CME CREDIT

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Multiple sclerosis: The importance of early recognition and treatment

ABSTRACT

Primary practitioners need to know how to expedite the diagnosis and treatment of multiple sclerosis (MS), because treatments that can slow its course appear to be most effective when started early. Several lines of evidence demonstrate that tissue damage occurs very early in the disease, and much of this damage is clinically silent.

KEY POINTS

After the diagnosis of MS is made and appropriate treatments started, patients require ongoing care. Primary care physicians play an important role in identifying and managing MS symptoms.

An effective partnership between the patient's primary care provider and neurologist can help patients remain active by addressing symptoms and complications of MS.

In clinical trials, interferon (IFN) beta-1a, IFN beta-1b, IFN beta-1a(R), and glatiramer acetate reduced the relapse rate by approximately 30%.

RECENT STUDIES AND NEW TREATMENTS are changing the approach to multiple sclerosis (MS). The studies have shown that, although clinical manifestations are intermittent and often mild early in the disease, pathologic damage accumulates from the onset. New treatments can slow the progression of neurologic manifestations, but must be started early in the course of the disease.

Primary care providers need to be familiar with MS, its complications, and different treatments to expedite diagnosis and coordinate treatment. They play a key role in identifying and managing the protean symptoms of MS.

CLINICAL FEATURES OF MS

MS is a chronic inflammatory disorder of the central nervous system (CNS—brain, optic nerves, and spinal cord) characterized pathologically by demyelination and axonal damage. In the United States, an estimated 250,000 to 350,000 people have MS.

Symptoms

Because the lesions in MS are multifocal and can develop in any location within the central nervous system, the possible clinical manifestations are diverse (TABLE 1). Symptoms vary markedly from patient to patient and in individual patients over time.

Motor deficits in MS include weakness, spasticity, and ataxia. **Weakness** usually is central in character and accompanied by **spasticity** (abnormal increased muscle tone), **hyperreflexia**, and **abnormal cutaneous reflexes** (eg, the Babinski sign). These physi-

TABLE 1

Typical neurologic manifestations of MS

MANIFESTATION	PERCENT OF PATIENTS WITH MANIFESTATION*	
	AT PRESENTATION	DURING THE COURSE
Visual loss or oculomotor dysfunction	49	100
Weakness	43	88
Sensory deficits	41	87
Incoordination	23	82
Bladder, bowel, or sexual dysfunction	10	63
Cognitive impairment	4	39

*Total percentages are greater than 100% because some patients had multiple symptoms

ADAPTED FROM POSER S, WIKSTROM J, BAUER HJ. CLINICAL DATA AND THE IDENTIFICATION OF SPECIAL FORMS OF MULTIPLE SCLEROSIS IN 1271 CASES STUDIED WITH A STANDARDIZED DOCUMENTATION SYSTEM. J NEUROL SCI 1979; 40:159–168.

MS patients list fatigue as their most troubling symptom

cal findings in a young patient with previous neurologic symptoms may raise the suspicion of MS. Involvement of the cerebellum or its connections leads to appendicular, truncal, gait, bulbar, or ocular **ataxia**.

Sensory loss can involve any combination of the limbs or trunk and any combination of the senses. Sometimes the pattern of sensory loss can be patchy or can simulate a peripheral nerve or spinal root distribution. Negative sensory symptoms (ie, loss of sensation) often are accompanied by positive sensory phenomena (see below). **Visual loss** in MS reflects the site of involvement of the afferent visual system. Unilateral loss of vision due to optic or retrobulbar neuritis is the most common pattern. Lesions of the efferent visual system produce abnormalities of eye movements. Diplopia and blurred vision are the most common symptoms.

Urinary symptoms. The most straightforward bladder manifestation is urinary frequency and urgency resulting from detrusor hyperactivity. However, urinary manifestations of MS more commonly include failure of the bladder both to store urine appropriately and to empty completely. Formal urodynamic studies often are necessary to delineate accurately the pathophysiology of the urinary dysfunction and to distinguish neurogenic mechanisms from structural causes. Similarly, **bowel symptoms** can include both constipation or urgency and incontinence.

Gait dysfunction caused by MS has special significance because the resultant disability has an impact on quality of life and self-image. Potential causes of gait dysfunction include weakness, spasticity, ataxia, vestibular symptoms, sensory loss, and visual disturbances. Evaluation by a physical therapist can help to sort out the principal cause or causes of gait dysfunction and decide upon compensatory strategies.

Commonly overlooked symptoms

Physicians frequently overlook several common symptoms of MS, including sexual dysfunction, cognitive impairment, fatigue, and pain. Because these manifestations can have a significant impact on quality of life, they are important to identify. Each has many possible causes in addition to MS, which need to be considered before attributing these symptoms to MS.

Sexual dysfunction. Although patients and health care professionals often are uncomfortable raising the issue of sexual dysfunction, it has an important impact on the patient's sense of self-worth and relationships with others. Erectile dysfunction is common in men, and altered libido and genital sensation are common in both men and women.

Cognitive dysfunction, which is common in MS, most often involves problems with concentration, processing speed, executive function (eg, planning), and visuospatial abilities. Formal neuropsychologic testing often is necessary to confirm the presence of cognitive dysfunction and to quantify its severity.

Fatigue. In a survey of patients with MS, fatigue was listed as the most troubling symptom.[1] Two types of fatigue are characteristic of MS. First, patients with MS often experience worsening in neurologic function with exertion, probably reflecting failure of nerve conduction in demyelinated pathways with repeated use or increased body temperature. Second, patients report a chronic lack of energy independent of exertion. Similar fatigue occurs in a variety of immune and infectious disorders and may result from chronic immune activation and elaboration of immune mediators.

TABLE 2

Classification of MS based on clinical course

Relapsing-remitting
Symptoms and signs develop in the context of clearly defined acute relapses followed by partial or complete recovery

Clinical manifestations are stable between relapses

Secondary progressive
After an initial relapsing-remitting course, manifestations worsen gradually with or without superimposed acute relapses

Primary progressive
Manifestations gradually worsen from disease onset without relapses

Progressive relapsing
Manifestations gradually worsen from disease onset with subsequent superimposed relapses

ADAPTED FROM LUBLIN FD, REINGOLD SC. DEFINING THE CLINICAL COURSE OF MULTIPLE SCLEROSIS: RESULTS OF AN INTERNATIONAL SURVEY. NEUROLOGY 1996; 46:907–911.

TABLE 3

Schumacher criteria for MS

All of the following must be present:

Onset of symptoms between ages 20 and 50

Manifestations indicating central nervous system white matter disease

Lesions disseminated in time and space

Objective abnormalities on examination

Manifestations develop as relapses lasting more than 24 hours, spaced 1 month or more apart, or gradual or stepwise progression

Alternative diagnoses eliminated

ADAPTED FROM SCHUMACHER GA, BEEBE GW, KIBLER RF, ET AL. PROBLEMS OF EXPERIMENTAL TRIALS OF THERAPY IN MULTIPLE SCLEROSIS: REPORT BY THE PANEL ON THE EVALUATION OF EXPERIMENTAL TRIALS OF THERAPY IN MULTIPLE SCLEROSIS. ANN NY ACAD SCI 1965; 122:552–568.

Pain. In addition to loss of sensation, patients with MS often complain of positive sensory symptoms, described as uncomfortable tingling, aching, or prickling. These often have a variable distribution and can change over time. At times patients experience frank pain, which may be sharp, lancinating, and paroxysmal or more chronic burning dysesthesia.

Classification is based on disease course

As outlined in TABLE 2, MS is classified on the basis of the time course over which manifestations develop.[2] Since this classification system is empiric and not based on biologic criteria, the pathogenic differences between disease forms remain uncertain. Nonetheless, this classification system provides the framework for an organized approach to diagnosis and long-term management and also allows clinical trials to define a more homogeneous population for study.

Relapsing-remitting. In approximately 85% of patients, MS initially has a relapsing-remitting course. Symptoms of a relapse typically develop over several days to weeks and then resolve over several weeks to months. The manifestations can resolve completely, or there may be residual neurologic deficits. Relapses occur on average every 1 to 2 years, although the relapse rate varies markedly both between patients and in individual patients over time.

Secondary progressive. Relapsing-remitting MS usually evolves into a secondary progressive course an average of 10 to 15 years after the disease onset.[3] When MS lasts 25 years or more, approximately 90% of cases with an initial relapsing-remitting course eventually convert to a secondary progressive course. In secondary progressive MS, preexisting neurologic deficits gradually worsen over time. Early in the transition from relapsing-remitting to secondary progressive MS there may be relapses superimposed on gradual worsening, but relapses usually become less evident over time.

Primary progressive. Approximately 15% of patients have gradually worsening manifestations from the onset without clinical relapses: so-called primary progressive MS. Compared with those with relapsing-remitting/secondary progressive MS, patients with primary progressive MS typically are older at onset, more often are men, have fewer abnormalities on magnetic resonance imaging (MRI) of the brain, and respond less readily to diseased-modifying immunotherapies.

Suspect MS in a young adult with relapsing neurologic symptoms

TABLE 4

Red flags for the potential mistaken diagnosis of MS

Onset of symptoms before age 20 or after age 50
Atypical course (eg, gradually progressive from onset without stabilization or remissions, or abrupt onset of symptoms)
Very prominent family history of a similar disorder
Prominent neurologic manifestations unusual for MS (eg, headache)
Systemic manifestations (eg, prominent rheumatic symptoms)
Unifocal neurologic manifestations even if relapsing
Absent features typical of MS (eg, lack of sensory or bladder involvement, or normal MRI), particularly in long-standing or severe disease
Atypical response to treatment (either lack of any response or an unusually rapid and dramatic response)

Progressive relapsing MS is defined as gradual neurologic worsening from the onset with subsequent superimposed relapses. It is suspected that progressive relapsing MS represents secondary progressive MS in which the initial relapses were unrecognized, forgotten, or clinically silent.

Cranial MRI is the most useful test for MS

DIAGNOSING MS

MS has no pathognomonic clinical, laboratory, or imaging finding. Therefore, the diagnosis ultimately is a clinical decision based on weighing the factors that support the diagnosis against those that fail to support it or point to the possibility of an alternative diagnosis. The Schumacher criteria[4] outline the clinical features typical of MS (TABLE 3). Imaging and laboratory studies are used to add support to the diagnosis and rule out other causes of symptoms.

Establishing the diagnosis of MS is straightforward in patients who exhibit classic clinical features and a relapsing-remitting or secondary progressive course. In this situation the likelihood of finding another disorder is small, and testing is unnecessary other than cranial MRI and selected blood work. However, certain "red flags" suggest that a diagnosis other than MS needs to be considered (TABLE 4). More extensive testing, guided by the clinical picture, is warranted in such cases to better confirm the diagnosis of MS and eliminate other disorders.

Cranial MRI is the most useful test in the diagnostic evaluation for MS. It is abnormal in approximately 90% of MS patients, although it may be normal or the findings nonspecific early in the disease course.

MRI of the brain should include long TR images (either fluid-attenuated inversion recovery [FLAIR] or T2-weighted sequences) plus T1-weighted images before and after administration of gadolinium.

Typical findings include multiple ovoid or patchy foci of increased signal on long TR images in the periventricular and subcortical white matter, corpus callosum, brainstem, and cerebellum (FIGURES 1 AND 2). Often, one or more (but usually not all) of the lesions enhance following administration of gadolinium. The enhancement results from leakiness of the blood-brain barrier and is thought to indicate lesions with active inflammation. Atrophy of the parenchyma and corpus callosum are well-recognized features of long-standing MS.[5]

Spinal MRI should be obtained if cranial MRI is negative, in older patients in whom nonspecific cerebral white lesions sometimes can be found, or if the patient's principal manifestations localize to the spinal cord.

Additional studies. Additional support for the diagnosis of MS can be obtained with the demonstration of **intrathecal immunoglobulin production** (increased IgG index or oligoclonal bands) on cerebrospinal examination or **abnormalities on evoked potentials**. In general, these studies are not necessary in patients with clinical and MRI features typical of MS but should be obtained if the clinical and MRI findings fail to adequately support the diagnosis of MS or if atypical features raise the possibility of an alternative diagnosis.

Laboratory tests are necessary to help exclude other disorders that can mimic MS. When a patient's clinical and radiologic manifestations are typical of relapsing-remitting or secondary progressive MS, only limited laboratory studies are necessary: for example an **antinuclear antibody** (ANA) titer and **erythrocyte sedimentation rate** to screen for connective tissue disorders, **serologic tests for syphilis, vitamin B_{12} level, thyroid-stimulat-**

ing hormone level to screen for thyroid disease, and a **complete blood count**. A low-positive ANA titer is common in MS and should not cause confusion. When the clinical picture is atypical, more complete laboratory studies are needed and are directed by the clinical setting.

Should the diagnostic criteria be redefined? Current diagnostic criteria do not allow clinicians to diagnose MS at the first clinical manifestation. However, in patients with an isolated inflammatory CNS syndrome consistent with an MS relapse, the presence of multiple lesions on brain MRI or evidence of intrathecal immunoglobulin synthesis in cerebrospinal fluid substantially increases the risk of an additional relapse.[6,7]

Until recently our practice was not to start therapy routinely at this stage. However, two recent studies[8,9] reported benefit from initiation of disease-modifying therapy with interferon (IFN) beta following a single demyelinating event. These findings have led to efforts to redefine the diagnostic criteria for MS to allow appropriate initiation of treatment at an early stage.

PATHOGENESIS OF MS

The underlying cause of MS remains unknown. The prevailing hypothesis is that MS results from a cell-mediated autoimmune attack directed against myelin antigens, but emerging evidence suggests that the immunopathogenesis probably is more complex.[10] The genetics of MS involves multiple genes conferring a genetic predisposition and possibly determining disease course and severity.[11] A variety of environmental factors have been implicated as potential causes of MS, particularly infectious agents. However, follow-up studies have failed to confirm any of these putative causes.

Historically, **demyelination** has been considered the main pathophysiologic mechanism producing neurologic manifestations in MS. While inflammatory demyelination and the resultant block of nerve conduction in affected pathways accounts for the reversible neurologic sequelae of acute relapses, several lines of evidence suggest that permanent disability results from **axonal damage**. Two recent autopsy studies[12,13] demonstrated that extensive axonal damage is a consistent and prominent feature of MS lesions. Cerebral atrophy on MRI is a frequent finding in patients with severe long-standing disease, and considerable brain atrophy can be detected in patients with early relapsing-remitting MS and only mild clinical disability.[14,15] Clearly, the pathophysiology involves permanent injury, even at an early stage of disease.

MRI appearance of MS: Typical lesion locations

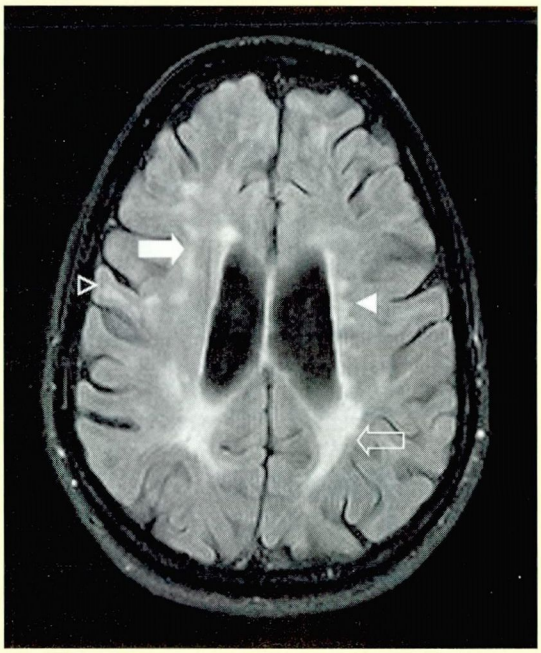

FIGURE 1. T2-weighted magnetic resonance image of a 24-year old woman with a 2-year history of relapsing-remitting MS. There are multiple white-matter lesions in a classic distribution, ovoid lesions oriented perpendicular to the lateral ventricles (Dawson's fingers, closed arrowhead), deep white-matter lesions (closed arrow), subcortical lesions involving U-fibers (open arrow head), and confluent lesions adjacent to the posterior horn of the lateral ventricle (open arrow). None of the lesions enhanced following gadolinium administration. There is moderate atrophy manifested as ventricular enlargement and prominent sulci. Despite early relapsing-remitting MS, this patient has severe radiological findings, placing her at increased risk for future disability.

MRI appearance of MS: Gadolinium enhancement

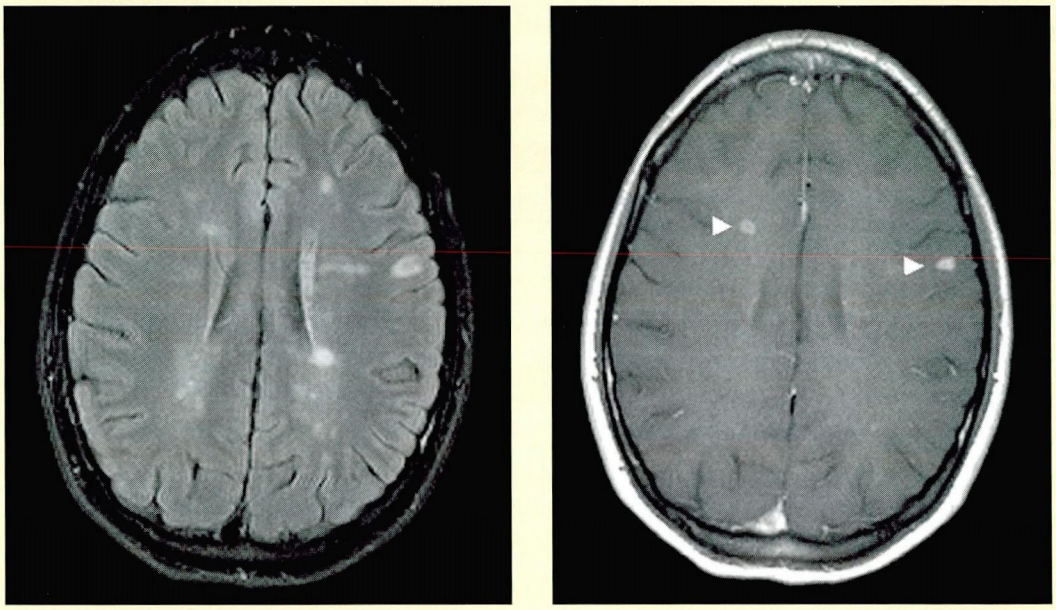

FIGURE 2. Left, T2-weighted magnetic resonance image of a 25-year-old woman with a 5-year history of relapsing-remitting multiple sclerosis. **Right,** gadolinium-enhanced T1-weighted image of the same patient. Some of the T2 lesions exhibit gadolinium enhancement.

Permanent tissue damage begins to accumulate early in the disease

Current concepts of the pathogenesis of MS are summarized in FIGURE 3. Approximately 60% to 70% of patients have multiple brain lesions on MRI at the time of the initial clinical event,[16,17] suggesting that subclinical inflammatory events often predate the clinical presentations. On average, patients have clinical relapses every 1 to 2 years during the relapsing-remitting phase of the disease. Serial MRI studies have shown that MRI-active lesions (defined as new or enlarging T2 lesions or lesions demonstrating gadolinium enhancement) develop up to 10 to 20 times more frequently than clinical relapses.

Thus, although relapsing-remitting MS appears to have clinically active and quiescent periods, inflammatory lesions are developing or evolving almost continuously. Although residual manifestations between relapses often are mild during this stage of disease, there is ongoing tissue damage, manifested as accrual of MRI lesions and progressive brain atrophy.[14,15,18] Thus, clinical relapses and the progression of disability are a poor reflection of the ongoing inflammation and resultant tissue damage at early stages of the disease.

A current hypothesis states that overt progression of disability occurs when ongoing irreversible tissue injury exceeds a critical threshold beyond which the nervous system can no longer compensate. This results in the apparent conversion from relapsing-remitting to secondary progressive disease. Ultimately, gadolinium enhancement becomes rare, and patients gradually worsen without acute relapses. It is thought that at this point the disease has become essentially a degenerative process, with neurologic deterioration independent of ongoing inflammation.

START THERAPY EARLY

An important implication of this hypothesis is that, to be maximally effective, disease-modifying immunomodulatory therapy should be started early in the relapsing-remitting phase and before permanent disability develops (TABLE 5).

For patients with relapsing-remitting MS, it is often difficult to decide when to start long-term therapy with an injectable medication, especially when they feel well much of the time. Some prefer to wait and see if they develop disability before starting treatment, in the hope of avoiding or at least delaying therapy. Physicians sometimes reinforce this sentiment by suggesting that the patient may have "benign" MS and may not develop disability in the future. However, the diagnosis of benign MS can only be made retrospectively. Although MS patients typically have mild manifestations between relapses and minimal residual disability for 5 to 10 years after disease onset, in nearly 60%, the disease evolves into a secondary progressive course with moderate to severe disability within 15 years of onset.[3] This increases to 90% at 25 years after diagnosis, which leaves the majority of patients disabled at a relatively young age. In a cohort of MS patients initially studied in 1987, 28% were thought to have benign MS. On follow-up 10 years later, however, only 7% still were considered to have benign disease.[19]

It is likely that the accumulation of irreversible tissue damage limits the potential for benefit from disease-modifying immunomodulatory therapy as the disease progresses and becomes a degenerative process. The Medical Advisory Board of the National Multiple Sclerosis Society recently recommended that disease-modifying therapy with one of the approved agents be considered in all patients with active relapsing-remitting MS to lessen the risk of disease progression and development of disability. We agree with this recommendation. The therapeutic nihilism of the past should be replaced by aggressive treatment and monitoring.

DISEASE-MODIFYING THERAPIES

Therapy for relapsing-remitting MS

After the diagnosis of MS is made, consideration should turn to disease-modifying therapy. Current therapies target the immune dysfunction in MS and resultant neural tissue damage with the goal of preventing or at least reducing the long-term risk of clinically significant disability. In clinical trials, measures of effectiveness of therapy have included relapse rate, progression of disability, and quantitative MRI analyses.

In early MS, the disease is active and progresses even during relapses

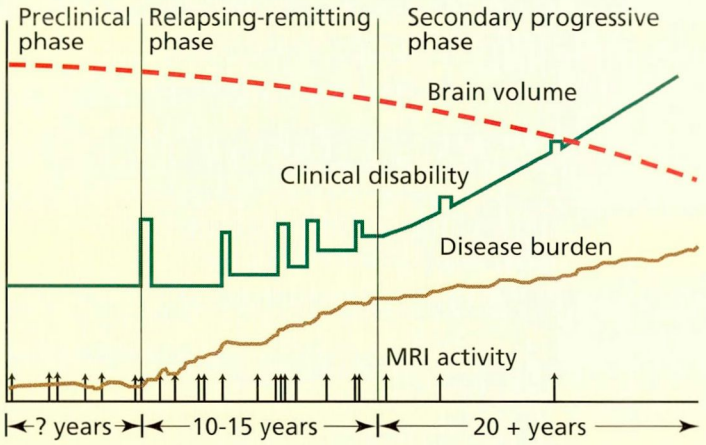

FIGURE 3. Typical clinical and MRI course of multiple sclerosis. **MRI activity** (vertical arrows) indicates an inflammatory process as measured on brain MRI by gadolinium enhancement or new T_2 hyperintense brain lesions. MRI activity typically is more frequent than clinical relapses (spikes in **clinical disability**), which indicates that more disease activity is taking place than is clinically apparent. Loss of **brain volume** and increase in **disease burden** (total volume of lesions), both measured on MRI, indicate permanent tissue damage, which is present early in the disease and gradually progresses over time.

Based on various combinations of these outcomes, three treatments are currently approved for use in relapsing-remitting MS in the United States: **IFN beta-1a** (Avonex),[20] **IFN beta-1b** (Betaseron),[18,21], and **glatiramer acetate** (Copaxone).[22] A second form of IFN beta-1a (**IFN beta-1a(R)**, Rebif) has been approved in Europe and Canada.[18] The IFN betas are recombinant products with an amino acid sequence that is identical or nearly identical to that of human IFN beta. Glatiramer acetate is a random polypeptide based on the amino acid sequence of myelin basic protein.

Although the definitive trials of these drugs examined different patient populations, had different end points, and produced somewhat different data, in our view these agents

TABLE 5

Why MS should be treated early

Most cases ultimately evolve into a secondary progressive course with some degree of permanent disability
Although benign MS exists, it is rare
The ability to predict prognosis in individual patients is limited
Clinical features correlate poorly with the ongoing inflammatory process, with resultant progressive irreversible tissue destruction in early, relapsing-remitting MS
Disease-modifying therapies are available that effectively reduce disease activity and accumulation of disability in relapsing-remitting MS, albeit incompletely; these therapies are preventative, not restorative
Extensive experience confirms that, despite troublesome side effects, these agents are safe in general
Accumulating irreversible pathology, decreasing inflammation, and evolution of MS into a degenerative process limit the effectiveness of disease-modifying therapies late in the disease
Emerging evidence suggests increased effectiveness of the available therapies when started early in the disease

Benign MS is rare

appear to have largely comparable clinical efficacy. All four agents reduced the relapse rate by approximately 30%, decreased the severity of the relapses, and had beneficial effects on measures of MS activity and lesion accrual on MRI. As for delay of disability progression, the data were most convincing for IFN beta-1a, which produced a 37% reduction in disability progression in a phase 3 trial. It is anticipated that the beneficial effects on relapses, disability progression, and MRI measures of disease activity demonstrated in clinical trials lasting for 2 to 3 years will translate into meaningful long-term benefit. However, this prediction is as yet unproven.

Based on the definitive clinical trials and extensive post-marketing experience, all of these agents clearly are safe and effective in relapsing-remitting MS.

Limitations of therapy. All of the available agents have limitations. All are expensive, costing approximately $10,000 per year. All are given by injection one or several times per week, which is inconvenient and unpleasant for most patients. And all of these agents have side effects, although serious adverse effects have been extremely rare (TABLE 6). Patients continuing with long-term disease-modifying therapies should receive education about potential side effects and aggressive management of side effects. In general, we recommend that a neurologist familiar with the use of these therapies be consulted when they are initiated.

The most important limitation of the agents available to treat relapsing-remitting MS is their partial effectiveness. A substantial proportion of patients in the active treatment groups in all of the studies continued to have relapses and worsening disability. Emerging evidence of pathological heterogeneity in MS[10] suggests that the partial efficacy of these agents for patients as a group may reflect the presence of responders and nonresponders to each agent in the population.[23] Ongoing monitoring of patients during treatment is important to detect nonresponders and modify therapy accordingly.

Mitoxantrone (Novantrone) was approved in October 2000 by the US Food and Drug Administration for "reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary-progressive, progressive-relapsing or worsening relapsing-remitting MS." Mitoxantrone has potent effects on both cellular and humoral immune mechanisms. Typically in MS it is given as an intravenous infusion every 3 months. In clinical trials, mitoxantrone treatment led to significant reductions in relapse rates, disability progression, and MRI measures of disease activity and lesion burden in patients with relapsing-remitting and secondary progressive MS.[24,25] In general, mitoxantrone has been well tolerated, the most common adverse effects being nausea, bone marrow suppression, amenorrhea, and infertility. Potential cardiac toxicity is related to total cumulative dose, which limits duration of treatment to about 2 years. Mitoxantrone is also associated with an increased risk of leukemia. Due to its potential toxicity, mitoxantrone should be administered by practitioners familiar with its use.

Treatment for secondary progressive MS

Treatment of secondary progressive MS is more problematic, and, until recently, there were no therapies demonstrated to be of benefit.

TABLE 6

Side effects of immunomodulating treatments

DRUG AND SIDE EFFECTS*	COMMENTS AND TREATMENTS
IFN beta	
Flulike symptoms	Usually decrease over time Treatments: acetaminophen, and/or NSAID pretreatment, evening administration
Injection-site reaction	Seen with IFN beta-1b and IFN beta-1a(R), which are given subcutaneously; rare with IFN beta-1a
Thyroid dysfunction	Greatest risk with preexisting thyroid dysfunction
Depression Headache Menstrual disorders Gastrointestinal symptoms Increased spasticity Alopecia Worsening of psoriasis Leukopenia Increased hepatic transaminases	All are rare
Glatiramer acetate	
Injection site reaction	Usually mild
Systemic post-injection reaction (flushing, shortness of breath, palpitations, diaphoresis, anxiety)	Noncardiac, self-limited, lasts several minutes; reassure patient
Mitoxantrone	
Blue sclera, stool, urine	Lasts 1–2 days after infusion
Leukopenia, thrombocytopenia	Although common, usually uncomplicated
Nausea, vomiting, headache	Mild if present
Alopecia	Usually only hair thinning
Amenorrhea, infertility	Can be irreversible
Heart failure	More common with higher doses; mitoxantrone should not be used in those with previous heart condition

*Listed from most common to least common

Sexual dysfuntion in MS has important effects on a patient's self-worth

A recently published European multicenter study[26] found IFN beta-1b to be effective in secondary progressive MS. However, European studies of IFN beta-1a(R) and North American studies of IFN beta-1b found that these agents failed to reduce disability progression, although the drugs did reduce the relapse rate and MRI measures of MS activity.

In another study, mitoxantrone decreased disability progression by 64%, the relapse rate by 69%, and new MRI lesions by 85%, in a group of patients with secondary progressive MS or active relapsing-remitting MS. The cardiac toxicity from mitoxantrone described above limits its use to several years.

Small studies suggested that bimonthly

TABLE 7

Symptom management in MS

SYMPTOM AND TREATMENT*	COMMENTS
Spasticity	Medication should be combined with a regular stretching program
Baclofen 5–20 mg two or three times a day	High doses may be helpful but may exacerbate weakness or ataxia
Tizanidine 4–8 mg three or four times a day	Less tendency to produce weakness compared with baclofen, but more sedating
Gabapentin 300–900 mg three or four times a day	Useful as adjunct therapy for spasticity when there is concomitant neuropathic pain
Diazepam 2–10 mg three times a day	Useful for nocturnal spasms
Clonazepam 0.5–5 mg three times a day	Useful for nocturnal spasms
Dantrolene 25–100 mg two to four times a day	Least cerebral side effects but produces obligate weakness
Neuropathic pain	
Gabapentin 300–900 mg three or four times a day	Well-tolerated but may require high doses Titrate to avoid sedation
Carbamazepine 200–400 mg three times a day	Sedating and may exacerbate ataxia Extended-release form is better tolerated
Phenytoin 300–600 mg daily	
Amitriptyline 25–150 mg daily at bedtime	Sedation and anticholinergic effects may be useful, or may be dose-limiting side effects
Nortriptyline 25–150 mg daily at bedtime	Less prominent sedation and anticholinergic effects than amitriptyline
Fatigue	Medication should be combined with a regular exercise program
	Need to rule out poor sleep, other medical conditions, and medication side effects
Amantadine 100 mg twice a day	Watch for livedo reticularis
Modafinil 100–200 mg twice a day	Also improves sleep
Pemoline 18.75–75 mg daily	Second-line drug
	Hepatotoxicity probably rare but must be monitored
Fluoxetine 20–40 mg daily	Useful when there is concomitant depression
Depression	Consider psychotherapy for patients with depression
Selective serotonin reuptake inhibitors (SSRIs)	"Energizing" effect of SSRIs can be helpful with fatigue
Tricyclic antidepressants	Useful when there is concomitant pain, detrusor hyperactivity, or sleep disturbance

*Treatments listed in approximate order of usefulness and usual use

SYMPTOM AND TREATMENT	COMMENTS
Vertigo	
Meclizine 25 mg every 6 hours	Sedating
Scopolamine patch every 3 days	
Ondansetron 8 mg twice a day	
Diazepam 2–10 mg three or four times a day	Sedating
Ataxic tremor	Medications are rarely effective
Ondansetron 8 mg twice a day	
Primidone 100–250 mg three or four times a day	
Gabapentin 300–900 three or four times a day	
Detrusor hyperactivity	
Oxybutynin 2.5–5 mg three times a day	Extended-release formulation is useful
Tolterodine 2 mg twice a day	Less systemic anticholinergic side effects than oxybutynin but may not be as potent
	Patients on anticholinergic therapy need to be monitored for incomplete bladder emptying
	Fluid restriction in the evening or low-dose desmopressin acetate may be useful for nocturia, but patients need to avoid restricting fluids during the day
Flaccid bladder	
Bethanechol 10–50 mg two to four times a day	Intermittent catheterization or urinary diversion often are more optimal
Detrusor-sphincter dyssynergia	
Terazosin 5–10 mg daily at bedtime	Often detrusor-sphincter dyssynergia occurs with detrusor hyperactivity; in that setting terazosin or intermittent catheterization can be combined with anticholinergic medication
Constipation	
Bulk-forming agents	Need to be combined with adequate fluid, dietary fiber, and regular exercise
Lactulose	
Bowel urgency	
Bulk-forming agents	Need to be combined with scheduled voiding; biofeedback sometimes is useful
Impotence	
Sildenafil 50–100 mg as needed	Largely has supplanted other approaches Need to rule out emotional factors, other medical conditions, or medication side effects

courses of intravenous methylprednisolone,[27] low-dose oral methotrexate,[28] and glatiramer acetate[29] may slow disability progression. Also, several studies reported cyclophosphamide to be of benefit in progressive MS.[30–32] Other studies, however, did not confirm the benefit of cyclophosphamide.[33] Owing to its potential toxicity, use of cyclophosphamide mainly has been restricted to patients with rapidly progressive disease.[34]

Clearly, the later stages of MS are more difficult to treat, and the key to successful treatment of MS is to slow the inflammatory process early in the disease. IFN beta and mitoxantrone, used empirically, are appropriate first-line treatments for secondary progressive MS. In selected patients, bimonthly intravenous doses of methylprednisolone, methotrexate, cyclophosphamide, and glatiramer acetate are additional options, although data supporting their utility in secondary progressive MS are less conclusive.

TREATMENT OF ACUTE RELAPSES

Evaluation

Consider infection in any patient with a relapse

For patients with known MS experiencing a typical relapse, evaluation should focus on possible precipitating factors, specifically infection. Although the mechanisms remain unclear, infections probably lead to acute MS relapses via immune activation. Fever associated with infections also can exacerbate previous neurologic manifestations in the absence of a true relapse. Increased body temperature decreases the efficiency of nerve transmission in demyelinated pathways, producing a pseudo-relapse. Therefore, infection needs to be considered in any patient with symptoms of a relapse, particularly if he or she has a fever. If a relapse has atypical symptoms, develops faster or slower than expected, or does not respond to steroid treatment, further laboratory and radiologic evaluation should be performed as dictated by the clinical picture.

Treatment

Mild relapses that do not interfere with function do not require treatment. For more severe relapses, corticosteroid therapy accelerates recovery and shortens the relapse duration. However, there is no convincing evidence that corticosteroid treatment improves the degree of recovery or the long-term course of disease.[35–37]

A typical regimen is 500 to 1,000 mg of methylprednisolone by daily intravenous infusion for 3 to 5 days, followed by a tapering dose of prednisone over several weeks. The optimal dose of intravenous methylprednisolone remains uncertain, as do the duration of treatment, whether comparable doses of methylprednisolone given orally are equally effective, and the need for an oral taper. Although some practitioners continue to treat relapses with oral prednisone alone, particularly mild relapses, the available data suggest that prednisone alone does not effectively shorten relapses.[37]

Treatment of symptoms and rehabilitation should not be neglected. Several prospective, randomized studies found that intensive inpatient rehabilitation for MS improves disability and quality of life, and these benefits can be long-lasting.[38–40] The mechanisms behind this improvement remain unclear. Physical therapy (especially to address gait), occupational therapy, speech therapy, and swallowing therapy each can be helpful, and proper referral should be guided by the clinical situation.

SYMPTOM MANAGEMENT

With increasing emphasis on disease-modifying therapy, management of symptoms is sometimes overlooked. However, identification and treatment of symptoms is an important aspect of MS management. A variety of symptoms that interfere with daily activities or quality of life can develop at any point in the disease course, either during an acute relapse or more chronically. Many of these potentially troublesome symptoms are amenable to treatment (TABLE 7).

Drug treatment

Patients may have multiple symptoms, and medications used to treat one symptom may exacerbate another. For example, medications used to treat spasticity sometimes produce fatigue. Therefore, it often is necessary to prioritize which symptoms are most troublesome.

The clinician must remember that because the manifestations of MS evolve over time, symptom management is an ongoing process, and medications need to be given an adequate

trial. Start the dosage at a low level and increase gradually until a therapeutic response is achieved or intolerable side effects occur. If one medication proves ineffective or cannot be tolerated, consider other medications.

Adjunctive treatment

Medications are not the only approach to treating MS symptoms. Adjunct therapies may augment the utility of medications (eg, use of a stretching program to complement medication in the treatment of spasticity; counseling in addition to antidepressant medication to treat emotional distress). The assistance of other allied health professionals such as social workers and psychologists is critical in addressing issues such as employment, disability, and family stress.

PREGNANCY AND REPRODUCTIVE HEALTH

Since MS is more common in women and typically presents in early adulthood, reproductive issues commonly arise. Gynecological care for women with MS does not differ significantly from routine practice, but there are some special concerns:

- Long-term immunosuppressive therapy may potentially increase the risk of cervical dysplasia and other neoplasms, as well as infections from intrauterine devices.
- Routine examinations are important and should include a breast exam and a Pap smear, especially for women with a history of genital condylomata.
- Urinary tract infections are common in MS patients with impaired bladder function, and frequent antibiotic use can alter the effectiveness of oral contraceptives through the induction of hepatic enzymes.

Several excellent reviews concerning pregnancy and MS have been published.[41,42] Older studies suggested that pregnancy could precipitate the onset of MS or worsen its course, leading many women with MS to avoid pregnancy. More recent studies showed no convincing evidence that pregnancy causes MS or is associated with an increased risk of onset of MS.[43] Similarly, there was no substantial deleterious effect of single or multiple pregnancies on the ultimate course of MS or accumulation of disability.

A large prospective study (PRIMS) of 269 pregnancies in 254 women with predominantly relapsing-remitting MS provided important information on pregnancy and MS.[44] This study confirmed that the relapse rate decreases during pregnancy, but increases during the 3 months after pregnancy. The increased risk of relapse in the postpartum period suggests that disease-modifying therapy should be restarted early after delivery in women with previously active disease. In such cases, breast-feeding needs to be avoided, since these therapies are not recommended while breast-feeding.

MS does not affect fertility or the course of pregnancy. There was no apparent increase in congenital abnormalities or complications of pregnancy, labor, or delivery in the PRIMS study.[44] Normally, no special precautions or measures need to be taken during labor or delivery, including with anesthesia. Pregnancy in most patients with MS should not be considered to increase risk, and it is no longer appropriate in most cases to advise women against pregnancy merely because they have MS.

We no longer advise against pregnancy solely on the basis of MS

HEALTH MAINTENANCE IN MS

The average life expectancy in MS patients is not substantially different than in the general population. Although a small minority of patients have rapidly progressive disease with premature death, a decreased incidence of traumatic injury balances life expectancy to near-normal.[45] Therefore, standard health maintenance guidelines should be applied to MS patients, including routine mammography, gynecological exams, colonoscopy, management of chronic conditions such as hypertension and diabetes, and immunizations.

The symptoms of MS overlap those of a variety of medical conditions. Clinicians need to remain vigilant so as not to miss the development of anemia, thyroid disease, vitamin B_{12} deficiency, or diabetes mellitus in MS patients. Furthermore, MS therapies can predispose to other medical conditions. Steroid use can precipitate or exacerbate hyperglycemia or hypertension. Corticosteroids and reduced exercise contribute to osteoporosis. Chronic immunosuppression increases the risk

of malignancy and infection. Many of the medications used to treat MS can cause drug-induced hepatitis.

In general, immunizations are safe and effective in MS patients.[46] Although there is a theoretical concern that activation of the immune system could precipitate a relapse, there is no clear evidence that immunizations are harmful to MS patients. We recommend influenza and pneumococcal vaccinations for disabled patients with respiratory compromise, such as patients who are wheelchair- or bed-restricted. In general, the indications for immunizations in patients with MS are the same as for the general population.

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