide mixture. It acts in the periphery and in the CNS. Its mechanism of action is presumed to involve bystander suppression, induction of anergy, induction of anti-inflammatory TH2 cells, and blockade of autoimmune T cells.
8. Natalizumab is a recombinant monoclonal antibody. It is a selective adhesion molecule inhibitor directed against α4-β1 integrin receptor on lymphocytes. It prevents binding to the vascular adhesion molecule (VCAM)-1 on endothelial cells and stops lymphocyte migration across BBB. It acts in the periphery and does not cross the BBB into the CNS.

TABLE 7-5 Immunomodulatory Agents for Multiple Sclerosis

Name	Dose	Frequency	Route
Avonex (IFN-β 1a)	30 μg	Once weekly	IM
Copaxone (glatiramir acetate)	20 mg	Once daily	s.c.
Rebif (IFN-β 1a)	44 μg	Three times weekly	s.c.
Betaseron (IFN-β 1b)	250 μg	Every other day	s.c.
Tysabri (natalizumab)	300 mg	Once monthly	IV

IM, intramuscular; s.c., subcutaneously; IV, intravenous.

9. Decisions about medication use should normally be executed by a practitioner with some knowledge and experience in the field. Practice patterns are changing rapidly as further data are made available about these agents.
   a. Relapses with significant impairment of function should be treated with high-dose intravenous (IV) corticosteroids.
      1) This principle is based on 30-year-old data, when adrenocorticotropic hormone (ACTH) was the preferred form of steroid therapy, and more recently, on data from the Optic Neuritis Treatment Trial. Disability is shortened, and in some instances the residual from an attack is lessened.
      2) Commonly used protocols now use methylprednisolone 1,000 mg/d administered IV over 1 to 2 hours for 3 to 5 days. Dexamethasone, orally or IV, can also be used in instances of methylprednisolone allergy. Most authorities do not use an oral taper of prednisone after the IV steroids.
   b. All relapsing–remitting patients should be on treatment. This principle is based on data from longitudinal studies of patients followed up clinically and with serial MRI studies. Such studies, mainly from Canada and Britain, have shown the following:
      1) Most relapsing patients will eventually develop disability. Only 10% of MS patients have benign MS and may not need therapy, but these patients are impossible to identify at the time of diagnosis and the diagnosis of benign MS can only be made retrospectively.
      2) After a single attack of demyelinating disease, the likelihood of a second attack is accurately predicted by the MRI findings. A patient with ON and more than two demyelinating lesions on an initial scan has five times the risk of a second neurologic event (thus acquiring a diagnosis of MS) as does a patient with negative scan findings.
      3) While patients with short-lived, limited, or spontaneously clearing attacks have a less severe course, these clinical predictors are highly unreliable in predicting eventual outcome.
      4) Also, while patients with less activity on their MRI scans (as measured by enhancement with gadolinium or increasing numbers of lesions) have a less severe course, these predictors are equally unreliable.
   c. Therefore, as it cannot be known if there are patients who could forgo treatment, the current recommendation is for all to be treated.
10. Therapeutic efficacy: Currently available immunomodulating agents (IMAs) decrease relapse rate annually by approximately 30% (IFNs and glatiramer acetate) and by 60% (natalizumab). They decrease new MRI lesions by 90% (natalizumab) and by 40% to 80% (glatiramer acetate and IFNs, respectively, depending on trial data). There is a suggestion of decreased disability progression over the duration of some trials (1 to 3 years). Long-term disability efficacy is not known.
11. General side effects of IMAs
   a. IFNs: Injection-site reactions, flu-like symptoms, neutropenia, liver function test elevation, formation of IFN-specific antibodies (partially inactivate effects of the drugs)
   b. Glatiramer acetate: Injection-site reactions, post-injection reaction, chest pain, facial erythema, tachypnea, fat necrosis at sites of prolonged injections
   c. Natalizumab: infusion reaction, opportunistic infections with fatalities (progressive multifocal leukoencephalopathy [PML], disseminated varicella-zoster virus infection), antibody formation
12. Guidelines for the use of the five drugs
   a. The five drugs are known by the abbreviation ABCRT and by their trade names:
      1) Avonex (IFN-β 1a, intramuscular [IM])
      2) Betaseron (IFN-β 1b)

3) Copaxone (glatiramer acetate)
4) Rebif (IFN-β 1a, subcutaneously [s.c.])
5) Tysabri (natalizumab)

b. The four approved drugs for relapsing MS produce approximately the same 30% reduction in annual attack rate. There is no valid method to choose among them based only on effectiveness. All are available only as injectable drugs. Natalizumab is more effective, but should only be used as a second-line agent after demonstrated inefficacy of the other injectable medications. The estimated risk of PML caused by natalizumab is estimated at 1 in 1,000 patients, but is not definitely known. Combining ABCRT drugs has no proved additional efficacy (although a combination trial of Avonex and Copaxone treatment, CombiRx, is ongoing). Natalizumab cannot be combined with any other therapies (with the exception of intravenous IV steroids that can be used for treatment of acute relapses) due to increased risk of PML.

c. The clinical trials to establish effectiveness have varied in their inclusion criteria, follow-up details, duration of treatment, and other parameters, and therefore cannot be easily compared. Recent "head to head" trials comparing effectiveness of high-dose IFN to glatiramer acetate (REGARD and BEYOND) showed no significant difference in outcome measures such as time to first relapse or number of new MRI lesions regardless of the treatment.

d. Frequency, mode of injection, dose, and side effects vary. Convenient prefilled syringes and automatic injection devices are available, and an extensive network of support services is readily available for patients.

e. Some IFN preparations seem to be more likely to produce abnormalities of liver chemistries or have been detected to produce neutralizing anti-IFN antibodies. The higher dose IFNs—Betaseron and Rebif—cause these problems more than does Avonex.

f. Most patients and doctors choose among drugs on the basis of ease of administration and side-effect profile. If side effects from one drug are limiting, a change can be made to another.

g. Some details of the issues affecting the choice among the five approved drugs:
1) Depression can be induced by IFNs, especially by higher dose IFNs. In a depressed patient, Copaxone might be preferred.
2) Widespread urticaria can occur with Copaxone, either early or late in treatment, and requires discontinuation.
3) Neutralizing antibodies (NAbs) are more likely to occur with higher dose IFNs. Their presence may be suggested if a patient again begins to have relapses after a period of stability. There is a commercially available test for NAbs but its frequent use is precluded by its high cost and by apparently meaningless variations in antibody levels. In large studies, the group of patients with NAbs had more relapses than the antibody-free patients.
4) Injection-site reactions can occur with any of the drugs administered s.c. They are most marked with Betaseron. Copaxone may cause areas of dimpling owing to adipose damage.
5) There appears to be a delay in onset of action of several months with Copaxone. In a patient with a very active MRI scan containing multiple areas of enhancement or in a patient with more than three relapses in the last 6 months, most MS specialists would use a high-dose IFN, such as Rebif.
6) Details of the prescriptions
   a) Avonex: 30 μg IM weekly. Dispensed as a kit for each month, containing medication and syringes.
   b) Betaseron: 250 μg s.c. every other day (q.o.d.). Dispensed as a kit. Usually begun at half-dose to reduce the flu-like symptoms at onset of therapy.

   c) Copaxone: 20 mg s.c. daily. Dispensed as a kit containing prefilled syringes; may be used with or without an auto-injection device.
   d) Rebif: 44 μg s.c. three times a week. It is usually begun with a schedule of escalating dose over 1 month. Dispensed as a kit with autoinjection device.
   e) Tysabri: 300 mg IV once every 28 days. It is administered in specialized MS centers. It requires an additional hour of observation to monitor for post-infusion allergic reaction.

13. Patients with secondary progressive disease need aggressive treatment early. As part of the natural history of most patients with MS, relapses slowly decline in number. In two IFN trials that contained a placebo arm lasting more than 2 years, the relapse rate in the placebo patients declined by about two-thirds. With successful treatment the relapse rate goes even lower. The natural history of MS, unfortunately, also is that most relapsing patients will enter the secondary progressive phase of the illness, and disability will steadily increase from that point. Therefore, at any one time, about half the patients with MS will be in the secondary progressive phase. It is likely that there has been some change or evolution in the basic pathology in these patients. The change cannot be recognized on MRI scans, except by the fact that atrophy of white matter and gray matter structures and enlargement of the ventricular system are found as its consequence. Once disability due to SPMS is well established and present for more than a few years, it is very unlikely to be reversible. For this reason, if aggressive therapy is decided upon, it should be used relatively early. For a patient who has been wheelchair-dependent for 3 years, it is probably too late.

Treatment for Secondary Progressive MS

1. IFNs: A number of trials of IFN-β, for SPMS have been reported. One trial in Europe seemed to show a positive effect, but these patients were having relapses in addition to steady progression, and the major effect seen was on the relapse rate. A trial organized in the United States probably contained fewer patients with "transitional" MS who were still having relapses. It showed no effect of IFN-β on disability. Accumulation of disability due to incomplete recovery from relapses can certainly occur, and this aspect of SPMS is preventable with IFN therapy.
2. Long-term IV steroids, usually given as a monthly bolus of 1,000 mg of methylprednisolone, are in use in many MS clinics. There has not been an adequate trial of such usage in either relapsing MS or SPMS. A more common usage is to give the steroid as a 3- to 5-day course, administered several times per year when apparent relapses are detected. If steroids are given frequently, bone density should be monitored and appropriate therapy instituted when osteopenia occurs.
3. Low-dose oral chemotherapy agents.
   a. Azathioprine has been in use for decades, especially in Europe. Meta-analysis of a large amount of data, typically of dosage ranges of 100 to 200 mg/d, shows a very small positive effect. It is not often used.
   b. Methotrexate has been used in dosages of 7.5 to 20 mg orally once a week. A sensitive assay of hand function in wheelchair patients showed a detectable minor effect of the drug. It is often used as an "add-on" in combination with Copaxone or an IFN. No class I or II data are available to support this usage.
   c. Mycophenolate mofitil (Cellcept), in doses typically used for transplantation recipients, has been reported in pilot studies.
4. IV chemotherapy agents: The rationale behind the use of these agents is that intense nonspecific immunosuppression will arrest the progressive phase of axon and myelin destruction. Two agents are now in widespread use, cyclophosphamide and mitoxantrone. They share the potential problems of infection, bone marrow failure, or other common difficulties with chemotherapy, and both have

a lifetime total dose limitation. This means that even if effective, another strategy has to be available for the time when that limit is reached. Additional agents are entering the MS treatment armamentarium, including rituximab, a drug that selectively targets and depletes CD-20+ B cells.

a. Mitoxantrone, commonly prescribed for myelogenous leukemia, is a member of the anthracenedione group. It inhibits DNA repair and causes crosslinks and scissions in nucleic acids. In patients with MS, it has a striking suppression of enhancement in lesions seen on MRI. Based on a 1998 trial of two dose levels of the drug compared with placebo, which showed a statistically significant effect on disability, mitoxantrone (Novantrone) has been approved by the Food and Drug Administration for use in SPMS. The drug is given IV once every 3 months at a dose of 12 mg/m^2 to a maximum dose of 140 mg/m^2. The maximum dose is usually reached in about 2 years. It is well tolerated. Cardiac toxicity can occur.

b. Cyclophosphamide has been in use for nearly 20 years for progressive forms of MS. The drug is an alkylating agent with powerful cytotoxic and immunosuppressive effects. No adequately controlled study has been carried out, although there are extensive class II data. The drug is usually given as a monthly bolus infusion of 800 mg/m^2 or increased from that level to obtain a nadir in total white blood cells (WBCs). Each infusion produces some nausea, anorexia, and modest alopecia. One obvious long-term risk of the drug is that of metaplasia and eventual malignancy of bladder mucosa. Long-term oral cyclophosphamide carries a significant risk of induction of other neoplasms, which has not been observed with the IV bolus program. Ovarian and testicular functions are impaired; women in their thirties who are treated commonly enter the menopause.

c. Both these drugs, if used, should be given by an oncologist or specialist familiar with their use and the potential complications of the treatment. Unfortunately, their records of success are only modest. Even if there is a response, one is faced with the problem of subsequent therapy after the maximum has been reached.

d. Rituximab has been shown to decrease relapse rate and MRI disease activity in Phase II double-blind, placebo-controlled trials in RRMS patients. Unfortunately, in a separate trial, it did not show an effect in PPMS patients. It has been associated with PML complications in cancer and autoimmune disease patient population.

General Treatment Comments

1. Patients with PPMS cannot be expected to respond to any disease-altering treatment.

a. PPMS, although certainly demyelinating, may not be the same disease as relapsing MS or SPMS. There is a preponderance of males, the lesions and clinical deficits are often located mainly in the spinal cord, and the lesions seen on MRI scans are often unimpressive. To make a firm diagnosis, additional evidence from evoked potentials testing or CSF examination is often required.

b. Many observations of the effects of IFNs, Copaxone, chemotherapy agents, and high-dose bolus steroids and the results of a number of clinical trials make it clear that PPMS does not reliably respond to any of these treatments. Symptomatic treatment should be emphasized, and in this arena, some progress can often be made in the individual patient.

2. MS is a lifelong illness and there is no current paradigm for discontinuation of treatment. The entity of benign MS does exist, and in every MS clinic there are patients who have had several relapses years or decades ago, who have no disability, who have MRI scans showing inactive disease, and who do not need any form of

treatment. Unfortunately, the current estimates are that only about 10% of patients have benign MS. If a patient is doing well on long-term IFN or Copaxone, the drug needs to be continued without interruption indefinitely. Nearly all of the clinical trials can be criticized for their short duration and for measuring endpoints that are not important. In the end, a significant treatment effect will be seen if the drugs prevent disability.

3. Patients need to be observed for signs of disease activity by clinical and/or MRI monitoring. Since the therapies for relapsing MS are only partially effective, some patients will respond and others will not. It may be a matter of careful judgment to decide if a patient's disease has come under control or not. Patients should be encouraged to report new symptoms. Periodic examinations should be performed. The role of periodic MRI scanning is less clear. A routine annual MRI scan probably is of little value. During that year, new enhancing lesions may have come and gone. Alternatively, a false impression of major disease activity may be furnished by a scan that happens to detect a small enhancing lesion of little import. Centers with access to frequent MRI scanning have shown that new lesions detected by MRI are about 10 times as frequent as clinically detected lesions.
4. When to switch or change?
   - **a.** A patient with little or no disability and no relapses on treatment should remain on treatment.
   - **b.** A patient with some disability and still working or able to work, but with abnormal gait or balance, should be observed carefully for the progressive disease. An MRI scan may be beneficial. A scan that reveals enhancement indicates that a change of therapy is needed. A patient beginning to use a cane is one at high risk for further progression.
   - **c.** A patient with major side effects from IFN, persisting flu-like symptoms after injection, depression, or headache, can be switched directly to Copaxone.
   - **d.** A patient with major side effects from Copaxone, urticaria or syncope after injection, can be switched to IFN.
   - **e.** A patient with relapses on Avonex can be switched to high-dose IFN, Betaseron or Rebif.
   - **f.** A patient who has several relapses a year on treatment should be classified as a treatment failure. Alternate or additional therapy must be sought. Consultation or a second opinion is desirable. NAbs may have formed making IFN treatment ineffective or less effective, or the patient may have entered the progressive phase or may simply be a nonresponder. In any case, a change is needed.

Special Considerations

1. Clinically Isolated Syndrome (CIS): MS often presents for the first time with ON, an acute brainstem syndrome, or TM. This first episode is known as CIS. Not all patients with CIS develop clinically definite MS (CDMS). Treatment with MS-specific medications should be offered to CIS patients based on results of CHAMPS trial (Avonex), BENEFIT trial (Betaseron) and PreCISe trial (Copaxone.) All three agents showed decreased rate of conversion to CDMS from CIS.
2. *ON* can be an early symptom of MS (CIS event), or a separate disease entity. Patients typically present with acute/subacute unilateral decrease or loss of vision, impairment of color vision, and pain on eye movements. Examination may show reduced visual acuity on the affected side, relative afferent pupillary defect (RAPD), and inflamed optic nerve head. Visual evoked response (VERs) often show prolonged latency of P100 wave; Goldman Visual Field test shows central scotoma or other visual field defect. MRI may show T1 postcontrast enhancement of the optic nerve on the affected side. ON can be treated with IV methylprednisolone at a dose of 1,000 mg for 3 to 5 days. This treatment hastens visual recovery but does not

improve the visual acuity (Optic Neuritis Treatment Trial). However, it decreases the rate of second clinical event over 24 months of follow-up, thus decreasing the probability of conversion to CDMS. Immunomodulating treatment may be offered based on CHAMPS study: IFN-β 1α 30 mg weekly injections reduced conversion rate to CDMS by 50% in treated patients but not in placebo group.

3. *TM* is an acute or subacute inflammation of the spinal cord. It is usually limited to two to three spinal segments and occupies less than two-thirds of cross-sectional cord diameter. Similarly to ON, it can be a precursor to MS (CIS event), or occur independently (postinfectious, infectious, or idiopathic TM). Symptoms may include ascending numbness and paresthesias in the legs, trunk, or perineum, leg weakness, difficulty with or a loss of bladder and/or bowel control, or back pain. Exam findings depend on the level of spinal cord involvement and may show decreased sensation to various modalities in the legs and/or the arms, spinal sensory level, paraparesis, abnormal deep tendon reflexes, and pathologic reflexes. Involvement of the entire cross-sectional cord diameter and complete loss of sensation with paraplegia is seen more often in postinfectious or infectious TM rather than in MS. Treatment with IV methylprednisolone 1 g $\times$ 3 to 5 days is usually undertaken, although in contrast with ON, there are no trials with clear evidence of efficacy.

OTHER DEMYELINATING DISEASES

1. Balo's concentric sclerosis is a rare variant of MS. It is characterized by alternating bands of demyelinated and myelinated white matter in concentric rings or irregular stripes. Lesions may be multiple or mixed with other, more typical MS plaques. It is often a feature of aggressive disease but it can occur in chronic MS.
2. Marburg variant of MS is a severe, sometimes monophasic disease form leading to advanced disability or death within a period of weeks to months. It is usually a clinical diagnosis based on the speed and severity of progression of neurologic disability. No treatment has consistently proven effective. MRI shows extensive, diffuse, confluent cerebral involvement giving the appearance of "MS cerebritis." Sometimes, a large solitary expanding lesion *(tumefactive MS; tumorlike demyelination)* can be seen. These patients often undergo brain biopsy which shows extensive inflammatory infiltrates and demyelination. High-dose steroids are often ineffective though they are usually tried. Transient improvement with aggressive chemotherapy regimens has been described. Some patients have a more benign course and are considered by some experts to represent a transitional demyelinating illness between MS and ADEM.
3. Acute demyelinating encephalomyelitis (ADEM) is a monophasic, acute, autoimmune demyelinating illness that typically occurs after an upper respiratory infection (URI) (50% to 75%) or vaccination. First symptoms are seen 7 to 14 days postinfection and most patients require a hospital admission within a week. Children are more prone to ADEM than adults. Clinical presentation varies by age: children often present with prolonged fever, headache, and brainstem syndrome (imbalance/gait instability, dysphasia/dysarthria, diplopia), while adults can have a milder illness with limb paresthesias and weakness. Suspect ADEM when:
   a. There is a close temporal relation between infection/vaccination and multifocal CNS process
   b. MRI shows >50% involvement of white matter and may also involve deep gray matter with enhancement present in most/all lesions
   c. CSF analysis shows mild lymphocytic pleocytosis, protein elevation, and typically no oligoclonal bands

   d. Biopsy is performed (usually only for tumefactive or solitary lesions) because ADEM pathology shows perivascular infiltration with macrophages and T cells and demyelination restricted to perivascular area (unlike MS)
   e. Examination hallmarks include confusion/disorientation, altered level of alertness, gait ataxia, dysmetria, dysarthria, brainstem signs, abnormal sensation, and pyramidal weakness
   f. Treatment options include IV corticosteroids, plasmapheresis, intravenous immunoglobulin (IVIG), and cytotoxic chemotherapy. Efficacy is variable. Full recovery is expected in more than 70% of patients; 10% to 20% are left with mild-moderate disability; sudden severe polysymptomatic onset implies worse prognosis and there is 5% mortality in this group of patients

4. Acute necrotizing hemorrhagic encephalopathy, or Weston Hurst disease, is a fulminant form of ADEM. Pathologic lesions are similar to ADEM. It is always preceded by respiratory infection (often, micoplasma). Microscopic hemorrhages and perivascular neutrophilic infiltrates as well as necrosis of small blood vessels and surrounding brain tissue can be seen on pathology specimens. Response to treatment is very limited and mortality is high in this disease, especially within the first 2 to 4 days after the diagnosis.

5. Neuromyelitis Optica (NMO) (Devic disease) is a variant of MS predominantly affecting the spinal cord (myelitis) and bilateral optic nerves. It can have a monophasic or a relapsing course. It is common in Africa and Asia, as well as in African and Asian Americans. Japan has the highest incidence of NMO with at least 10,000 affected persons. Myelitis usually spans more than three spinal segments and often is accompanied by swelling of the spinal cord. Pathology in the spinal cord and optic nerves shows extensive demyelination, cavitating necrosis, acute axonal injury, and loss of oligodendrocytes. IgG anti-NMO antibodies, directed against the aquaporin-4 water channel, are positive in 73% of patients with NMO. Oligoclonal bands are present in 85% of these patients. Brain MRI may show few T2 hyperintense lesions while spinal cord MRI usually shows extensive lesions. Natural history of NMO is that of a rapidly progressive and disabling neurologic illness: 50% of patients are wheelchair bound within 5 years of the diagnosis, and 60% of patients become functionally blind within the same time frame. Immunosuppression is partially effective in nonrandomized trials. IV methylprednisolone and plasma exchange can be used. Rituximab has recently showed efficacy in trials with significantly improved disability scores and decreased attack rate in NMO patients.

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