

Differential Diagnosis, Clinical Features, and Prognosis of Multiple Sclerosis

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INTRODUCTION

The diagnosis and prognosis of multiple sclerosis (MS) has changed dramatically over the years from the first descriptions from St. Lidwina of Schiedam (1380–1433) and Augustus D’Este (grandson of George III) between 1822 and 1848 to the pathological descriptions of Cruveilhier (1829–1842) and Carswell (1838). Serious study and synthesis of clinical and pathological human MS began with the work of Jean Martin Charcot at the Salpetriere in Paris in the last three decades of the 19th century. Recently, there has been a trend to classify MS as an immune-mediated demyelinating disease of the central nervous system (CNS). This classification is useful as a diagnostic tool, as demonstrated by Schumacher (1962) and Poser (1983). The new diagnostic criteria (1), which is discussed in detail in the remainder of this chapter, has changed the diagnosis, prognosis, and treatment of MS.

DIAGNOSIS

The cornerstone of the MS diagnosis remains the neurological history and physical examination. There are no clinical findings that are unique to this disorder, but some are highly characteristic (Table 1). Common presenting MS symptoms are listed in Table 2. The typical patient presents as a young Caucasian adult female with two or more clinically distinct episodes of CNS dysfunction, with at least partial resolution. The history and physical examination are most important for diagnostic purposes, although numerous laboratory tests support the diagnosis (Table 3). To improve the homogeneity of MS patient groups being studied, the Schumacher Committee on Diagnostic Criteria for MS (2) elaborated six items that are required to diagnose clinically definite MS: objective CNS dysfunction, involvement of white-matter structures, two or more sites of CNS involvement, relapsing-remitting or chronic (more than 6 months) progressive course, age 10–50 years at onset, and no better explanation of symptoms as assessed by a competent

From: *Current Clinical Neurology: Multiple Sclerosis*
Edited by: M. J. Olek © Humana Press Inc., Totowa, NJ

Table 1
Common Clinical Features of Multiple Sclerosis

Clinical features suggestive of multiple sclerosis	Clinical features not suggestive of multiple sclerosis
Onset between ages 15 and 50	Onset before age 10 or after 60
Relapses and remissions	Steady progression
Optic neuritis	Early dementia
Lhermitte sign	Rigidity, sustained dystonia
Internuclear ophthalmoplegia	Cortical deficits, such as aphasia, apraxia, alexia, and neglect
Fatigue	Deficit developing within minutes
Worsening with elevated body temperature	

Table 2
Presenting Symptoms in Multiple Sclerosis Patients

Symptom	Males (%)	Females (%)	Total (%)
Sensory disturbance—limbs	25.1	33.2	30.7
Visual loss	15.1	16.3	15.9
Motor (subacute)	10.4	8.3	8.9
Diplopia	8.5	6.0	6.8
Gait disturbance	8.3	3.2	4.8
Motor (acute)	4.2	4.4	4.3
Balance problems	4.0	2.5	2.9
Sensory disturbance—face	2.5	2.9	2.8
Lhermitte's phenomenon	2.3	1.6	1.8
Vertigo	1.5	1.8	1.7
Bladder disturbance	1.1	0.9	1.0
Limb ataxia	1.3	0.9	1.0
Acute transverse myelopathy	0.6	0.8	0.7
Pain	0.8	0.3	0.5
Unclassified	2.5	2.6	2.5
Polysymptomatic onset	11.9	14.5	13.7

Adapted from refs. 68 and 69.

Table 3
Comparison of Sensitivity of Laboratory Testing in Multiple Sclerosis

	Visual evoked response (%)	Brainstem auditory evoked response (%)	Somato-sensory evoked potentials (%)	Oligo-clonal bands (%)	Magnetic resonance imaging (%)
Clinically definite multiple sclerosis*	80–85	50–65	65–80	85–95	90–97

*Numbers show the percentage of patients with abnormal study results.

neurologist. These criteria made no use of laboratory studies. Such stringent criteria would exclude some patients with MS; for example, they were fulfilled in only 95% of a group of patients who came to autopsy study. The criteria were modified for diagnosis in 1983 by Poser et al. (3), expanding the age at onset to 59 years and using data derived from laboratory studies, including analysis of cerebrospinal fluid (CSF), evoked potentials (EP), and neuroimaging. These criteria were developed to ensure that only patients with MS were included in research studies. Recently, McDonald et al. (1) have proposed new diagnostic criteria, which include stringent guidelines for magnetic resonance imaging (MRI) and timing intervals to determine possible or definite multiple sclerosis. The outcomes are classified as:

- The diagnosis of MS is given if diagnostic criteria are fulfilled.
- The diagnosis of possible MS is given if the criteria are not completely met.
- The diagnosis of not MS is given if the criteria are fully explored and not met.

Another significant change with the newer criteria (sometimes referred to as the McDonald criteria) is the incorporation of MRI findings. The new diagnostic criteria are shown in Table 4 and in the next section. The new criteria consider CSF analysis, EPs, and neuroimaging, as well as creating a category for patients with clinically isolated syndromes. This information allows patients to be treated at an earlier phase in their disease and will provide the greatest effect on the long-term prognosis of the disease for most patients.

Magnetic Resonance Imaging Demonstration of Space Dissemination for McDonald Diagnostic Criteria for Multiple Sclerosis (4,5)

Three out of four of the following:

1. One gadolinium-enhancing lesion OR nine T2-hyperintense lesions if there is no gadolinium-enhancing lesion;
2. At least one infratentorial lesion;
3. At least one juxtacortical lesion; and/or
4. At least three periventricular lesions.

If the first scan is performed less than 3 months after the onset of the clinical event, a second scan done 3 months or more after the clinical event showing a new gadolinium-enhancing lesion provides sufficient evidence for dissemination in time. However, if no enhancing lesion is seen at this second scan, a further scan, not less than 3 months after the first scan that shows a new T2 lesion or an enhancing lesion, will suffice.

RADIOLOGICAL STUDIES

MRI is the test of choice to support the clinical diagnosis of MS. The characteristic lesion demonstrated on MRI is the cerebral or spinal plaque. Pathologically, plaques consist of a discrete region of demyelination with relative preservation of axons, although spectroscopic and pathological studies suggest axonal loss may be an integral part of the demyelinating process (6). Histological examination of active

Table 4
McDonald Diagnostic Criteria for Multiple Sclerosis (1)

Clinical presentation	Additional data needed for multiple sclerosis (MS) diagnosis
Two or more attacks; objective clinical evidence of two or more lesions	None
Two or more attacks; objective clinical evidence of one lesion	Dissemination in space, demonstrated by MRI OR Two or more MRI-detected lesions consistent with MS plus positive CSF OR Await further clinical attack implicating a different site
One attack; objective clinical evidence of two or more lesions	Dissemination in time, demonstrated by MRI OR Second clinical attack
One attack; objective clinical evidence of one lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space, demonstrated by MRI OR Second clinical attack OR Two or more MRI-detected lesions consistent with MS plus positive CSF and dissemination in time, demonstrated by MRI
Insidious neurological progression suggestive of MS	Positive CSF and dissemination in space, demonstrated by: (1) Nine or more T2 lesions in: brain, (2) Two or more lesions in spinal cord, or, (3) Four to eight plus one spinal cord lesion OR Abnormal visual evoked response (VER) associated with four to eight brain lesions, or with fewer than four brain lesions plus one spinal cord lesion demonstrated by MRI AND Dissemination in time, demonstrated by MRI OR Continued progression for 1 year

Notes: Positive CSF-oligoclonal bands (detected preferably by isoelectric focusing) or raised immunoglobulin-G index.

plaques reveals perivascular infiltration of lymphocytes (predominantly T-cells) and macrophages with occasional plasma cells. Perivascular and interstitial edema may be prominent.

Plaques suggestive of MS are typically found on MRI in the periventricular region, corpus callosum, centrum semiovale, and, to a lesser extent, deep white-

matter structures and basal ganglia. MS plaques usually have an ovoid appearance, and lesions are arranged at right angles to the corpus callosum as if radiating from this area. The plaques appear hyperintense on proton density and T2-weighted studies and are hypointense (if visible at all) on T1-weighted images.

MRI detects many more MS lesions than computed tomography (CT) and is able to detect plaques in regions that are rarely abnormal on CT, such as the brain stem, cerebellum, and spinal cord. Most lesions seen on MRI correlate with pathologic lesions (7). However, some lesions that are extensive on MRI show only small plaques on pathological examination, suggesting that much of the abnormal MRI signal may be a result of increased water content of the brain around such plaques resulting from presumed disruption of the blood–brain barrier.

Patients with clinically definite MS have typical white-matter lesions on MRI in more than 90% of cases. However, CNS lesions resulting from other disorders (e.g., ischemia, systemic lupus erythematosus [SLE], Behçet's disease, other vasculitides, human T-cell lymphotropic virus [HTLV]-1, and sarcoidosis) may appear similar to MS lesions on MRI. This is particularly true for ischemic lesions, which make MRI criteria much less reliable for the diagnosis of MS in patients older than 50 years (8).

In contrast, the frequency of abnormal signals on spinal cord MRI in normal individuals is only 3%, because the non-MS hyperintense signal seen in older patients on cranial MRI does not occur in the spinal cord. Newer technology MRI detects lesions in the spinal cord in 75% of patients with definite MS (9).

The overall sensitivity and specificity of MRI depend on the diagnostic criteria employed. In one study of 1500 brain MRI scans that included 134 scans of patients with a clinical diagnosis of MS, using the criteria of three or four areas of increased signal intensity resulted in a high sensitivity for the diagnosis of MS (90 and 87%, respectively) but a low specificity (71 and 74%, respectively) and positive predictive value (23 and 25%, respectively) (8). Accuracy was improved with criteria that included at least three areas of increased signal intensity plus two of the following features: lesions abutting body of lateral ventricles, infratentorial lesion location, and size >5 mm. Using these criteria, specificity improved to 96%, positive predictive value increased to 65%, and sensitivity decreased slightly to 81%.

MRI scanning is more sensitive and specific for predicting evolution to clinically definite MS than other studies, such as CT scans, CSF parameters, or EPs (10). This was illustrated in a 2-year follow-up of 200 patients referred for suspected MS that found 30% (50% of those under age 50 years) had developed clinically definite MS, of whom 84% had initial MRI scans that were strongly suggestive of MS (11). In contrast, the number of patients who had CSF oligoclonal bands, abnormal visual EPs, or an abnormal CT when initially studied were 69, 69, and 38%, respectively. In a second, 5-year study of 89 patients, progression to clinically definite MS occurred in 37 out of 57 (65%) with an initially abnormal MRI, and only 1 of 32 (3%) with a normal MRI (12). Again, MRI was a better predictor of progression to clinically definite MS than CSF analysis.

Patients who progress to clinically definite MS have a higher lesion load at presentation than those who do not progress (13). Increasing initial lesion load also correlates with a decreasing time to development of MS clinically. Lesion load may also have implications for long-term prognosis.

However, the extent of cranial MRI abnormalities does not necessarily correlate with the degree of clinical disability. Patients with small numbers of lesions may be quite disabled, whereas others can function well despite a large burden of disease detected by MRI. There are several possible explanations for this observation: lesions may occur in areas that are clinically silent, small lesions in the spinal cord can cause major disability in the absence of cerebral lesions, MRI may miss lesions that are clinically relevant (1), such as those in cortex, basal ganglia, and brain stem, and large plaques detected by MRI may not have functional correlates but reflect increased tissue water without impairment of neural function.

The amount of ongoing MRI activity (new or enlarging lesions and/or gadolinium-enhancing lesions) exceeds the observed clinical activity by a factor of 2 to 10 (14). This not only may reflect the factors discussed above but also may result, in part, from underreporting of minor symptoms and underrecognition of minor signs in patients with MS. However, it does suggest that MS is a much more dynamic and active disease than is clinically apparent and that MRI is essential to studies of therapy in MS.

Efforts continue to delineate differences in the MRI appearance of acute or active lesions and chronic lesions. Acute lesions tend to be larger with somewhat ill-defined margins and become smaller with sharper margins as resolution occurs. This presumably reflects resolution of edema and inflammation present at the time of acute plaque formation, leaving only residual areas of demyelination, gliosis, and enlarged extracellular space with remission. The MRI appearance of primary progressive MS shows a smaller total disease burden, a greater preponderance of small lesions, fewer gadolinium-enhancing new lesions, and acquisition of fewer lesions per unit time than the secondary progressive form of MS.

Gadolinium-DTPA, a paramagnetic contrast agent that can cross only disrupted blood-brain barrier, has been used to assess plaque activity (15). Gadolinium increases signal intensity on T1-weighted images. The accumulation of gadolinium in plaques is associated with new or newly active plaques and with pathologically confirmed acute inflammation in MS. Gadolinium enhancement usually remains for <1 month but may persist up to 8 weeks in acute plaques. Gadolinium enhancement diminishes or disappears after treatment with corticosteroids, a therapy believed to restore integrity of the blood-brain barrier permeability.

It is difficult to distinguish the edema of an acute plaque from the gliosis and demyelination of a chronic plaque with conventional MRI technology. Phosphorus MR spectroscopy can provide information on phospholipid metabolism, and proton spectroscopy can generate information about other metabolic components, such as *N*-acetylaspartate (NAA), an exclusively neuronal marker, creatine phosphate (Cr) (energy), choline (membrane component), and lactic acid (LA). Chronic MS brains

have a reduced amount of NAA in comparison to C and Cr; a reduced NAA/Cr ratio is the common means of expressing such reduction. This reduced ratio implies loss of neurons or axons, which is consistent with pathological studies and appears to parallel disability in MS (16).

CEREBROSPINAL FLUID

CSF findings alone cannot make or exclude the diagnosis of MS, but they can be useful adjuncts to clinical criteria. The CSF is grossly normal in MS; it is clear, colorless, and under normal pressure. Total leukocyte count is normal in two-thirds of patients, exceeding 15 cells/ μ L in fewer than 5% of patients and only rarely exceeding 50 cells/ μ L (a finding that should raise suspicion of another etiology). The predominant cell type is the lymphocyte, the majority of which are T-cells. CSF protein (or albumin) level is normal in the majority of patients with MS. Albumin determinations are preferable because albumin is not synthesized in the CNS and thus gives a better indication of blood–brain barrier disruption than does total protein, some of which may be synthesized within the CNS (i.e., immunoglobulin [Ig]). Albumin levels are elevated in 20–30% of patients, although less than 1% of patients have a level twice that of normal (Table 5). A common finding in MS is an elevation of CSF immunoglobulin level relative to other protein components, implying intrathecal synthesis. The immunoglobulin increase is predominantly IgG, but the synthesis of IgM and IgA is increased also. The IgG shows an excess of IgG λ and κ light chains. The IgG level may be expressed as a percentage of total protein (normal <11%), as a percentage of albumin (normal <27%), by use of the IgG index (normal value <0.66), or by use of a formula for intra-blood–brain barrier synthesis of IgG. An abnormality of CSF IgG production as measured by the IgG index or IgG synthesis rate is found in more than 90% of patients with clinically definite MS, and different formulas have differing sensitivity and specificity. The sensitivity of IgG as a percentage of protein or albumin is slightly lower (Table 5) (17).

Linked to the elevation of IgG is the finding of oligoclonal bands (OCBs) in the cathodal region of an electrophoretic analysis of CSF. When normal CSF is electrophoresed, the cathodal region shows only a homogeneous blur of immunoglobulin. In MS and other conditions usually associated with inflammation, electrophoretic analysis reveals numerous discrete bands distinct from the background; these bands represent excess antibody produced by one or more clones of plasma cells. In subacute sclerosing panencephalitis, the majority of these OCBs represent antibody directed against the causative agent, measles virus. However, in MS, there is no disease-specific antigen yet identified against which the majority of bands are directed. The pattern of banding remains relatively consistent in individual patients during the disease course, although bands may be added over time. Occasionally, patients with definite autopsy-proved MS do not have OCBs.

A common method for electrophoresis uses agarose gels, but a more sensitive assay is the use of isoelectric focusing on polyacrylamide gels. OCBs are found in 85–95% of patients with clinically definite MS (Table 5). Up to 8% of CSF samples

Table 5
Cerebrospinal Fluid Abnormalities in Multiple Sclerosis

	Albumin (%)	IgG/TP (%)	IgG/ Albumin (%)	IgG Index (%)	Oligoclonal Banding of Ig (%)
Clinically definite multiple sclerosis (MS)	23	67	60–73	70–90	85–95
Normal controls	3		36	3	7*

Abbr: IgG/TP, immunoglobulin (Ig) G value/total protein.

*Other neurological diseases.

from patients without MS show OCBs and most are from cases of chronic CNS infections, viral syndromes, and autoimmune neuropathies. The presence of OCBs in patients who are monosymptomatic predicts a significantly higher rate of progression to MS than the absence of bands: 25 vs 9% at a 3 year follow-up (18). However, one must not assume that the presence of OCBs is equivalent to a diagnosis of MS, given the number of false-positive results that can occur and the variability in technique and interpretation in different laboratories.

The presence of myelin components and antimyelin antibodies in CSF and other body fluids has been used to a limited extent as a measure of CNS myelin destruction and presumed demyelinating activity in the CNS (19).

EVOKED POTENTIALS

Evoked potentials (EPs) are the CNS electrical events generated by peripheral stimulation of a sensory organ. The use of EPs is the detection of a CNS abnormality of function that may be clinically undetectable. In the case of MS, detection of a subclinical lesion in a site remote from the region of clinical dysfunction supports a diagnosis of multifocal disease. The EPs also may help define the anatomical site of the lesion in tracts not easily visualized by imaging (optic nerves and dorsal columns). The three most frequently used EPs are somatosensory EP (SSEP) both upper and lower extremities, visual (VER), and brainstem auditory-evoked responses (BAER). MRI technology has largely eliminated the use of EPs, given the much greater anatomical information obtained and the much higher sensitivity of MRI in the diagnosis of MS (Table 3).

Patients with clinically definite MS have abnormal VERs in 85% of cases. The VER is particularly useful in patients who lack clear clinical evidence of dysfunction above the level of the foramen magnum, such as those with a chronic progressive myelopathy. Ocular or retinal disorders must be excluded before attributing abnormal VERs to demyelination in the optic pathways.

Table 6
Summary of Ancillary Testing in Multiple Sclerosis

Test	Percentage abnormal with definite multiple sclerosis (%)
Brainstem auditory evoked response	50–65
Somatosensory evoked potentials	65–80
Visual evoked response	80–85
Cerebrospinal fluid (CSF) Immunoglobulin (Ig) G Index	70–90
CSF oligoclonal bands	85–95
Brain magnetic resonance imaging	90–97

SSEPs are abnormal in 77% of patients with MS, including approximately one-half of those who do not have sensory signs or symptoms. Some patients with clinical evidence of posterior column dysfunction may have abnormal SSEPs.

BAER abnormalities are less frequent in MS than VER or SSEP abnormalities, being present in 67% of patients with MS.

Consistent with these findings, guidelines from the American Academy of Neurology state that VERs are probably useful to identify patients with clinically definite MS, SSEPs are possibly useful, and there is insufficient evidence at this time to recommend BAER as a useful test for diagnostic purposes (20).

Synthesis of the previous data on ancillary testing is presented in Table 6.

AGE OF ONSET

Most studies agree that the median age of onset is 23.5 years of age. The peak age of onset is approximately 5 years earlier for women than for men. The mean age of onset is 30. Relapsing-remitting MS tends to have an earlier onset, averaging 25–29 years, compared with the relapsing-remitting progressive type with an average of onset of 25–29 years, and a mean age of conversion to progressive MS of 40–44 years. Primary progressive MS has a mean age of onset of 35–39 years. The onset of MS can occur as late as the seventh decade, although rarely. Mean age of onset is 30.6 years, median is 27 years, and peak incidence is 25 years.

SEX DISTRIBUTION

Autoimmune diseases in general and MS in particular affect more women than men. In a summary of 30 incidence and prevalence studies, a cumulative ratio of female to male subjects was 1.77:1.00.

MORTALITY

Mortality caused by MS is difficult to ascertain because of poor data collection and reporting. The US Department of Health and Human Services report of deaths

in 1992 indicates that 1900 US citizens died of MS in that year, giving MS a US mortality of 0.7 per 100,000. The mean age of death of all patients with MS was 58.1 years, compared with a national average of 70.5 for all causes of death. The life expectancy of patients with MS was therefore calculated to be 82.5% of the normal life span. In Denmark, in an exceptionally complete survey of the country, median survival after diagnosis for men was 28 years and for women 33 years, compared with matched population death rates of 37 and 42 years, respectively. In another study, MS mortality figures were calculated for England and Wales from 1963 to 1990. During this time, there was a steady and consistent decline in the death rate attributable to MS compared with the overall death rate. Patients with MS tended to live longer, and other diseases were more likely to be the cause of death. Current estimates indicate that about half of the deaths in MS patients directly result from their disease, slightly more than half if accidents, and suicide are included as indirect causes.

ROLE OF IMMUNE SYSTEM STIMULI

Because the pathogenesis of MS is believed to involve the immune system, it has been hypothesized that a stimulus of the immune system (e.g., a vaccine) may trigger the disease. However, two well-designed studies have refuted this theory, one finding no association between hepatitis B vaccination and the development of MS (21), and the other finding no association between several different vaccines and disease relapse in patients with MS (22).

On the other hand, a possible infectious stimulus of the immune system has received more support in the literature. Many viruses have been associated with MS, although none has been conclusively linked to the disease (23). A role for Epstein-Barr virus (EBV), which causes infectious mononucleosis, is supported by observations that there is an increased risk of MS after infectious mononucleosis (24) and that MS is rare among people without serum anti-EBV antibodies (25). Furthermore, a prospective serologic study of women in the Nurses' Health Study found significant elevations in anti-EBV antibody titers before the onset of MS, particularly antibody to the EBV nuclear antigen 2 (EBNA-2) (26). Although these findings do not confirm that EBV is an etiologic agent, they are suggestive and warrant further study. For further information on the immune response and the role of B-cells in MS, please refer to Chapter 6.

GEOGRAPHIC AND RACIAL DISTRIBUTION

More than 250 prevalence surveys have been conducted, serving as the basis for the delineation of geographic risk for MS. High-frequency areas of the world, with current prevalence of 60 per 100,000 or more, include all of Europe, including Russia, southern Canada, the northern United States, New Zealand, and the southeastern portion of Australia. In many of these areas, the prevalence is more than 100 per 100,000, with the highest reported rate of 300 per 100,000 occurring in the Orkney Islands. In the United States, the prevalence is 0.1%, or a total of 250,000 persons with MS.

Low-risk areas include most of South America, Mexico, most of Asia, and all of Africa. One possible conclusion is that MS is a place-related illness, with a latitude gradient. However, notable exceptions then need to be explained. Japan, situated at the same latitude as areas of high prevalence in Europe, is a low-risk area. Second-generation Japanese in the United States retain their parents' low risk of MS. The white population of South Africa, of medium MS prevalence, is surrounded by a black population in which the disease is uncommon. Native North Americans, especially of pure Amerindian background, have a low prevalence, but they are surrounded by a white population with a medium or high MS risk.

It seems plausible then that race is a determinant of MS risk, with populations of white extraction, especially from Northern Europe being the most susceptible. People of Asian, African, or Amerindian origin have the lowest risk, whereas other groups are variably intermediate. Migration data have often been used to support the view that a transmissible agent is involved in the pathogenesis of MS. The data indicate that persons migrating from an area of high risk to an area of low risk after the age of puberty carry their former high risk with them. With migration during childhood, the risk seems to be that of the new area to which the person has migrated. The data are not always clear-cut. Japanese in Japan are at low risk for MS. People of Japanese extraction who are living in the United States have a higher risk, although this risk is less than their neighbors of Northern European extraction. However, those Japanese who migrate to this country do not acquire the risk of their new area. Comparable data are available for persons moving to Israel from Europe (high risk).

The frequency of familial occurrence of MS has varied from 3 to 23% in different studies. The studies with the higher percentages are those in which ascertainment was more intense; that is, the more one looks, the more one finds. An overall risk in first-, second-, and third-degree relatives of at least 15% seems a reasonable estimate. The risk is highest for siblings and decreases progressively for children, aunts, uncles, and cousins (Table 7). For genetic counseling purposes, it may be stated that the sibling risk is 3–5%, approximately 30–50 times the background risk for this same population. In some studies, unaffected family members have had abnormalities on MRI, implying that the risk may be even higher. The risk applies to blood relatives; only a few studies of adopted children have been done, but they show no increased risk. One unexplained finding is the marked deficiency of transmission from father to son.

Twin studies have shown the familial nature of MS in dramatic fashion. The risk for dizygotic twin pairs is the same as that for siblings; that is, 3–5%. The risk for monozygotic twins is at least 20%, and if the subjects are followed for long periods of time and if various nonclinical data are included, the risk may reach 38.5% (27). Because the highest rates for the genetic basis of MS are less than 50%, there must be a contribution by nongenetic factors. There are several candidate genes for MS, including human leukocyte antigen, T-cell receptor, MBP, portions of the immunoglobulin chain, and mitochondrial genes. Three entire genomic scans for MS susceptibility genes have been reported, without an identifiable region of major interest (26–28). The data argue for nonmendelian polygenic inheritance.

Table 7
Risk of Developing Multiple Sclerosis in Family Members

A. Parent with multiple sclerosis (MS)	Son	Daughter
Mother	3.8%	3.7%
Father	0.8%	2.0%
B. Sibling with MS sister brother		
Female	5.6%	2.2%
Male	3.5%	4.1%
C. Twin with MS either sex		
Identical	25–40%	
Nonidentical	4%	

Source: Modified from ref. 70.

CLINICAL SYMPTOMS AND PHYSICAL FINDINGS

Although the clinical syndrome of MS is classically described as a relapsing-remitting disorder that affects multiple white-matter tracts within the CNS, with usual onset in young adults, the disorder displays marked clinical heterogeneity. This variability includes age of onset, mode of initial manifestation, frequency, severity and sequelae of relapses, extent of progression, and cumulative deficit over the course of time. The varied clinical features reflect the multifocal areas of CNS myelin destruction (MS plaques), although discrepancies occur between the extent of clinical and pathological findings.

There are no clinical findings that are unique to MS, but some are highly characteristic of the disease. Common presenting symptoms of MS are listed in Table 2. The typical patient presents as a young adult with two or more clinically distinct episodes of CNS dysfunction with at least partial resolution.

CRANIAL NERVE DYSFUNCTION

Impairment of the Visual Pathways

Optic neuritis (ON) is the most frequent type of involvement of the visual pathways, usually presenting as an acute or subacute unilateral syndrome characterized commonly by pain in the eye accentuated by ocular movements, which is then followed by a variable degree of vision loss (scotoma) affecting mainly central vision. Bilateral ON does occur, but one needs to distinguish whether it is truly simultaneous or sequential. Bilateral simultaneous ON is rare in MS, and its occurrence in isolation may suggest another diagnosis, such as Leber's hereditary optic atrophy or toxic optic neuropathy. In bilateral ON in MS cases, the impairment begins asym-

metrically and is usually more severe in one eye. Recurrence is highly variable. In a large ON treatment trial, 15% of placebo-treated patients developed recurrent (ipsilateral or contralateral eye) ON within 6 to 24 months after the initial bout of ON (31). Mapping of visual fields reveals a central or cecocentral scotoma (central scotoma involving the physiological blind spot). The finding of a bitemporal hemianopia is rare in MS; if present, it should raise the suspicion of a mass lesion compressing the optic chiasm. Although uncommon, homonymous field defects can be seen in MS caused by involvement of the optic radiations.

Patients with ON have a relative afferent pupillary defect (Marcus Gunn pupil). The afferent pupillary defect is tested by shining a bright light alternately in each eye (the swinging flashlight test), and in the case of unilateral optic nerve dysfunction the abnormal pupil paradoxically dilates when the light is shifted from the normal to the affected eye. The interpretation of this sign becomes difficult when the degree of optic nerve impairment is similar in the two eyes. When the acute ON lesion involves the head of the optic nerve, one observes disc edema (papillitis), a finding more commonly seen in children than in adults. More often, the lesion of the optic nerve is retrobulbar, and fundusoscopic examination is normal in the acute stage. Later, the optic disc becomes pale as a result of axonal loss and resultant gliosis. This pallor predominates in the temporal segment of the disc (temporal pallor). After an attack of acute ON, 90% of patients regain normal vision, typically during a 2- to 6-month period. Desaturation of bright colors, particularly red, is often reported by patients who have recovered from ON; some also report a mild nonspecific dimming of vision in the affected eye.

Uhthoff's phenomenon refers to a decrease in visual acuity after an increase in body temperature. This can occur after exercise, a hot bath, or fever. This phenomenon, which reflects subclinical demyelination or preexistent injury to the optic nerve, may occur without a history of clinical involvement of the optic nerve. A similar phenomenon can occur at other sites of CNS dysfunction with an increase in body temperature.

Bitemporal hemianopia is rare in MS and, if present, should raise the suspicion of a mass lesion compressing the visual pathways. Homonymous field defects are uncommon but can be seen in MS resulting from involvement of the optic radiations.

Because many patients with MS present with ON as their first neurologic event, it is interesting to consider how many patients who have ON go on to develop MS. The reported risk of progression to clinically diagnosed MS ranges from 15 to 75%. In one population-based study, 39% of 95 patients with isolated ON progressed to clinically definite MS by 10 years of follow-up, 49% by 20 years, 54% by 30 years, and 60% by 40 years (32). There was no difference in the risk of developing MS between men and women. The presence of oligoclonal bands in the CSF of such patients has been associated with an increased risk of developing MS.

MRI can help differentiate groups of patients with ON who are likely or unlikely to develop MS (31). Between 50 and 72% of patients with ON have cranial MRI

appearances consistent with MS. Of those with lesions on MRI, there is a 55 to 70% risk of developing clinically definite MS or laboratory-supported definite MS within 5 years (12). In contrast, patients with isolated ON and no evidence of disseminated lesions on MRI have only a 6 to 16% risk of developing MS after 4 years or more of follow-up. The incidence of MRI abnormalities in children with ON is less than in adults; this observation, coupled with clinical experience, suggests that the rate of progression to MS in children with isolated ON may be less than in adults.

IMPAIRMENT OF THE OCULAR MOTOR PATHWAYS

Impairment of individual ocular motor nerves is infrequent in MS. When present, the involved nerves are, in decreasing order of frequency, Cranial Nerves VI, III, and, rarely, IV. More frequent findings are those that reflect lesions of vestibulo-ocular connections and internuclear connections. Nystagmus is a common finding in MS. One form of nystagmus particularly characteristic of MS is acquired pendular nystagmus, in which there are rapid, small amplitude pendular oscillations of the eyes in the primary position resembling quivering jelly. Patients frequently complain of oscillopsia (subjective oscillation of objects in the field of vision). This type of nystagmus usually is seen in the presence of marked loss of visual acuity. Internuclear ophthalmoplegia, defined as abnormal horizontal ocular movements with lost or delayed adduction and horizontal nystagmus of the abducting eye, is secondary to a lesion of the medial longitudinal fasciculus on the side of diminished adduction. Convergence is preserved. When present bilaterally, it is usually coupled with vertical nystagmus on upward gaze. Although most suggestive of MS, a bilateral internuclear ophthalmoplegia can be observed with other intraaxial brainstem lesions, including brainstem glioma, vascular lesions, Arnold-Chiari malformations, and Wernicke's encephalopathy. Ocular pursuit movements are frequently saccadic rather than smooth. Ocular dysmetria may coexist with other signs of cerebellar dysfunction and other ocular oscillations, such as intrusive saccadic movements (square wave jerks).

IMPAIRMENT OF OTHER CRANIAL NERVES

Impairment of facial sensation, subjective or objective, is a relatively common finding in MS. The occurrence of trigeminal neuralgia in a young adult is frequently an early sign of MS. Facial myokymia, a fine undulating wavelike facial twitching, and hemifacial spasm can be caused by MS, but other causes of a focal brainstem lesion must be excluded. Unilateral facial paresis can occur, but taste sensation is almost never affected. In these syndromes, as with acute oculomotor palsy, the nerve is affected in its course within the neuraxis, rather than peripherally. Vertigo is a reported symptom in 30 to 50% of patients with MS and is commonly associated with dysfunction of adjacent cranial nerves. Resulting symptoms include hyperacusis or hypoacusis, facial numbness, and diplopia. Complete hearing loss,

usually unilateral, is an infrequent complaint. Malfunction of the lower cranial nerves is usually of the upper motor neuron type (pseudobulbar syndrome).

IMPAIRMENT OF THE SENSORY PATHWAYS

Sensory manifestations are a frequent initial feature of MS and are present in almost every patient at some time during the course of disease. The sensory features can reflect spinothalamic, posterior column, or dorsal root entry zone lesions. The sensory symptoms are commonly described as numbness, tingling, pins and needles, tightness, coldness, or swelling of limbs or trunk. Radicular pains, unilateral or bilateral, can be present, particularly in the low thoracic and abdominal regions, or a band-like abdominal sensation may be described. An intensely itching sensation, especially in the cervical dermatomes, usually unilateral, suggests MS.

The most frequent sensory abnormalities on clinical examination are the following: varying degrees of impairment of vibration and joint position sense, decrease of pain and light touch in a distal distribution in the four extremities, and patchy areas of reduced pain and light touch perception in the limbs and trunk. A bilateral sensory level is a more frequent finding than a hemisensory (Brown-Séquard) syndrome. Patients commonly report that the feeling of pinprick is increased or feels like a mild electric shock or that the stimulus spreads in a ripple fashion from the point at which it is applied. The sensory useless hand is a characteristic but uncommon feature, consisting of an impairment of function secondary to a pronounced alteration of proprioception, without loss of power. A lesion of the relevant root entry zones in the spinal cord is postulated in such cases.

IMPAIRMENT OF MOTOR PATHWAYS

Corticospinal tract dysfunction is common in MS. Paraparesis, or paraplegia, is a much more common occurrence than is significant weakness in the upper extremities. With severe spasticity, extensor or flexor spasms of the legs and sometimes the trunk may be provoked by active or passive attempts to rise from a bed or wheelchair. The physical findings include spasticity, usually more marked in the legs than in the arms. The deep tendon reflexes are exaggerated, sustained clonus may be elicited, and extensor plantar responses are observed. All of these manifestations are commonly asymmetrical. Occasionally, deep tendon reflexes may be decreased because of lesions interrupting the reflex arc at a segmental level, and one may observe an inverted reflex wherein one reflex, such as the triceps, is lost and the efferent component is represented by a contraction of a muscle below the lesion, such as the triceps muscle. The Achilles' reflex can be absent in lesions of the sacral segments of the spinal cord with or without concomitant sphincter and sexual problems. Occasionally, reduced reflexes reflect hypotonia resulting from cerebellar pathway lesions. Amyotrophy, when observed, most frequently affects the small muscles of the hand; lesions of the motor root exit zones may produce muscle denervation caused by axon loss. Secondary entrapment neuropathies are

also a cause of muscle atrophy in patients with MS. A common pattern of disease evolution seen in the spinal form of MS is an ascending pattern of weakness that begins with involvement of the lower extremities and spreads to involve first one upper extremity and then the other, beginning in the intrinsic hand muscles. Frequently, there is an associated weakness of the trunk muscles with abnormal posture and involvement of respiratory muscles.

IMPAIRMENT OF CEREBELLAR PATHWAYS

Cerebellar pathway impairment results in gait imbalance, difficulty in performing coordinated actions with the arms, and slurred speech. Examination reveals the usual features of cerebellar dysfunction, such as dysmetria, decomposition of complex movements, and hypotonia, most often observed in the upper extremities. An intention tremor may be noted in the limbs and head. Walking is impaired by truncal ataxia. Ocular findings of nystagmus, ocular dysmetria, and frequent refixation saccades suggest cerebellar or cerebellovestibular connection dysfunction. Speech can be scanning or explosive. In severe cases of MS, there is complete astasia (inability to stand), inability to use the arms because of a violent intention tremor, and virtually incomprehensible speech. Cerebellar signs are usually mixed with pyramidal (corticospinal) tract signs.

IMPAIRMENT OF BLADDER, BOWEL, AND SEXUAL FUNCTIONS

The extent of sphincter and sexual dysfunction often parallels the degree of motor impairment in the lower extremities. The most common complaint related to urinary bladder dysfunction is urgency, usually the result of uninhibited detrusor contraction, reflecting a suprasegmental lesion. As the disease progresses, urinary incontinence becomes more frequent. With involvement of sacral segments of the spinal cord, symptoms of bladder hypoactivity may evolve, such as decreased urinary flow, interrupted micturition, and incomplete bladder emptying. An atonic dilated bladder that empties by overflow results from loss of perception of bladder fullness and is usually associated with urethral, as well as anal and genital hypoesthesia, and sensory deficits in the sacral dermatomes. A dysynergic voluntary sphincter, interrupting bladder emptying, will lead to frequent small volume urinations, combined with a large postvoiding residual. When evaluating bladder incontinence or urgency in patients with MS, one must exclude other causes, particularly in multiparous women. Urinary tract infections are common in MS, especially in women. These infections usually do not cause fever and back pain and may increase the extent of bladder dysfunction.

Constipation is more common than fecal incontinence and can reflect both upper and lower motor neuron impairment in addition to decreased general mobility. Almost all patients with paraplegia require special measures to maintain regular bowel movements.

Sexual dysfunction, although frequently overlooked, is a common occurrence in MS. Approximately 50% of patients become completely sexually inactive second-

ary to their disease, and an additional 20% become sexually less active. Men experience various degrees of erectile dysfunction, often with rapid loss of erection at attempted intercourse, whereas loss of ejaculation is less common. Most women preserve their orgasmic capabilities, sometimes even in the presence of complete loss of bladder and bowel function. Sexual dysfunction can be the result of multiple problems, including the direct effects of lesions of the motor and sensory pathways within the spinal cord in addition to psychological factors involved with self-image, self-esteem, and fear of rejection from the sexual partner. Mechanical problems created by spasticity, paraparesis, and incontinence further aggravate the problem.

COGNITIVE IMPAIRMENT

Data from formal neuropsychological studies indicate that cognitive involvement has been underreported in MS. Neuropsychological test results have shown that 34–65% of patients with MS have cognitive impairment. The most frequent abnormalities are with abstract conceptualization, recent memory, attention, and speed of information processing. Patients refer to memory loss or frustration. The abnormalities are usually not apparent during a routine office visit. In a fast-paced environment with multiple stimuli, the cognitive deficit of the MS patient is most obvious. Aphasia, neglect syndrome, cortical blindness, or marked behavioral problems are rare.

Two kinds of recent data have added urgency to the need to assess cognitive deficits: the demonstration by Trapp and colleagues (6) of ongoing axon loss in central white matter beginning at the earliest stages of MS and the demonstration that thinning of the corpus callosum, enlargement of the ventricular system, and other evidences of brain atrophy can be measured accurately by MRI and also begin earlier than previously believed.

Cross-sectional studies have shown some degree of affective disturbance in up to two-thirds of patients with MS (33). Depression is the most common manifestation and is, in part, secondary to the burden of having to cope with a chronic, incurable disease. Some data suggest that depression is more common in patients with MS than in others with chronic medical conditions, in whom the lifetime risk of depression was 12.9% in one study. This contrasts with a study of 221 patients with MS, in whom the risk for depression was 34% (32). Some data indicate a comorbid association, presumably genetic, between bipolar illness and MS. Frontal or subcortical white-matter disease may also be a contributory causative factor. Euphoria is usually associated with moderate or severe mental impairment. Patients may manifest a dysphoric state with swings from depression to elation. On occasion, acute cerebral lesions can manifest as a confusional state.

EPILEPSY

Epilepsy is more common in patients with MS than in the general population, occurring in 2 to 3% of patients (33). Convulsions may be either tonic-clonic or partial complex. They generally are benign and transient and respond well to antiepileptic drug therapy or require no therapy. The prevalence of cortical syn-

dromes, such as aphasia, apraxia, and agnosia, is low. As an example, in a study of 5715 patients with MS, 51 (0.89%) experienced seizure activity (36). Generalized tonic-clonic seizures were most common (35 patients, 69%), followed by simple or complex partial seizures (11 patients, 22%). Of the 45 patients who received antiepileptic drug therapy, 35 (78%) became seizure free, whereas 5 (11%) had intractable seizures.

CLINICAL FEATURES DISTINCTIVE OF MULTIPLE SCLEROSIS

Although there are no clinical phenomena that are unique to MS, some are highly characteristic of the disease (Table 1). Bilateral internuclear ophthalmoplegia has been mentioned. Lhermitte's phenomenon is a transient sensory symptom described as an electric shock radiating down the spine or into the limbs on flexion of the neck. It may be infrequent or occur with the least movement of the head or neck. Although most frequently encountered in MS, this symptom can be seen with other lesions of the cervical cord, including tumors, cervical disc herniation, postradiation myelopathy, and after trauma.

Paroxysmal attacks of motor or sensory phenomena may arise as a manifestation of demyelinating lesions. Within the brainstem, lesions can cause paroxysmal diplopia, facial paresthesia, trigeminal neuralgia, ataxia, and dysarthria. Motor system involvement results in painful tonic contractions of muscles of one or two (homolateral) limbs, trunk, and occasionally the face, but these rarely occur in all four limbs or the trunk. These paroxysmal attacks usually respond to low doses of carbamazepine and frequently remit after several weeks to months, usually without recurrence.

Heat sensitivity is a well-known occurrence in MS (Uhtoff's phenomenon); small increases in the body temperature can temporarily worsen current or preexisting signs and symptoms. This phenomenon is encountered in other neurological diseases but to a lesser extent and is presumably the result of conduction block developing in nerves as the body temperature increases. Normally, the nerve conduction safety factor decreases with increasing temperature until a point is reached at which conduction block occurs; this point of conduction block is reached at a much lower temperature in demyelinated nerves.

Fatigue is a characteristic finding in MS, usually described as physical exhaustion that is unrelated to the amount of activity performed. Many patients complain of feeling exhausted on waking, even if they have slept soundly. Fatigue can appear also during the day but may be partially or completely relieved by rest. There is a poor correlation between fatigue and the overall severity of disease or with the presence of any particular symptom or sign. Unlike cognitive deficit, no MRI findings correlate with fatigue, or with depression (37–40). Fatigue is often seen in association with an acute attack and may precede the focal neurological features of the attack and persist long after the attack has subsided.

DIAGNOSTIC CRITERIA

The new McDonald criteria (Table 4) has several advantages. The former categories of possible, probable, and definite MS have become obsolete. The MRI criteria are based on extensive data of Barkof and Tintore and are designed to retain sensitivity while enhancing specificity. They will have little usefulness in patients with clear-cut demyelinating syndromes, such as ON or a brainstem syndrome; in such cases, many clinicians will be satisfied with less stringent MRI criteria. In patients with obscure symptoms, the criteria will help avoid premature diagnosis and treatment. In addition, criteria for primary progressive MS are proposed. Revisions to the McDonald criteria have been proposed. For example, the role of spinal cord lesions must be evaluated and included. It may take some time before the final criteria are decided on and accepted as the standard for diagnosis.

There remains the clinical problem, distinct from research criteria, of the patient early in the course who does not meet such diagnostic criteria. In the setting of a monophasic neurological illness that is clinically consistent with MS and in the presence of multifocal white-matter lesions on MRI consistent with demyelinating plaques, the diagnosis of MS is almost certain. In Brex et al.'s long-term study (41), which followed patients with initial demyelinating episodes for up to 14 years, in practical terms, no diagnoses were encountered other than suspected MS or definite MS. In addition, follow-up studies have shown that a significant percentage of patients with MRI lesions detected at onset do not progress to clinically symptomatic MS, after many years of follow-up. The issue of the monophasic demyelinating disease is discussed in the section on Clinically Isolated Syndromes. Such patients may be classed as suspected MS; they may in fact represent particularly benign forms of the disease.

A common error is to overinterpret multiple hyperintense lesions on MRI as equivalent to MS. Clinical symptoms must be consistent with MS. A few white-matter lesions in T2-weighted MRI scans are not infrequent, particularly in the elderly, and do not indicate a diagnosis of MS. CNS vasculitides, such as SLE, Sjögren's disease, polyarteritis nodosa, syphilis, retroviral diseases, and Behçet's disease, may all produce multifocal lesions with or without a relapsing-remitting course. SLE can present as a recurrent neurological syndrome before the systemic manifestations of this disease declare themselves. Behçet's syndrome is characterized by buccogenital ulcerations in addition to the multifocal neurological findings. Although rare, acute disseminated encephalomyelitis (ADEM) must be considered in the differential diagnosis. An MS-like phenotype associated with mitochondrial gene defects has been described, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); it is of note that when there are multiple MS cases in a family, maternal transmission is more frequent than paternal transmission.

More important than features characteristic for MS are features that should prompt the clinician to reconsider the diagnosis of MS. Many physicians fail to

pursue further diagnostic steps when a patient is diagnosed with MS. Features that should alert the clinician to the possibility of other diseases include:

- Family history of neurological disease.
- A well-demarcated spinal level in the absence of disease above the foramen magnum.
- Prominent back pain that persists.
- Symptoms and signs that can be attributed to one anatomical site.
- Patients who are over 60 years of age or younger than 15 years at the onset of disease.
- Progressive disease.

None of these features excludes the diagnosis of MS, but in these situations, one should explore the possibility of other etiologies before accepting the diagnosis.

The differential diagnosis of MS is limited in the setting of a young adult who has had two or more clinically distinct episodes of CNS dysfunction with at least partial resolution. Diagnostic difficulties arise in patients who have atypical presentations, monophasic episodes, or progressive illness.

- The unusual nature of some sensory symptoms and the difficulty patients experience in describing such symptoms may result in a misdiagnosis of hysteria.
- A monophasic illness with symptoms attributable to one site in the CNS creates a large differential that includes neoplasms, vascular events, or infections.
- The most trouble arises with progressive CNS dysfunction; great care must be taken in these patients to exclude treatable etiologies (compressive spinal cord lesions, arteriovenous malformations, cavernous angiomas, and Arnold-Chiari malformation), infection (HTLV-1), HIV, or hereditary disorders (adult metachromatic leukodystrophy, adrenomyelo-leukodystrophy, and spinocerebellar disorders).

COURSE

The most characteristic clinical course of MS is the occurrence of relapses (Fig. 1), which can be defined as the acute or subacute onset of clinical dysfunction that usually reaches its peak from days to several weeks, followed by a remission during which the symptoms and signs resolve partially or completely. The minimum duration for a relapse has been arbitrarily established at 24 hours. Clinical symptoms of shorter duration are less likely to represent what is considered as a true relapse (i.e., new lesion formation or extension of previous lesion size). Worsening of previous clinical dysfunction can occur concurrently with fever, physical activity, or metabolic upset and last for hours to a day or more. Such worsening is believed to reflect conduction block in previously demyelinated axons. Relapses of MS vary markedly regarding CNS site involved, the frequency of attacks (the free interval between relapses ranges from weeks to years), the mode of onset (from quite sudden to subacute), and the duration, severity, and quality of remission. The frequency of relapses is highly variable and depends on the population studied and the closeness of observation and recording by patients and physicians. Summaries of many studies provide an average figure of 0.4–0.6 relapses per year. Patients followed closely in clinical trials have higher relapse rates, probably reflecting self-selection and closer reporting and examinations in such studies. The attack rate in the placebo group in clinical studies ranges from 0.8 to 1.2 attacks per year. In

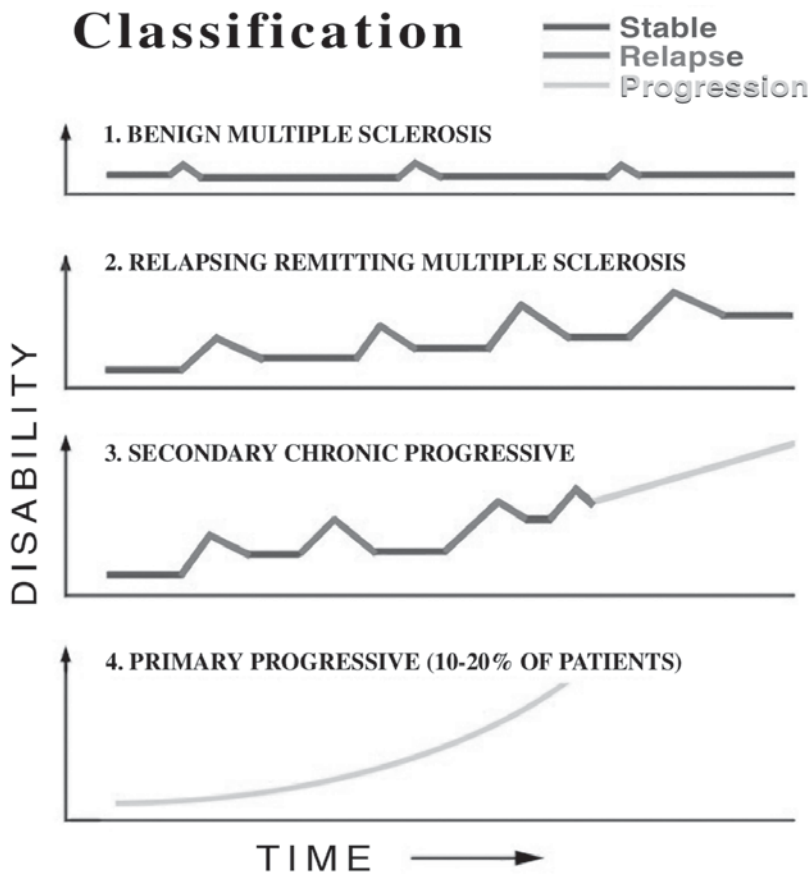


Fig. 1. Relapsing-remitting MS: Clearly defined relapses with full recovery or with sequelae and residual deficit on recovery. The periods between disease relapses are characterized by a lack of disease progression. Primary-progressive MS: Disease progression from onset with occasional plateaus and temporary minor improvements allowed. Secondary-progressive MS: Initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions, and plateaus. Two severity outcomes are also described.

general, relapses are more frequent during the first years of the disease and tend to wane in later years. A course marked by relapses, interspersed by periods during which the disease seems relatively dormant, is termed relapsing-remitting.

The course of MS can be expressed in patients as follows:

1. Severe relapses, increasing disability, and early death.
2. Many short attacks, tending to increase in duration and severity.
3. Slow progression from onset, superimposed relapses, and increasing disability.

4. Slow progression from onset without relapses.
5. Abrupt onset with good remission followed by long latent phase.
6. Relapses of diminishing frequency and severity, slight residual disability only.
7. Abrupt onset, few if any relapses after first year, no residual disability (42).

Approximately 15% of patients never experience a second relapse. The exact frequency of such benign MS is unknown, however, because many such individuals never come to medical attention. Autopsy studies found significant numbers of cases with CNS pathology consistent with MS and yet no documented clinical evidence of such disease. Similarly, MRI studies have shown MS-like plaques in T2-weighted scans in patients who have never had a neurological episode. Asymptomatic relatives of patients with MS have MRI lesions consistent with demyelination in up to 15% of these relatives (43). The use of MRI may expand the spectrum of MS by detecting milder cases that previously were not included in prognosis studies.

A standardization of terms has been agreed on to determine the pattern and course of the illness (44). Four categories of disease are described:

- *Relapsing-remitting MS*: Clearly defined relapses with full recovery or with sequelae and residual deficit on recovery. The periods between disease relapses are characterized by a lack of disease progression.
- *Primary-progressive MS*: Disease progression from onset with occasional plateaus and temporary minor improvements allowed.
- *Secondary-progressive MS*: Initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions, and plateaus.
- *Progressive-relapsing MS*: Progressive disease from onset, with clear acute relapses, with or without full recovery. The periods between relapses are characterized by continuing progression.

Two severity outcomes are also described:

1. Benign MS is a disease in which the patient remains fully functional in all neurological systems 15 years after the disease onset.
2. Malignant MS is a disease with a rapid progressive course, leading to significant disability in multiple neurological systems or death in a relatively short time after disease onset.

Data from a clinic-based study of 1100 patients (45) who represented the population of the region found that 66% of patients at onset had relapsing and remitting disease, 15% had relapsing-progressive, and 19% had progressive disease from the onset. Patients evolved from a relapsing-remitting course to a progressive course; 85% of patients began with a relapsing course, but the proportion continuing as relapsing disease decreased steadily, so that by 9 years from onset, only 50% were still relapsing. Likewise, the probability of reaching 6 on the Kurtzke disability score was 50% 16 to 17 years after onset. The course of MS with onset after the age of 40 was progressive in more than 60% of patients.

The rate of clinical progression of MS is variable. The commonly used index of clinical disability, the Kurtzke disability status score (DSS), or the expanded version called the expanded disability status score (EDSS), uses numbers ranging from

0, for normal examination and function, to 10, for death caused by MS. This scale is nonlinear, with great emphasis on ambulation capabilities with scores above 4.

Most MS populations have bimodal distributions of EDSS scores, with peaks at values of 1 and 6 (ambulation with unilateral assistance). The time spent by a patient at a given level of disability varies with the score. Thus, for patients with DSS scores of 4 or 5, median time spent at these levels was 1.2 years, whereas for those at DSS 1, median time to stay at that level was 4 years, and at DSS 6, 3 years. These results have powerful implications for the conduct of clinical studies with respect to patient selection, stratification, and duration of follow-up: if many patients of DSS 1 or 6 are included, little movement is seen in a group followed for 1 or 2 years. The rate of progression with chronic progressive disease in the placebo groups of three clinical trials ranged from 0.5 to 0.7 points per year on the DSS scale.

In a cohort of 308 patients followed for 25 years, the following data emerged (46):

- 80% of the patients had reached the progressive phase by 25 years.
- 15% of the patients had died.
- 65% of the patients had reached EDSS 6 (requiring aids for walking).
- 50% of the patients reached EDSS 6 within 16 years of onset.

The EDSS, although universally used in clinical trials, has numerous serious limitations. Even with special training and examiner blinding, interrater and intrarater variations in scoring are common. EDSS scores of 4 and higher depend almost entirely on the ability to walk. Developing dementia, vision loss, or weakness of hands may pass undetected by the scoring. An obvious implication of these facts is that other outcome measures should be used as well, and that minor changes in EDSS alone should not be overinterpreted.

The Multiple Sclerosis Functional Composite Scale (MSFC) is a more recent clinical tool designed to avoid the problems encountered with the EDSS. The MSFC consists of three parts: (1) Paced Auditory Serial Addition Test (PASAT), (2) 9-Hole Peg Test (9HPT), and (3) Timed 25-Foot Walk (T25FW). These three measures take into account cognition, upper extremity, and lower extremity functions. A z-score is obtained for each measure, and a combined z-score is then derived. The MSFC has been validated in several clinical trials. The tests can be performed by a nonphysician and are highly reproducible and predictable (47–49).

EFFECT OF EXOGENOUS FACTORS ON THE COURSE

The role of several exogenous factors either influencing the development of MS or inducing disease exacerbations has been examined using epidemiological techniques. A disproportionately high number of relapses occur in patients with MS who have suffered recently from viral infections, and a high number of infections are followed by acute attacks. Increased interferon (IFN)- γ and tumor necrosis factor (TNF)- α produced by cells of the immune system during viral infections may play a role in this increased relapse rate by increasing expression of major histocompatibility complex class II antigens and adhesion molecules on cells

of the immune system and CNS, with a resultant increase in the number of activated T-cells being attracted to the CNS. Controversy exists about a link between occurrence of stressful events and exacerbation of MS. Trauma is not implicated in disease induction or relapse, although in the experimental animal model EAE, lesions are most prominent at sites of preexistent traumatic lesions. Performance of neurological diagnostic procedures, such as myelography and lumbar puncture, has not been linked with aggravation of the MS disease course, neither has administration of local or general anesthetics. Recent data do not establish a link between vaccination and disease exacerbations, and few clinicians withhold immunization programs, for example, for influenza or hepatitis.

EFFECT OF PREGNANCY ON THE COURSE

MS is a disease that predominantly affects women and has a maximum incidence during childbearing years. The influence of pregnancy on MS has been repeatedly examined, with evidence that relapses are reduced late in pregnancy and are more frequent than expected in the 3-month postpartum period. However, this is not the finding in all studies. There is general agreement that the overall prognosis is no different in women who have been pregnant compared with those who have not. Studies of women with MS reveal no increase in stillbirths, ectopic pregnancies, or spontaneous abortions. These data would suggest that pregnancy has no ill effect on MS and that MS has no negative effect on the fetus or the course of pregnancy. In a study of postmenopausal women, there (50). An important issue in the pregnant woman with MS is to avoid exposing the fetus to toxic drugs (Table 8).

PROGNOSIS

Although great individual variability exists regarding disease prognosis, several factors have been identified as possible prognostic indicators. The rate of clinical progression of MS is variable. The commonly used index of clinical disability, the DSS, or the expanded version (EDSS), uses numbers ranging from 0 for normal examination and function to 10 for death caused by MS. This scale is nonlinear, with great emphasis on ambulation capabilities with scores higher than 4. Most MS populations have bimodal distributions of EDSS scores, with peaks at values of 1 and 6 (ambulation with unilateral assistance). The time spent by a patient at a given level of disability varies with the score. Thus, for patients with DSS scores of 4 or 5, median time spent at these levels was 1.2 years, whereas for those at DSS 1, median time to stay at that level was 4 years, and at DSS 6, 3 years. These results have powerful implications for the conduct of clinical studies with respect to patient selection, stratification, and duration of follow-up: if many patients of DSS 1 or 6 are included, little movement is seen in a group followed for 1 or 2 years. The rate of progression with chronic progressive disease in the placebo groups of three clinical trials ranged from 0.5 to 0.7 points per year on the DSS scale.

A large database of 1844 MS patients was analyzed to determine predictors of disability. This study concluded that it takes longer to reach landmarks of irreversible disability in younger female patients with relapsing disease, patients present-

Table 8
Safety in Pregnancy of Drugs Used in the Treatment of Multiple Sclerosis

Category B: Animal data showing no harm to the fetus; no human data available
 Glatiramer acetate (Copaxone)

Pemoline

Oxybutynin

Fluoxetine (and other selective serotonin reuptake inhibitors)

Desmopressin

Category C: Animal data shows harm to the fetus; no human data available

Corticosteroids

Interferon (IFN)- β -1a (Avonex/Rebif)

IFN- β -1b (Betaseron)

Baclofen

Amantadine

Tizanidine

Carbamazepine

Category D: Known to cause fetal harm when administered to pregnant women

Azathioprine

Cladribine

Cyclophosphamide

Mitoxantrone (Novantrone)

Category X: Contraindicated for use during pregnancy

Methotrexate

Source: Modified from ref. 50.

ing with ON, and patients with fewer relapses in the first years of the disease. The study also showed that these good prognostic clinical variables held true for patients up to an EDSS of 4 but did not seem to remain predictive of the time course of disability past 4 to landmarks 6 and 7 (51).

Another MS study between 1976 and 1987 in Norway verified these results and also evaluated primary progressive (PP) patients. The probability of being alive after 15 years was 94.8%. The probability of managing without a wheelchair was 75.8%, of walking without assistance was 60.3%, and of not being awarded a disability pension was 46%. The probability of still having a relapsing remitting (RR) course after 15 years was 62%. Analysis of the total MS population showed that patients with PPMS had more than 7.5 times higher risk of reaching EDSS = 6 than patients with RRMS (52).

Between 1990 and 1998, 98 newly diagnosed patients were evaluated for prognosis using six risk factors:

1. Age at onset (<40 vs >40)
2. Symptoms at onset (isolated sensory or cranial nerve vs motor or sensory plus motor)
3. MRI (at first attack vs CDMS)

4. Interval between first and second attack (>2.5 or <2.5 years)
5. Attack frequency in first 2 years (<2 or >2)
6. Completeness of recovery from initial attack (good vs poor)

Analysis showed 17% with low risk of progression (0–1 risk factors) and 24% with high of progression (4–6 risk factors). The high-risk group did significantly worse in terms of final EDSS and progression to higher EDSS. At the time of diagnosis of CDMS, MRI findings suggestive of MS were seen in 84%, suspicious in 13%, and negative in 3% (53).

Sex: MS appears to follow a more benign course in women than in men.

Age at onset: The average age at onset of MS is 29 years. Onset at an early age is seemingly a favorable factor, whereas onset at a later age carries a less favorable prognosis. As previously stated, the pattern of disease varies in different age groups, with the relapsing-remitting form being more common in younger patients and the progressive form being more common in the older age group. Data are lacking regarding whether prognosis differs as a function of age in patients with similar patterns of disease.

Initial disease course: The relapsing form of the disease is associated with a better prognosis than progressive disease. A high rate of relapses early in the course of illness may correlate with shorter time to reach EDSS 6, as does a short first interval between attacks.

Initial complaints: Among initial symptoms, impairment of sensory pathways or cranial nerve dysfunction, particularly ON, are found in several studies to be favorable prognostic features, whereas pyramidal and particularly brainstem and cerebellar symptoms carry a poor prognosis. Both benign and fulminant forms of MS are recognized. There is no agreement among workers in the field as to the meaning of these terms. It is the general experience that a patient whose disease has had a benign course for 15 years only rarely develops a more severe course. Patients with mild disease (EDSS score 0–3) 5 years after diagnosis only uncommonly progress to severe disease (EDSS score 6) by 10 years (7.5% of patients) and 15 years (11.5% of patients) (46). The term malignant MS is variably used by different workers; some use it to imply a rapid course, others to a clinical course in which there are frequent severe relapses with little recovery. Clues to etiology, susceptibility, and resistance factors must be present in such extremes of the clinical spectrum, but they remain elusive at present. Entities such as Devic's disease, Baló's concentric sclerosis, and particularly Marburg's disease are more fulminant variants of MS with early disability and even death.

OPTIC NEURITIS

The incidence of MRI abnormalities in children with ON is less than that in adults, which, when coupled with clinical experience, suggests that the rate of progression to MS in children with isolated ON may well be less than that in adults. Five-year data from the original Optic Neuritis Treatment Trial revealed that the 5-year cumulative probability of developing clinically definite MS was 30% and

did not differ by treatment group (oral prednisone, IV methylprednisolone, and placebo). However, MRI was a strong predictor; the 5-year risk of developing clinically definite MS was 16% in patients with no brain MRI lesions and 51% in patients with three or more lesions (31).

MYELOPATHIC SYNDROMES

Acute Myelopathy

Patients presenting with acute complete transverse myelitis have a cited risk of MS of only 5–10%. However, partial or incomplete myelitis is a much more common clinical entity and bears more relevance to MS. Studies examining the issue of acute partial myelitis as an initial presentation of MS found that 57–72% of such patients had cranial MRI abnormalities consistent with MS. Follow-up from 3 to 5 years found that 60–90% of these patients developed MS, whereas 10–30% of those with normal MRI developed MS (12). CSF studies suggest that patients with monosymptomatic disease with positive OCBs have a higher risk of evolution to MS than those without OCBs, although CSF results do not help further in prognosis when compared with MRI alone. CSF analysis would be most useful in a situation in which MRI is not available.

Chronic Myelopathy

In patients with chronic progressive myelopathy, 60–70% have cranial MRI abnormalities consistent with MS in the absence of clinical evidence of disease above the level of the spinal cord. What remains unclear is whether the remaining 30% have a disease other than MS or whether MS can manifest as a purely spinal disorder. Probably both situations apply; improved spinal neuroimaging should help resolve this issue.

VARIANTS OF MULTIPLE SCLEROSIS

Diseases affecting CNS myelin can be classified on the basis of whether a primary biochemical abnormality of myelin exists (dysmyelinating) or whether some other process damages the myelin or oligodendroglial cell (demyelinating). Demyelinating diseases in which normal myelin is disrupted include autoimmune, infectious, toxic and metabolic, and vascular processes (Table 9). Dysmyelinating diseases in which a primary abnormality of the formation of myelin exists include several hereditary disorders (Table 9), infectious demyelinating disease (progressive multifocal leukoencephalopathy), toxic and metabolic demyelinating diseases, and vascular demyelinating disease (Binswanger's disease). A list of differential diagnoses can be found in Table 10.

MS is a condition with many variable forms, but in most cases the common signs and symptoms described are readily apparent, and with proper laboratory confirmation, the diagnosis is not difficult. Some patients have their entire clinical illness confined to the optic nerves. One optic nerve may be affected sequentially

Table 9
Diseases of Myelin

<i>Autoimmune</i>
Acute disseminated encephalomyelitis
Acute hemorrhagic leukoencephalopathy
Multiple sclerosis
<i>Infectious</i>
Progressive multifocal leukoencephalopathy
<i>Toxic/metabolic</i>
Carbon monoxide
Vitamin B ₁₂ deficiency
Mercury intoxication (Minamata disease)
Alcohol/tobacco amblyopia
Central pontine myelinolysis
Marchiafava-Bignami syndrome
Hypoxia
Radiation
<i>Vascular</i>
Binswanger's disease
<i>Hereditary disorders of myelin metabolism</i>
Adrenoleukodystrophy
Metachromatic leukodystrophy
Krabbe's disease
Alexander's disease
Canavan-van Bogaert disease
Pelizaeus-Merzbacher disease
Phenylketonuria

after another, or there can be simultaneous bilateral visual loss, a state that is uncommon in classic MS. In some instances, a head MRI will show scattered intracerebral lesions in addition to lesions of the optic nerves or CSF examination will show OCB, attesting to some degree of dissemination of the lesions. Children and preadolescent patients are more likely than adults to have recurrent or simultaneous optic neuropathy. The distinction from an MS variant can be challenging. Sarcoidosis is commonly a diagnostic consideration in patients with bilateral ON. However, there are several inflammatory demyelinating disorders that bear an unknown relationship to MS. They are listed here as variants of MS, rather than as separate illnesses, because it is often found, after long follow-up, that the disease has reverted to a more standard variety of MS.

Recurrent Optic Neuropathy

There are patients whose entire clinical illness is confined to the optic nerves. They may have sequential affection of one nerve, then the other, or they may have

Table 10
Differential Diagnosis in Multiple Sclerosis

<i>Inflammatory diseases</i>
Granulomatous angiitis
Systemic lupus erythematosus
Sjögren's disease
Behçet's disease
Polyarteritis nodosa
Paraneoplastic encephalomyelopathies
Acute disseminated encephalomyelitis/postinfectious encephalomyelitis
<i>Infectious diseases</i>
Lyme neuroborreliosis
Human T-cell lymphotropic virus type 1 infection*
Human immunodeficiency virus infection
Progressive multifocal leukoencephalopathy*
Neurosyphilis*
<i>Granulomatous diseases</i>
Sarcoidosis
Wegener's granulomatosis
Lymphomatoid granulomatosis
<i>Diseases of myelin</i>
Metachromatic leukodystrophy (juvenile and adult)*
Adrenomyeloleukodystrophy*
<i>Miscellaneous</i>
Spinocerebellar disorders*
Arnold-Chiari malformation
Vitamin B ₁₂ deficiency*

*Indicates disorders that are predominantly important to differentiate in the setting of progressive disease.

simultaneous bilateral vision loss, a state that is quite uncommon in classic MS. In some instances, MRI of the head shows (in addition to lesions of the optic nerves) scattered intracerebral lesions, or a CSF examination shows OCB, attesting to some degree of dissemination of the lesions. Children and preadolescent patients are more likely than adults to have recurrent or simultaneous optic neuropathy. Rarely there is slowly progressive optic neuropathy, similar to that seen with optic nerve sheath tumors, such as meningioma. The distinction from an MS variant can be challenging. In bilateral ON, sarcoidosis is commonly a diagnostic consideration.

Devic's Disease (Neuromyelitis Optica)

A combination of bilateral optic neuropathy and cervical myelopathy comprise this condition, which most authorities now classify as a variant of MS. Reported cases indicate that the myelopathy tends to be more severe, with less likelihood of

recovery, and that the neuropathological features at autopsy are those of a much more severe necrotic lesion of the cord rather than incomplete demyelination (54). In some patients, the optic neuropathy and the myelopathy occur at the same time; in others, one or the other component is delayed. The longer the interval, the more like typical MS is the pathology. Because the optic nerve and the cervical spinal cord are two of the locations in the nervous system in which MS lesions are typically found, many patients could be classified as having Devic's disease or syndrome. Little is to be gained by this nomenclature, because Devic's syndrome can be a manifestation of acute disseminated encephalomyelitis (ADEM) (*see* Acute Disseminated Encephalomyelitis), or rarely of other autoimmune disease, such as SLE. This is especially true of patients with relapsing Devic's syndrome, comprising approximately one-half of the patients. In a few patients, the distinction between an MS variant and SLE (so-called lupoid sclerosis) is essentially impossible to make, and some of these are patients with neuromyelitis optica (NMO). A study of 80 patients with NMO revealed that predictors of a relapsing course were longer interattack interval between the first two clinical events, older age at onset, female sex, and less severe motor impairment with the sentinel myelitis event. A history of other autoimmune disease, higher attack frequency during the first 2 years of disease, and better motor recovery after the index myelitis event were associated with mortality resulting from relapsing NMO with almost one-third of the deaths secondary to recurrent myelitis with respiratory failure and concomitant medical complications (55).

Slowly Progressive Myelopathy

A syndrome of slowly progressive spinal cord dysfunction can present a major diagnostic challenge. If there are no sensory signs or symptoms, the entity known as primary lateral sclerosis, one of the group of motor neuron disease, may be the cause. HTLV-1 infection, vitamin B₁₂ deficiency, and human immunodeficiency virus infection all can be excluded by appropriate testing. Spinal dural arteriovenous fistula can cause a steadily or stepwise progressive myelopathy, usually in the lower spinal segments. Adrenomyeloneuropathy should be considered. Numerous patients remain who do not fit into these categories and whose spinal MRI results are repeatedly negative. VERs, CSF OCBs, and MRI of the head show no sign of demyelination elsewhere. No firm diagnosis is possible. Minor clues that MS is present may be furnished by a Lhermitte's sign that has come and gone or by undue sensitivity to elevated temperature. The degree of compression of the cervical cord by intervertebral disc disease is often an issue in the middle-aged patient, because a majority of persons have some degree of disc disease. There is little doubt that some laminectomies have been carried out for cervical spondylosis where MS was the final correct diagnosis. Progressive myelopathy caused by MS is part of the primary progressive MS group and carries the poor prognosis typical of that group. The choice of therapy is difficult. Some patients do better for a time with monthly IV corticosteroid therapy.

Acute Tumor-Like Multiple Sclerosis (Marburg Variant)

Some patients with demyelinating disease present with a large acute lesion of one hemisphere or rarely other locations, such as the spinal cord. Mass effect may occur, with compression of the lateral ventricle and shift across the midline. The clinical abnormalities in such patients are variable: they may be slight even in a patient with a massive lesion, whereas confusion, hemiparesis, or neglect syndrome may be seen in another patient with a lesion that appears no different. Much of the T2 bright lesion volume is often caused by edema and may be rapidly responsive to corticosteroids. (This change with corticosteroids also may occur with glioma or CNS lymphoma and is, therefore, not a useful diagnostic criterion.) Biopsy is often required.

In a series of 31 patients with Marburg variant, the prognosis was good, most patients recovered well clinically, and their lesion volume rapidly cleared (56). In 24 of the patients, the demyelinating lesion was solitary, whereas in the others there were one or more satellite nodules. Six of the patients were older than 57 years. At follow-up, 28 of the patients did not develop additional evidence of demyelinating activity during a 9-month to 12-year period. Others have reported a higher rate of recurrent disease, particularly a conversion to more ordinary types of MS, both clinically and by scan criteria (57).

Acute Disseminated Encephalomyelitis (ADEM)

This variant is classically described as a uniphasic syndrome occurring in association with an immunization or vaccination (postvaccination encephalomyelitis) or systemic viral infection (parainfectious encephalomyelitis). Pathologically, perivascular inflammation, edema, and demyelination within the CNS are present. Clinically, patients present with the rapid development of focal or multifocal neurological dysfunction. Prototypical illness arises after acute measles infection or rabies vaccine administration. Uncertainty regarding the diagnosis occurs when patients with clinical features of ADEM occur on the background of viral infections or vaccine administration not significantly linked with the syndrome by epidemiological criteria.

Neurological sequelae complicate 1 in 400 to 1 in 1000 cases of measles infection (58). Multiple subgroups of patients have been described, including those with diffuse cerebral features, focal or multifocal cerebral findings, cerebellar dysfunction, and spinal cord abnormalities; patients do not develop peripheral nerve damage or relapses of disease.

In addition to measles, an array of other viral and bacterial infections have tentatively been associated with ADEM, including rubella, mumps, herpes zoster, herpes simplex, influenza, EBV, coxsackievirus, *Borrelia burgdorferi*, mycoplasma, and leptospira. Acute encephalomyelitis occurring in the background of nonspecific viral illness is difficult to diagnose with certainty and to distinguish from episodes of MS.

The occurrence of neuromyolytic accidents as a consequence of the Pasteur rabies vaccine prepared from spinal cords of rabbits inoculated with fixed rabies virus was recorded soon after introduction of the treatment: the incidence of encephalomyelitis associated with the original Pasteur rabies vaccine prepared in rabbit brain has been estimated at 1 per 3000 to 35,000 vaccinations. Similar neurological complications were observed as a consequence of the Jenner vaccine used for the prevention of smallpox. Postvaccination ADEM does not result from the direct cytopathic effects of the virus but rather to immune-mediated mechanisms directed against specific components of the CNS (59).

ADEM also has been associated with other vaccines, including pertussis, rubella, diphtheria, and measles. The association between influenza vaccination, particularly the swine flu vaccine, and ADEM has been the subject of medicolegal controversy.

ADEM has been reported after the administration of some drugs. These drugs include sulfonamides and paraaminosalicylic acid (PAS)/streptomycin.

All of these associations can only be substantiated by strong epidemiological evidence or by the development of a pathognomonic laboratory finding for ADEM. However, neither of these circumstances currently exists.

Clinical features of the postvaccination and parainfectious syndromes are similar, except that the postrabies vaccination complications frequently involve the peripheral nervous system as well as the CNS. Many patients with postrabies immunization illness have only mild clinical features of fever, headache, or myalgia without CSF pleocytosis.

The hallmark clinical feature of the disorder is the development of a focal or multifocal neurological disorder after exposure to virus or receipt of vaccine. In some, but not all cases, a prodromal phase of several days of fever, malaise, and myalgias occurs. The onset of the CNS disorder is usually rapid (abrupt or up to several hours), reaching peak dysfunction within several days. Initial features include encephalopathy ranging from lethargy to coma, seizures, and focal and multifocal signs reflecting cerebral (hemiparesis), brain stem (cranial nerve palsies), and spinal cord (paraparesis) involvement. Other reported findings include movement disorders and ataxia. Each of these findings may occur as isolated features or in various combinations.

Features deemed characteristic of ADEM include simultaneous bilateral ON, loss of consciousness, meningismus, loss of deep tendon reflexes and retained abdominal reflexes in the presence of Babinski's reflexes, central body temperature of $>100^{\circ}\text{F}$ (37.8°C), and severe shooting limb pains. By comparison, features characteristic of MS are unilateral ON, diplopia, hyperactive reflexes, and preserved awareness. Headache is an equivocal feature.

Recovery can begin within days, with complete resolution noted on occasion within a few days but more often over the course of weeks or months. Relapses are rare. Recovery from ADEM is more rapid compared to MS and usually more complete.

The mortality rate varies among reported series but is usually estimated at 10 to 30%, with complete recovery rates of 50% cited. Poor prognosis is correlated with severity and abruptness of onset of the clinical syndrome. Measles virus-associated ADEM may carry a worse prognosis than vaccine-associated disease. In earlier series, the occurrence of acute hemiplegias, which were interpreted as vascular occlusions and akin to the syndrome of acute hemiplegia of childhood, carried a particularly unfavorable prognosis regarding recovery.

Multifocal CNS lesions are generally evident on MRI that are initially indistinguishable from those observed in MS (60). Pathologically, ADEM produces scattered small perivenous lesions, often uniform in size, but this feature is not reliably detected by MRI. After several weeks, ADEM lesions show at least partial resolution without the appearance of new lesions, unlike MS. In some cases, lesions can persist. MRI in ADEM, as with MS, is more sensitive than CT scanning, which may, in some cases, reveal enhancing lesions.

The usual CSF formula is normal pressure, little or no (<100 cells/ μL) increase in cell count, and a modest increase in protein. Well-documented cases exist with totally normal CSF pressure, cell counts, and protein content. Cases with high cell counts, including some polymorphonuclear cells and high protein values, represent a more necrotizing disease process. The high counts usually return to normal within a few days. The CSF Ig content is not usually increased, and OCB patterns are not usually observed. The content of myelin basic protein (MBP) in the CSF may be increased, as it can be in many conditions in which myelin destruction occurs, as in MS, or as part of more widespread tissue destructive process, such as cerebral infarction.

In many patients with postrabies vaccination and postmeasles ADEM, systemic blood lymphocyte sensitivity to MBP can be demonstrated *in vitro*, even though generalized cellular reactivity is depressed in patients with systemic measles virus infection. Although technically difficult to assess, CSF lymphocyte sensitivity to MBP may be even more marked than is systemic lymphocyte sensitivity. The occurrence of cases without MBP sensitivity indicates that this assay is insufficiently sensitive to establish or exclude the diagnosis of ADEM.

The diagnosis of ADEM can usually be made with confidence in the setting of a clear-cut antecedent event strongly associated with the disorder, such as measles infection or vaccination. The occurrence of an acute focal or multifocal CNS syndrome subsequent to a more nonspecific viral illness or vaccination in which the epidemiological link with ADEM is weak creates a wider differential diagnosis:

- An initial episode of what will prove to be MS: The presence of increased CSF IgG levels may favor MS. Follow-up MRI may be needed to distinguish the two disorders because the initial MRI scans can appear similar (60). The occurrence of a nonspecific viral illness before the onset of the clinical neurological syndrome does not distinguish between MS and ADEM because the incidence of exacerbations of MS is increased after such infections.
- CNS vasculitis with or without systemic features (such as disseminated intravascular coagulation or serum sickness)

- Multiple cerebral infarcts, particularly embolic from infected cardiac valves
- Chronic meningitis or granulomatous disease (sarcoidosis).

In addition, encephalitis, abscess, or tumor needs to be excluded if the main clinical feature is unifocal.

ACUTE HEMORRHAGIC LEUKOENCEPHALITIS

Acute hemorrhagic leukoencephalitis is a rare entity that represents a hyper-acute form of ADEM (61). The most frequent antecedent history is that of an upper respiratory infection. Given the nonspecific nature of the antecedent event and the lack of a specific diagnostic clinical laboratory test, the exact incidence and full clinical spectrum of the disorder can only be estimated and is based largely on descriptions of autopsy-proved cases.

The clinical manifestations, including focal or multifocal signs, seizures, and obtundation, mimic ADEM but develop more abruptly and are more severe. Relapse after initial recovery has been described. Fever is common.

The CSF usually demonstrates increased pressure, protein, and both white and red cells. The peripheral white blood cell count also is usually increased.

CT scans in suspected clinical cases show an initially normal scan followed by low-density white-matter lesions developing within 72 hours of the first symptoms. With improvement, the lesions on CT may largely resolve. MRI may yield additional information on lesion evolution.

The differential diagnosis of this syndrome includes entities that present as rapidly evolving focal cerebral disorders with fever and obtundation. These include brain abscess and encephalitis, particularly resulting from herpes simplex, in addition to those syndromes considered in the section on ADEM (*see* Acute Disseminated Encephalomyelitis).

ACUTE AND SUBACUTE TRANSVERSE MYELITIS

Acute and subacute transverse myelitis is defined as the development of isolated spinal cord dysfunction over hours or days in patients in whom there is no evidence of a compressive lesion. In the combined experience of several series reviewing complete transverse myelitis, 37% of patients reported a preceding febrile illness. The initial symptoms are paresthesias, back pain, or leg weakness; 37% of patients had the maximal deficit within 1 day, 45% in 1 to 10 days, and 18% in more than 10 days (62).

Patients presenting with acute complete transverse myelitis have a cited risk of MS of only 5–10%. However, partial or incomplete myelitis is a much more common clinical entity and bears more relevance to MS; 57–72% of patients with acute partial myelitis as an initial presentation have cranial MRI abnormalities consistent with MS (12,63). Over 3 to 5 years, 60 to 90% of these patients develop MS, whereas 10–30% of those with a normal MRI developed MS. CSF studies suggest that patients with monosymptomatic disease and positive OCBs have a higher risk of evolution to MS than those without OCBs, although CSF results do not help

further in prognosis when compared to MRI alone. CSF analysis is most useful in the situation where MRI is not available.

CEREBELLITIS

Acute, isolated ataxia has been observed after many different viral illnesses, but most frequently in association with varicella infections. Cerebellar ataxia accounts for 50% of the postvaricella neurological syndromes, which overall occur in 1 in 1000 cases of childhood varicella (64).

The prognosis for recovery is excellent, although the duration of symptoms varies from a few days up to 3 to 4 weeks. That most cases remit spontaneously and the etiology (direct invasion vs autoimmune) is unresolved leaves the issue of corticosteroid therapy unsettled.

CLINICALLY ISOLATED SYNDROMES (CIS)

Clinically isolated syndromes (CISs) are single, monosymptomatic attacks compatible with MS (e.g., ON) that can create a diagnostic and therefore therapeutic, dilemma. More than 80% of patients with a CIS and MRI lesions go on to develop MS, whereas approximately 20% have a self-limited process (41). Identifying those 80% may have particular importance because some studies suggest that starting disease modifying therapies early in the course of MS improves outcomes.

The newer McDonald criteria incorporate MRI findings, potentially allowing for earlier diagnosis of patients with clinically isolated syndromes because two clinical events are not necessary. However, it is not clear that these criteria are sufficiently accurate in patients with CIS to make decisions regarding disease modifying therapy.

At least two studies have evaluated the ability of the McDonald criteria to predict which patients with clinically isolated syndromes will go on to develop MS (65,66). One study prospectively evaluated 50 patients with CIS by clinical and MRI examinations at 3 months, 1 year, and 3 years of follow-up. At 1 year, fulfillment of the newer criteria had a sensitivity, specificity, and accuracy of 83% (65). The second study was an analysis of 139 patients that is limited by a retrospective design and that MRI was performed at 1 year rather than 3 months and inconsistently used contrast (66). Nevertheless, the sensitivity, specificity, and accuracy in predicting conversion to MS were similar to the previous report (74%, 86%, and 80%, respectively).

The conversion rate from a clinically isolated syndrome to clinically definite multiple sclerosis, defined as the patient's development of a second clinical attack, was evaluated by several investigators (Table 11). The conversion rate with an initially normal brain MRI was 6% after 5 years, 11% after 10 years, and 19% after 14.1 years. Only 4% of the patients with an initially normal brain MRI followed for 10 years reached an EDSS greater than 5.5, whereas patients with > 10 MRI lesions at onset had a conversion rate from 80 to 88% and up to 73% reached a score >5.5 on the EDSS.

Table 11
Risk of Multiple Sclerosis After Monosymptomatic Episodes*

Investigator (Ref)	Follow-up	Patients	MRI	Conversion		
			lesions (initial)	rate to CDMS	EDSS > 3	EDSS > 5.5
Morrissey 1993 (12)	5 years	32	0	6%	0	
		6	1	17%	0	
		18	2–3	67%	17%	
		13	4–10	92%	30%	
		16	>10	80%	56%	
O’Riordan 1998 (71)	10 years	27	0	11%	0	4%
		3	1	33%	0	0
		16	2–3	87%	31% 27%	13%
		15	4–10	87%	75%	20%
		20	>10	85%		35%
Brex 2002 (41)	14.1 years	21	0	19%	0	0
		18	1–3	89%	31% 53%	12.5%
		15	4–10	87%	80%	38%
		17	>10	88%		73%

* The conversion rate to clinically definite MS (CDMS) indicates that the patient had a second clinical episode.
Adapted from refs. 12, 41, and 71.

Recently, patients with CIS were tested for serum antibodies to myelin oligodendrocyte protein (MOG) and MBP to predict time to definite MS. A second relapse occurred in 95% seropositive for both antibodies, 83% seropositive for MOG antibodies, and only 23% of seronegative patients (67). Thus, additional prospective studies demonstrating greater accuracy in patients with clinically isolated syndromes are necessary before diagnosis based on the new criteria alone can be used to begin disease-modifying therapy. Assessment of B-cell measurements in the CSF may be more accurate as discussed in Chapter 6. In either case, early detection can lead to early treatment which has been shown to slow the disease progression.

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