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Current Perspectives in the Pathogenesis and Treatment of Multiple Sclerosis

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Abstract: Multiple sclerosis arises from a combination of genes and environment. It has abundant clinical symptoms, varied clinical courses, and probably different histopathological subtypes. In the past 10 years, 6 therapies that partially treat MS have been developed, and more are likely to be approved in the near future.

Key Words: Multiple sclerosis, histopathology, treatment

Definition

Multiple sclerosis is a brain disease caused by white blood cell invasion of the brain and spinal cord. The invading T cells and monocytes spread outward from the venules and cause demyelination and axonal disruption.

Clinical Subtypes of MS

Eighty-five percent of cases are relapsing/remitting (Figure 1.A). Early in the disease, inflammation causes an episode of neurological dysfunction followed by partial or total recovery. These attacks usually occur every 2 years. After about 10 years, the attacks become less frequent, but MS transforms into a progressive disease, seemingly neurodegenerative. The other 15% of patients have a progressive disease from the outset (Figure 1.B). Once the progressive phase is reached, the average rate of decline is the same for the different subtypes of MS.

Clinical symptoms

Clinically, there is no "typical" patient because the MS lesions are somewhat random and can involve any part of the central nervous system. Thus, vision, brainstem, sensory, motor, autonomic systems, and cognition can all

be affected. However, some areas of the brain do show a predilection for MS plaques and the following descriptions are for the most common events.

The optic nerves are involved in 20% of patients as the first symptom. Loss is usually in the center of the visual field with ill-defined margins, develops over hours to days, is often associated with pain when the eye is moved, and resolves in several weeks. This is to be expected as inflammation develops diffusely, and slowly, and it irritates pain-sensitive structures surrounding the optic nerve (Figure 1.C). In contrast, in ischemic/embolic optic nerve occlusion, a sudden curtain falls over half of the visual field, there is an abrupt altitudinal step-off in the visual field, pain is atypical, loss is permanent or only for seconds, and patients are older with cardiovascular risk factors.

Many patients develop an "internuclear ophthalmoplegia". On gaze to the right, for example, the adducting left eye is unable to move completely to the right and there is coarse nystagmus of the abducting right eye. This is a classic finding in MS, and if it is bilateral in a young person it is almost diagnostic of MS. It illustrates an important principle in MS—the lesions have a predilection for the ventricular system. The "medial longitudinal fasciculus" (MLF) integrates these eye

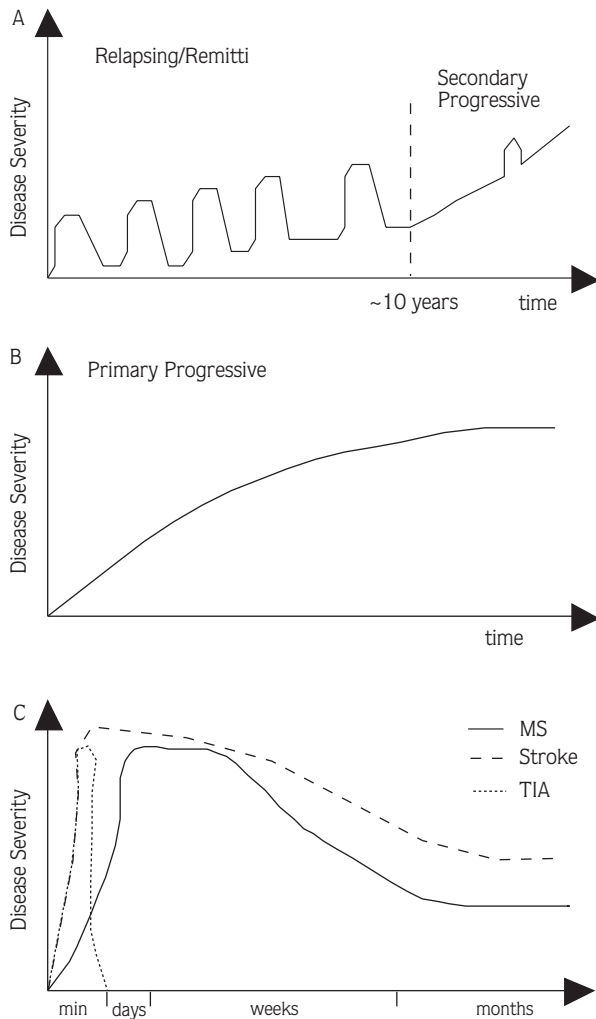


Figure 1. A. The course of MS is typically relapsing/remitting at first. Attacks decrease in frequency and then symptoms progressively worsen—"secondary progressive MS." The latter phase typically arises about 10 years after diagnosis, when the patient is unable to walk more than 500 m. B. Fifteen percent of MS patients have a progressive course without attacks—"primary progressive MS." C. New symptoms crescendo over hours to days, last for days to weeks and then gradually disappear, sometimes completely. This contrasts with cerebrovascular disease, where symptoms appear suddenly and resolve quickly (transient ischemic attack, TIA) or cause permanent deficits (infarct).

movements, and connects the medial rectus portion of the third nerve nucleus with the nuclei controlling the VI nerve. The MLF runs along the brainstem aqueduct—part of the ventricular system—and is therefore likely to be interrupted by MS plaques.

Spasticity, leg weakness, and bladder urgency are also typical, especially in later, progressive forms of MS. This illustrates another anatomic principle. Random plaques in the spinal cord are likely to interrupt long tracts. Primary progressive MS is predominantly a myelopathy, and over many years relapsing/remitting MS often leads to accumulation of spinal cord plaques.

Some generalized symptoms are commonly overlooked, but are extremely important. Fatigue is the number one complaint in MS. Eighty percent of patients have generalized lassitude/tiredness/malaise or rapidly tire after motor activity. These complaints are worse with stress and heat. The external environment or internal sources such as virus infections or the normal circadian temperature elevation in the afternoon will increase body temperature. This susceptibility to heat, termed Uhthoff's phenomenon, is from slowed conduction in heat-sensitive demyelinated fibers.

Fatigue can be accompanied by weakness, but it is different from motor weakness. MS fatigue is an overwhelming lack of energy and feeling of exhaustion. It is often continuous, and can also be triggered by minimal effort. Motor weakness, spasticity, disturbed sleep-wake cycles, effects of cytokines in the brain, and abnormalities of the hypothalamic pituitary axis may contribute to fatigue.

Mental function is reduced in 2 ways. Because of the accumulation of subcortical and cortical plaques the majority of patients have slowed cognition. This is often undetectable in casual conversations, but is a major source of disability. Secondly, as described by Charcot 150 years ago, some patients develop "pseudobulbar" affect, laughing or crying at minor provocations.

Diagnostic tests

MRI is abnormal in 98+% of patients. T2 lesions are small to medium-sized balls or spikes radiating out from the ventricle and corpus callosum into the surrounding white matter ("Dawson's fingers") (Figure 2.A). T1 lesions appear as black holes, often a result of permanent axonal damage. Gadolinium-enhancing lesions last 2-6 weeks, like clinical attacks, but the correlation with exacerbations is surprisingly low ($r = 0.25$, where $r = 1$ is a perfect correlation).

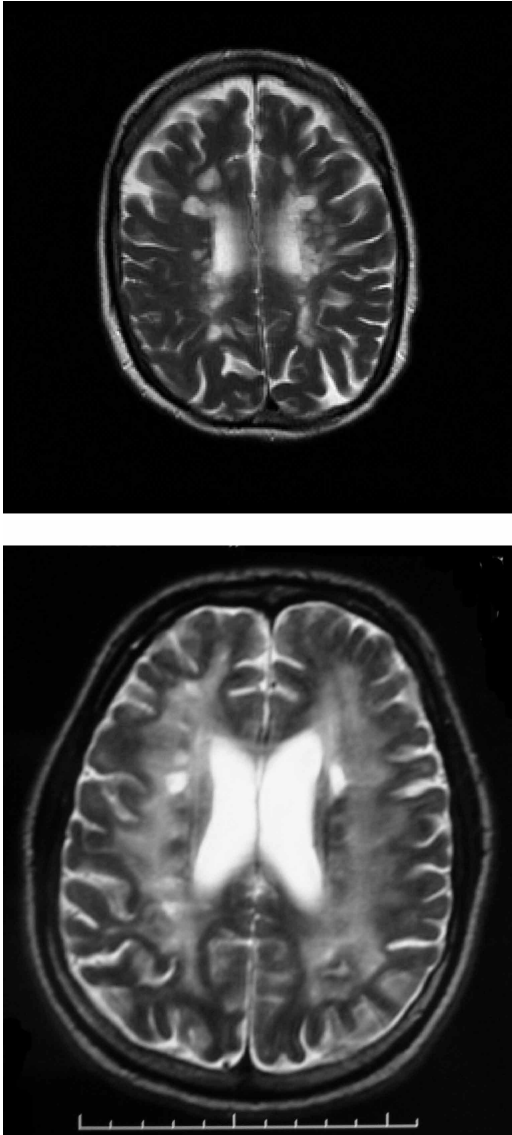


Figure 2. A. Typical T1-weighted MRI in MS with globular periventricular lesions, some projecting out laterally from the ventricles—"Dawson's fingers."

B. With vascular disease, in contrast, lesions are more likely to appear in the centrum semiovale, and not next to the ventricles. This is a case of CADASIL, a hereditary disorder caused by vascular occlusions associated with a non-demyelinating leukoencephalopathy.

Cerebrospinal fluid is abnormal in 95% of patients. The most important component is 2 or more oligoclonal bands, signifying chronic inflammation.

Evoked responses are functional tests that show the speed of central neuronal conduction—this reflects the

degree of demyelination. A decrease in amplitude indicates axonal damage, whereas delayed responses suggest focal demyelination. These tests can determine areas of demyelination, sometimes sub-clinical, and can reflect the course of the disease.

Visual-evoked responses measure conduction from the eyes to the occipital cortex, thus measuring more than optic neuritis. They can be positive even if there is no obvious visual loss. Brain stem auditory-evoked responses reveal brain stem lesions, and measure conduction horizontally through the brain. Somatosensory-evoked potentials show abnormalities in the pathways from the spinal cord to the cortex. In a small study that needs confirmation, they correlated best with impaired position sense. Vibration sense, the most common sensory abnormality in MS, is abnormal because the 128 Hz signal rapidly fatigues in demyelinated axons. Magnetic-evoked motor potentials may be another sensitive measure of spinal cord function in MS; techniques are under development.

There are some other evoked responses that are used at specialized laboratories. These include event-related potentials (for cognitive evaluation), vestibular-evoked myogenic potentials (saccular responses to loud acoustic stimuli that are recorded from the ipsilateral sternocleidomastoid muscle), and dichotic listening.

Prognosis

The prognosis is better than popularly believed. Women with MS have a normal lifespan; men die 3-5 years earlier than men without MS. Part of the explanation is that MS patients are less likely to develop cancer, presumably because they have "better" immune systems than normal. Because this chronic disease begins in young people, it results in years of inability to work and care for the family, caretaker costs, and drug expenses. The typical untreated patient will be using a cane after 12 years. MS will have a significant effect on the quality of life and on average will cost \$2,200,000 over a lifetime.

Some factors augur a good prognosis—young, female, relapsing/remitting, optic neuritis, sensory symptoms, few MRI lesions, and a normal neurological exam. Other factors are bad—male, progressive course, and motor, brainstem, or cerebellar symptoms.

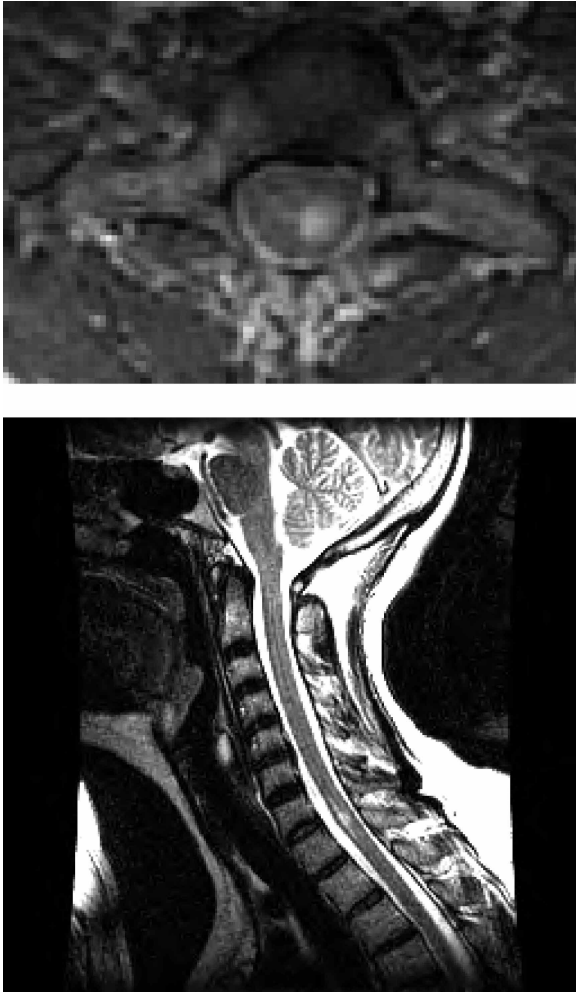


Figure 3. T2-weighted MRI of the spinal cord with a plaque in the left dorsal column (lower right in figure). Only one segment is involved. In transverse myelitis, the lesions typically affect multiple contiguous segments. Accumulation of similar lesions will compromise the long tracts of the spinal cord, causing weakness, spasticity, bladder symptoms, and, as in this case, reduced vibratory sensation.

Incidence

The average patient in the US is a 28-year-old woman with higher than average income and intelligence. MS is more common in women in Turkey; other demographic characteristics await study. The onset ranges from late teens into the 50s. Women tend to develop relapsing/remitting MS a few years earlier than men, and outnumber men in a 2:1 ratio. Men are more likely to have progressive forms of MS.

The prevalence ranges from 190/100,000 people in certain hot spots such as the Orkney and Shetland islands,

north of Scotland; to 100/100,000 in the northern US and Europe; to 30/100,000 in the southern US and Europe. The incidence in Turkey is estimated to be 20-50/100,000. (This number needs to be confirmed with an epidemiologic study.) The yearly incidence of new cases of MS in the US is 3.2/100,000.

Geographic Distribution

MS becomes more common with distance from the equator. This is likely to arise from genetic and environmental factors. Northern European genes confer the most risk, Oriental genes the least. MS is rare in American Indians, Turkmen, Uzbeks, Kazaks, Gypsies, Native black Africans, and New Zealand Maoris. Migration studies suggest that moving to an area of high incidence before the age of 15 increases the risk of developing MS; the converse is also true. After 15, exposure to a presumed environmental factor has no effect. In support, there is no evidence for conjugal transmission of MS.

What environmental agents might cause MS? Viruses such as measles, EBV, HHV-6, adenoviruses, and endogenous retroviruses have been suspected but are now deemed unlikely by most investigators. In some laboratories, chlamydia is found in more MS brains than in controls, but the relevance is unclear. Antibodies to many viruses, but also to ANA and other self-antigens, are increased in MS. The excessive immune response in MS may thus lead to false assumptions about causes of MS.

Heredity

No single gene causes MS. It is polygenic, and so close relatives have a higher risk of developing MS. The relative risk is 1 if no one in the family has MS, 25 in first-degree relatives and dizygotic twins, and 200 in monozygotic twins of an MS patient.

Susceptibility genes

The presence of MS is most strongly linked to HLA-DR2 in Northern Europeans, suggesting an immune etiology for MS. In Japan, DR2⁺ patients are most likely to develop “Western” MS. However, DR2⁻ Japanese typically develop Devic’s disease, with involvement of the optic nerves and spinal cord, but without disseminated brain plaques. In the Mediterranean basin, other HLA types are linked to MS. Since HLA genes control immune

responses, it is not surprising that there are population differences in some assays of immune cell cytokine secretion. The clinical course or response to drug therapy may also differ in subtle ways between populations. Also important are subtypes of pathology (below).

Disease-modifying genes

The tempo of MS is affected by some genes that may have nothing to do with susceptibility. These include ApoE4 (faster progression), ciliary neurotrophic factor, CNTF (worse MS when the gene is missing, as in 3% of Europeans), and possibly IL-1 and chemokine receptors.

Role of environment

Infections

Although there is no clear evidence that any infective agents cause MS, infections can trigger attacks. One of 3 upper respiratory infections causes an exacerbation in MS patients, and the residual symptoms are more severe. Bacterial infections double the rate of exacerbations, including the bladder infections that are common in MS. Smoking raises the attack rate by 60%. Immunization, however, does not increase the rate of exacerbations, and prevents immune-activating infections.

Nutrition

Epidemiologic and some dietary studies suggest that fish and vegetable oils offer modest protection against relapses. They can also help in controlling weight (see below).

Pathology

An animal model, EAE

Experimental allergic encephalomyelitis (EAE) is an animal model of MS. It drives much of the thinking about immune and pathological mechanisms in the human disease. EAE is induced by immunizing with brain antigens (myelin basic protein, myelin-oligodendroglial protein, and others) in a fine lipid emulsion of complete Freund's adjuvant. Ten days later, immune cells invading the spinal cord and brain cause clinical symptoms—ascending from a drooping tail, to hind leg weakness and spasticity, bladder retention, and

sometimes to front leg weakness and difficulty in breathing. Symptoms begin to resolve after a week or so, in clear parallel to an exacerbation of MS.

The inflammatory cells surrounding blood vessels are initially myelin-reactive CD4 T cells, which then recruit macrophages and nonspecific T cells. These cells cause demyelination, but usually not as much demyelination as in MS. Many of the drugs used in MS prevent EAE. However, EAE is not a perfect model. CD8, and not CD4, T cells correlate with damage in MS. MS patients' cells show minimal proliferation to myelin basic protein, the usual inducer of EAE. Moreover, some drugs that prevent EAE (e.g., interferon- γ , anti-TNF receptor antibodies) actually worsen MS.

MS pathology

In MS, immune cells invade the brain, where they damage and destroy oligodendroglia and some neurons. For unknown reasons, T cells and macrophages are activated in the peripheral blood beforehand. These activated cells express adhesion molecules, including VLA-4, which they use to attach to the endothelial cells of the post-capillary venules in the brain. The immune cells secrete matrix metalloproteases that soften up the tight junctions and cell membranes of the endothelial cells (ECs) forming the blood-brain barrier (BBB). These proteases help the immune cells to penetrate directly through the ECs and underlying basement membrane.

Once inside the BBB, immune cells spread out from the venule. A wave of CD4 T cells leads the way and attracts CD8 T cells and monocytes. These cells secrete toxic cytokines and also directly attack brain cells. Myelin and myelin-forming cells are damaged and nearby astrocytes hypertrophy. Neurons are also injured, and many ultimately die.

Monocytes outnumber T cells by 8:1 in early lesions and over 20:1 in chronic plaques. Monocytes and CD8 cells correlate with MRI damage and with the severity of the lesion.

Typically there are 2 phases of MS. First, there is T cell-driven inflammation with enhancing MRI lesions. After approximately 10 years, MS evolves into a degenerative/progressive disease, with few T cells but many monocytes and less enhancement on the MRI.

There are 4 pathological subtypes of MS, based on biopsy and autopsy studies of scores of MS brains (Table 1). These include (I) perivenular demyelination with sharp margins, activated macrophages in contact with myelin, some early damage but later reappearance of oligodendroglia, and lesions in the periventricular white matter, some radiating outward from the ventricles on MRI (Figure 2). Pattern (II) is similar to (I), but with immunoglobulin and complement deposited at the site of active myelin destruction. (I) and (II) resemble EAE.

Table 1. Four histopathological patterns in MS.

Pattern	Plaque Margins	IgG and Complement	Oligodendroglia
I	Sharp	-	can remyelinate
II	Sharp	++	can remyelinate
III	Indistinct	-	++ death
IV	Sharp	-	++ death

(III) Vague margins, vascular endothelial damage sometimes causing thrombosis, and death of oligodendroglia. (IV) Similar to (I), but with destruction of oligodendroglia, seen most in primary progressive MS. These patterns are unlikely to be 4 completely different diseases, but rather reflect heterogeneity in genetic background and environmental exposure.

The change over time and the different subtypes of pathology suggest that the ideal therapy may differ in early vs. late MS and between subtypes. For instance, interferon-β (IFN-β), Copaxone, and chemotherapy all work best in early relapsing/remitting MS. All are directed at the early T cell-mediated inflammation. They have minimal effect on progressive MS, suggesting that the disease process is altered. Neurodegeneration might be treated with a therapy that induces trophic factors for oligodendrocytes and neurons. Current therapies have theoretical benefit: “inflammatory cells” are sometimes capable of producing trophic factors—IFN-β induces leukemia inhibitory factor (LIF) and nerve growth factor (NGF) and interleukin-10; Copaxone induces brain-derived neurotrophic factor (BDNF). In contrast, chemotherapy destroys all dividing cells and may eliminate these beneficial subpopulations.

The spectrum of demyelinating diseases

Demyelinating diseases range from

- *Post-infectious or post-vaccinal encephalomyelitis*, of varying severity, but never to recur (the human counterpart of EAE)
- *Subclinical MS* (detected at autopsy and possibly equivalent in number to diagnosed cases)
- A single episode of *optic neuritis* or *Transverse myelitis*
- *Mild Relapsing-remitting MS (benign MS)*, possibly 5-10% of diagnosed cases)
- *Typical Relapsing/remitting MS* that evolves to *Secondary progressive* disease as described in Figure 1.A
- *Primary progressive MS* (Figure 1.B)
- Explosive onset of demyelination with death in several years (*Marburg’s variant*)
- *Acute disseminated encephalomyelitis*
- *Acute hemorrhagic leukoencephalitis of Weston Hurst.*

Therapy of MS symptoms

Since there is no cure for MS, management of symptoms should be a priority. Fatigue, cognitive loss, psychological problems, spasticity, autonomic dysfunction, tremor, and pain are major problems with MS. To eliminate or even to lessen these complaints could make a patient’s life more comfortable.

Identifying the components of fatigue is important for treatment. A sudden onset or increase in fatigue requires a search for other systemic diseases. It should be distinguished from emotional symptoms such as depression; psychiatric referral may be helpful. Fatigue affects cognition, social and family relationships, and employment status. It is important to explain the possible reasons for fatigue to the patient, family, and employer. Work hours and environment should be modified to prevent unemployment, which could worsen the psychiatric and motor complaints. Amantadine, pemoline, and recently modafinil, are effective for many patients (Table 2). Modafinil promotes waking via the activation of the histaminergic system. In placebo-controlled studies, a 200 mg daily AM dose significantly improved

Table 2. Treatment of MS Symptoms.

Symptom	Drug	Dosage Range	Comment
Fatigue	Amantadine	100-400 mg/d	P.O., 1
	Modafinil	100-400 mg/d	P.O., 1
	Methylphenidate	5-20 mg/d	P.O., 1, 3
	Pemoline	18.75-140 mg/d	P.O., 1, 3, 4
Pain	Gabapentin	300-1200 mg/d	P.O., 1
	Carbamazepine	200-1600 mg/d	P.O., 1, 3, 4
	Oxcarbazepine	300-1200 mg/d	P.O., 1
	Lamotrigine	100-400 mg/d	P.O., 1
	Topiramate	15-400 mg/d	P.O., 1
Spasticity	Baclofen	5-80 mg/d	P.O., I.T., 1
	Tizanidine	1-36 mg/d	P.O., 1, 2
	Diazepam	2-20 mg/d	P.O., 1, 2, 3
	Clonidine	0.05-0.2 mg/d	P.O., patch, 1
	Dantrolene	25-100 mg/d	P.O., 1
	Amitriptyline	25-75 mg/d	P.O., 1, 2
	Cyproheptadine	4-36 mg/d	P.O., 1, 2
	Dronabinol	5-15 mg/d	P.O., 1, 2
Cognitive Loss	Rivastigmine	3-6 mg/d	P.O.
	Galantamine	8-24 mg/d	P.O., 1
	Donepezil	5-10 mg/d	P.O.
	Memantine	20 mg/d	P.O.
Depression	Sertraline	50-150 mg/d	P.O.
	Citalopram	20-60 mg/d	P.O., 2
	Amitriptyline	50-300 mg/d	P.O., 2
	Fluoxetine	10-40 mg/d	P.O., 2
Bladder Dysfunctions	Oxybutynin	2.5-10 mg/d	P.O.
	Tolterodine	2-8 mg/d	P.O.
	Desmopressin	0.1-0.3 mg/d	nasal sp., 4
	Terazosin	1-5 mg/d	P.O.
Sexual Dysfunction	Sildenafil	25-100 mg	*, 3
	Papaverine	30 mg	I.C.
	Phentolamine	1 mg	I.C.
Tremor	Clonazepam	0.1-2 mg/d	P.O., 1, 2
	Primidone	25-250 mg/d	P.O., 1
	Propranolol	80-240 mg/d	P.O., 1, 4
	Isoniazid	800-1200 mg/d	P.O., 1, 4
	Glutethimide	750-1250 mg/d	P.O., 1

1: Should be titrated to lowest effective dose

2: Has sedative side effects

3: Should be given with caution

4: Needs follow up

P.O.: Orally

I.C.: Intracorporeal

I.T.: Intrathecal

* 1 h before "sexual interaction"

fatigue. Methylphenidate has value, but should be used with caution. The combination of lofepramine (specific noradrenaline reuptake inhibitor), L-phenylalanine (a precursor of noradrenaline), and vitamin B12 injections reduced fatigue in a very short period of time in one series of reports, but needs replication. Aerobic exercise is an important addition to drugs. Gentle exercise that does not elevate body temperature, such as swimming or short walks, is recommended.

Pain is a frequent complaint in MS patients. MS plaques can directly cause trigeminal neuralgia, Lhermitte's sign, and optic neuritis. Spasticity, osteoporosis, frozen joints, and immobility are secondary causes of pain in MS. Trigeminal neuralgia and other neuralgic pains respond to gabapentin, oxcarbazepine, carbamazepine, lamotrigine, topiramate, non-steroidal anti-inflammatory drugs, and misoprostol. Because of Na channel redistribution in demyelinated axons, some patients are very sensitive to Na channel blockers such as carbamazepine.

Physical therapy is the best initial choice for treatment of spasticity. Reducing spasticity also prevents the symptoms of immobility such as frozen joints, osteoporosis, and pain. Baclofen, a GABA agonist, and tizanidine, an α 2-adrenergic agonist, reduce spasticity and pain during physical activity. These drugs should be started at low doses and gradually increased to achieve the best result with minimum side effects. Other agents that can moderately reduce spasticity are benzodiazepines, clonidine, gabapentin, tricyclic antidepressants, cyproheptadine, and dantrolene. These can be used alone or in combination. Cannabinoids may improve spasticity and pain but they should be used with caution.

When oral medication is not adequate, botulinum toxin injections can be considered for small muscle groups. Intrathecal baclofen administration with a radio-programmable pump significantly lessens spasticity and pain without systemic side effects. Intrathecal applications of opioids such as morphine and fentanyl, or non-opioids such as clonidine and bupivacaine, also provide pain relief. For patients who do not respond to physiotherapy and spasmolytic medication, the surgical choices are spinal cord stimulation, tenotomy, myotomy, and posterior rhizotomy.

Cognitive loss may lead to inability to work, and affects the whole course of MS and its treatment. Slowed neuronal interaction impairs learning and memory, and delays information processing—including physician-patient interactions. It is sometimes hard to distinguish from depressive symptoms and fatigue. This symptom requires close support from family members and caregivers. Rehabilitation is the most important step. Rivastigmine, donepezil, and galantamine are oral cholinesterase inhibitors that are at least as effective in MS as in AD. Memantine, an antagonist of high concentrations of glutamine, is also effective and possibly neuroprotective.

Affective disorders, including depression, bipolar disorder, and pathologic laughter and weeping, are common but often overlooked in MS. IFNs could increase depression in patients with pre-existing depression. Although depression is seen among many chronically disabled patients, strategically placed plaques in MS may contribute to the pathophysiology of depression. Selective serotonin reuptake inhibitors can be used for treatment and also may reduce fatigue. Low doses of amitriptyline have beneficial effects on pathologic laughing and weeping. Successful treatment of affective disorders improves compliance with other therapies.

Bladder dysfunction in MS affects both storing and emptying, and treatment must be individualized for every patient. Urgency and frequency characterize a hyperactive bladder. Anticholinergic agents such as oxybutynin, tolterodine, and propantheline bromide can be used for this bladder hyperreflexia, and may synergize with an anticholinergic tricyclic medication. If there are cognitive problems, anticholinergic effects on the CNS should be avoided, and tolterodine may be the best choice. Desmopressin acetate nasal spray may prevent severe nocturia that cannot be treated with fluid restriction or long-lasting anticholinergics. Intravesicular botulinum toxin injections can also reduce spasticity.

Excessive sphincter hyperreflexia can be treated with anti-spasticity medication (baclofen, gabapentin) and/or α -1 blockers (terazosin hydrochloride). These patients are at risk for bladder infections because of high post-voiding residual. Intermittent self-catheterization is the most effective treatment for this. Patients with bladder dysfunction should acidify urine with supplements of cranberry juice or vitamin C (1-2 g/d) to prevent infection.

There are non-drug options for incontinence. Pelvic muscle exercises and electrostimulation via a small rectal or vaginal probe may strengthen weak muscles. Several devices (short-term penile clamps for men and urethral plugs for women) and diapers are available for incontinence and dribbling. Risk for infection must be considered while using external devices. Ablative surgery of hyperactive sphincter should be avoided unless medication and devices fail.

Sexual dysfunction can arise from MS plaques in the cord or hypothalamus. However, psychological components and side effects of medication always have to be considered causes. Female sexual dysfunction should not be ignored. Sildenafil has been used for both sexes. It is effective in many men and some women. Topical drugs such as nitroglycerin, minoxidil, and papaverine, and intracavernosal papaverine, phentolamine, and alprostadil could be used with caution for erectile dysfunction. External vacuum devices and penile prostheses are other options for treatment. Yohimbine, L-arginine, and apomorphine have little effect on erectile dysfunction. Expert urological, gynecological, and psychiatric consultation should be used before and during the treatment. The spouse should usually be informed about the symptoms and treatment options.

Constipation is very common in MS patients. Immobility, fluid restriction (patients drink less due to bladder dysfunction), and side effects of anticholinergic drugs all cause bowel problems. Management includes increasing dietary fiber and fluid intake, caffeine, and restriction of constipating medications. Physical therapy is mandatory. Timed (daily) and unhurried defecation, and stool softeners may be helpful. Anticholinergics reduce fecal incontinence, but also cause constipation.

Tremor is from involvement of the cerebellum and its outflow pathways. It is most likely to affect the arms, but occasionally affects the legs, neck and trunk, causing dysarthria, titubation, and gait ataxia. It is difficult to treat. Clonazepam and benzodiazepines seem to lessen tremor. Primidone, carbamazepine, glutethimide, and isoniazid are anecdotally beneficial. In severe cases stereotactic thalamotomy or thalamic electrostimulation is effective, but less than in Parkinson's disease, because MS lesions are more diffuse.

Dry mouth and associated oral disease, due to side effects of anticholinergic therapy and improper nourishment, need dental care. Oral health impacts

positively on general health, and any infection in MS activates the immune system. Obesity, a consequence of immobility, can be controlled by a strict diet and physical rehabilitation. Spasticity, immobility, sensory loss, and incontinence are all risk factors for pressure sores. This source of infection should be treated immediately, as infections can trigger exacerbations of MS. Postural changes, incontinence management, pressure-relieving beds, and cessation of smoking can prevent pressure sores. Osteoporotic bone fractures have been reported in MS from steroid treatment and disuse, and immobility. Management may include physical exercise, calcium and vitamin-D, bisphosphonates, and cessation of smoking.

The neurologist must constitute and conduct a team to manage symptoms. Cognitive, physical, psychological, and social problems require a coordinated approach by experienced health and social services. Physical rehabilitation including stretching, even yoga, is an essential part of symptomatic management and significantly alters disability. Patients always seek a reliable neurologist. Capricious changing of physicians should be avoided. Finally, 3 generations are affected by a diagnosis of MS. Partners and other family members may need emotional support, and effects on children should not be ignored.

Therapy of MS

Steroids (glucocorticoids)

The management of acute attacks in MS traditionally includes steroids. Glucocorticoids decrease MHC class II protein expression and inhibit the transcription and activity of pro-inflammatory cytokines (IL-1, 3, 6, 8, TNF- α , GM-CSF and IFN- γ), cause apoptosis of T cells and decrease their activation. Glucocorticoids also inhibit endothelial cell activity and stabilize the damaged BBB. They shorten MS relapses, but do not impact long-term prognosis.

For many decades, there has been no standard protocol for steroid therapy of MS. The most popular steroid protocol for MS is a daily 1 g methylprednisolone (slow) IV infusion for 3-5 days. Oral tapering after a high-dose IV course of steroids is advisable, based on experience in animal models and other inflammatory diseases. Most clinicians feel that after many courses of glucocorticoids, there is less effect on relapses. Many advise limiting the number of courses to 3 a year. Long-

term steroids are not indicated for any form of MS. In addition, there is no clear benefit of monthly or 3-4 monthly courses of oral steroids. High-dose oral glucocorticoids probably have the same outcome as the IV form (oral dexamethasone pills or methylprednisolone liquid). Precautions against side effects of steroids include avoiding aspirin and nonsteroidal drugs and supplementation with potassium, vitamin D, and calcium.

Glatiramer acetate (Copaxone)

Glatiramer acetate is a random polymer of 4 amino acids (L-glutamate, lysine, alanine, and tyrosine at a ratio of 1.4:3.4:4.2:1). It binds strongly to the MCH and was initially thought to block T cell recognition of brain antigens because there are some similarities between myelin basic protein and glatiramer. It is now thought that it induces a Th1 to Th2 shift, and that these Th2 cells home to the brain in search of MBP-like molecules. In the CNS, the Th2 cells secrete anti-inflammatory cytokines.

Copaxone reduces the attack rate, appears to slow progression, and reduces new enhancing MRI lesions, all by 1/3. T1 black holes also tend to revert to more normal appearing brain tissue after 6 months of therapy. It has minimal side effects other than skin erythema and a rare "immediate post-injection reaction," where patients feel impending doom for 10 min.

Interferon- β

IFN- β -1b and IFN- β -1a have multiple effects on immunity, and the majority of the effects benefit MS. Type I IFNs inhibit secretion of IFN- γ (a much different Th1 cytokine that causes MS exacerbations), but induce IL-10 in T cells (an anti-inflammatory Th2 cytokine). They also inhibit migration of T cells through the endothelial cells of the BBB, and may induce apoptosis of activated T cells.

Betaferon, Avonex, and Rebif reduce the attack rate and slow progression by 1/3. They reduce new enhancing MRI lesions by 90%. As a result, T1 black holes tend not to develop. IFN- β is most effective when used early; in later purely progressive MS there is little change in progression.

The main side effects are initial flu-like symptoms that disappear after weeks and occasional lymphopenia and elevated liver function tests. The subcutaneous forms

cause skin erythema, and occasionally cause skin necrosis, more so with Betaferon than with Rebif. However, severe skin lesions with Betaferon have been reduced with the new auto-injector device, and so the current incidence is unknown.

Chemotherapy

In increasing rank of efficacy, azathioprine, methotrexate, cyclophosphamide, and mitoxantrone reduce exacerbation rates. They seem to be most effective in early relapsing MS. This is counterbalanced by the long-term risk of developing a malignancy, by liver toxicity, and complications of immunosuppression. In addition, mitoxantrone is limited to 2-3 years of treatment because it is cardiotoxic.

Intravenous immunoglobulins have reduced the relapse rate in Europe, but have had minimal effect in the USA. The discrepancies may stem from different donor pools or in the preparations themselves. Plasmapheresis has no benefit in most patients.

New treatments and future drugs

Natalizumab (Tysabri, formerly Antegren) is a monoclonal antibody that binds to VLA-4 antigen on very-late activated memory T cells, and prevents them from sticking to brain endothelial cells. This monthly intravenous drug reduced relapses by 50%, slowed progression, and reduced MRI enhancement by 90% in a 6-month study. The relapse rate was slowed by 66% in a phase III study. Tysabri, which received accelerated approval from the FDA in November 2004, is suspended because of 1 confirmed fatal case and 1 resolving case of progressive multifocal leukoencephalopathy (PML) in MS patients receiving this treatment in conjunction with IM IFN- β 1a. Effects of monotherapy with natalizumab are under review.

Statins lower cholesterol, but also appear to reduce inflammation. They dramatically reduce MHC class II expression and Th1 immune responses, and inhibit EAE in mice. They are safe in MS, and efficacy trials are planned. One caution: in experimental studies, statins have both pro-inflammatory and anti-inflammatory effects. The net effect is not known. Effects on the IFN- β pathway are likely.

Peroxisome proliferator-activated receptor (PPAR- γ) agonists (pioglitazone, rosiglitazone) are used to enhance insulin effects in diabetes. They are also anti-inflammatory and prevent EAE. MS trials are in the formative stages.

Pregnancy prevents exacerbations as effectively as any approved drugs (although this is canceled out by rebound exacerbations after delivery). Estriol is one of the hormones that rise during pregnancy. Estriol is less thrombogenic than other estrogens. It inhibits EAE, and, in a small study, it reduced exacerbations in relapsing/remitting MS. A large trial is awaiting approval.

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