

Multiple Sclerosis
Optic-Neuritis
Symptoms.

Nerve-Number

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DONALD W. PATY
CHARLES POSER

Clinical Symptoms and Signs of Multiple Sclerosis

The spectrum of clinical symptoms and signs that are now recognized as caused by multiple sclerosis (MS) is very wide. No longer can Charcot's triad of nystagmus, scanning speech, and intention tremor be used to characterize most patients. In fact, MS can be considered "the great imitator" in neurologic disease. Virtually any of the classic clinical syndromes of the central nervous system (CNS) can be caused by MS.

Although it is primarily a disease of young adults, MS is being diagnosed more and more frequently, with both typical and atypical MS, in the elderly. In fact the age of onset can range from less than 10 years to more than 50 years, and in rare instances in the sixth and seventh decades. The average age of onset is 32 years for both men and women, but the distribution is somewhat skewed toward the older age so that the age-specific incidence curve is not symmetrical. One recent survey has shown a mean prevalence in the United States of 58 per 100,000.¹ This is believed to be an underestimate by a factor of two. There is a general north-south gradient to the prevalence, with a frequency considerably greater in the northern parts of the United States and in Canada than in the south. Recent studies in Canada suggest that

the prevalence may be as high as 130 per 100,000 population.² Prevalence in the southern United States is estimated at about 35/100,000.¹

There are also racial and familial factors that influence incidence. MS is primarily a disease of northern European racial stock. It is less common in persons of southern European stock and much less common in other races. It is least often seen in Orientals and in native African blacks (although two cases have now been verified), and has an intermediate frequency in North American blacks.

The familial occurrence may be caused by the same factors that produce varying racial susceptibilities. The frequency of familial MS in British Columbia is more than 17 percent.³ These familial and racial risks are probably determined by the histocompatibility (HLA) genotype, with certain patterns producing an increased susceptibility.⁴ Unfortunately, the HLA linkages that have been noted in population surveys cannot consistently be seen in family studies.⁵ Empiric risk tables are available for determining the familial risks of MS⁶: for example, the child of a young mother with MS has a lifelong risk for developing MS of 1 in 70.⁷

The sex distribution is generally three

The Diagnosis of MULTIPLE

SCLEROSIS

Edited by:

Charles M. Poser, M.D.

Lecturer on Neurology
Harvard Medical School
Attending Neurologist
Beth Israel Hospital
Formerly, Professor of Neurology
Boston University School of Medicine
Boston, Massachusetts

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DONALD W. PATY, M.D.
F.R.C.P. (C)

Professor and Head, Division of Neurology,
Director of Multiple Sclerosis Research
Program, University of British Columbia,
Vancouver, British Columbia, Canada

W. IAN MCDONALD, F.R.C.P.

Professor of Clinical Neurology, Institute of
Neurology, University of London, The
National Hospital, Queen Square, London,
England

LABE SCHEINBERG, M.D.

Professor of Neurology and Rehabilitation
Medicine, Albert Einstein College of Medicine,
New York, New York

GEORGE C. EBERS, M.D.

Associate Professor, Department of Clinical
Neurological Sciences, University of Western
Ontario, Director, Multiple Sclerosis Clinic,
University Hospital, London, Ontario,
Canada

With the assistance of
Joan Crawford Poser, M.A.

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women to two men. This is true for all ages of onset. Some surveys have suggested a slightly younger age of onset for women, although this has not been a consistent observation.

CLINICAL COURSE

Relapsing and Remitting

Most young patients (more than 70 percent) begin with a relapsing and remitting course in which the recovery following each episode is complete. The frequency of relapses is totally unpredictable. A relapse can be defined as a new or significant recurrent neurologic dysfunction that reflects a disturbance of white matter function in the CNS lasting more than 24 hours. Frequently, symptoms and signs develop that last less than 24 hours. A recurrence of symptoms cannot be taken as evidence of an acute relapse. The recurrences are likely caused by metabolic or physiologic influences on a previously damaged and demyelinated area of CNS and are called pseudoexacerbations.⁸

Chronic Progressive

Thirty percent of MS patients run a chronic progressive course from the outset. This is more common in older patients, particularly in older men, who have a poor prognosis, usually becoming greatly disabled over time. Most of these patients have a chronic spinal form, although progressive cerebellar and cerebral syndromes are also seen. Diagnosis is particularly difficult in these chronic progressive patients. It is in these situations that laboratory tests can be the most useful. If these patients are followed long enough, the clinical diagnosis can usually be made by careful documentation of changes in visual acuity or visual evoked potentials indicating optic neuritis (ON), or extraocular movement changes with ocular pareses indicating

a brainstem lesion. The clinical follow-up may take 5 or 10 years.

Combined Relapsing and Remitting with Chronic Progressive

Most patients eventually have a combined syndrome in which they begin with relapses and remissions and evolve into a chronic progressive course. In the progressive phase the degree of disability can be shown to get steadily worse, with some superimposed acute fluctuations. The most predictable indicator for a poor prognosis is the onset of the chronic progressive phase.

Benign MS

At least 20 percent of MS patients have a benign course.⁹ This means a normal life span of relatively unencumbered physical activity. It is common to see patients in their 70s who have had recurrent symptoms for 40 to 50 years. This particular clinical course cannot be predicted early in the disease, but it is more likely to develop in patients with a younger age of onset.¹⁰ There may be a very significant pool of undiagnosed MS in the population, since it can be so benign as to escape clinical detection. A careful neuro-pathologic examination can identify previously undiagnosed MS in approximately one per 1000 unselected general autopsies.¹¹

Malignant MS

Fewer than 5 or 10 percent of patients run a very malignant clinical course. When this occurs, it is usually in younger patients. The manifestations are many severe relapses during the first year followed by early chronic progressive deterioration. These patients can be severely disabled or dead within a few years of the first symptom. Unfortunately, no one can identify these patients at the onset. One form of MS that tends to be malignant is the cerebral syndrome in the young. The

early onset of cerebellar symptoms is associated with a malignant clinical course.

There are lesser degrees of severity that should be mentioned so as not to be confused with truly malignant MS. Some patients have a very rapid onset of significant disabling symptoms, but in them the severity is more related to the location of the lesion than it is to the generalized intensity of disease activity. The designation of malignant disease should be confined to those patients with extensive and disseminated involvement of the CNS leading to severe and complete disability, including mental, cerebellar, and motor symptoms. The designation of malignant MS should not be applied to those patients who need a wheelchair early because of spinal cord involvement alone. This is probably caused by the unfortunate placement of plaques in eloquent areas of the spinal cord rather than by a truly malignant disease process. Paraplegic patients in particular often stabilize after many years, as though the disease had become completely "burned out."

RELIABLE FEATURES IN THE HISTORY

Certain symptoms are characteristic of MS, which will be described, with some indication of their reliability (Table 1). The use of a purely historical symptom to indicate dissemination in space requires that that particular symptom be both reliable and typical of MS. Neurologic symptoms without this feature of reliability cannot be used in this way.

Background features, such as place of birth, place of residence before the teenage years, family history, and race, can be used to heighten or lower the suspicion of MS (Table 2). For example, a young woman of Scandinavian extraction born and raised in the northern part of United States, with a history of MS in a sibling, and who develops fluctuating neurologic symptoms, particu-

larly paresthesias, is very suspect for having MS. Even with this high-risk background, great care must be taken in using symptoms to identify dissemination in space.

The symptoms that can be used with confidence are those of typical ON, Lhermitte's symptom, a sensory useless hand, acute transverse myelitis, diplopia suggestive of an internuclear ophthalmoplegia (INO) and tic douloureux in a young adult. In many instances, sensory symptoms that are disturbing to the patient, such as tingling, pins and needles sensations, painful paresthesia, dysesthesia, and Lhermitte's symptom cannot be substantiated by objective evidence of sensory impairment. Most of these symptoms, although clearly caused by MS, are not reliable enough to be used as evidence for dissemination in space. Table 1 lists the initial symptoms in our series of patients. Table 3 shows some rough indicators of prognosis that may be detectable at the time of first presentation.

Optic Neuritis

The history of acute or subacute loss of central vision with peripheral sparing in one eye, associated with pain on movement of the globe, and lasting more than 24 hours in a young adult, with later complete recovery, is almost certainly that of ON. This symptom complex, even without medical documentation, could be used on a historical basis to indicate a lesion in the optic nerve. Occasionally an acute exudative choroiditis or central serous retinopathy can present similar symptoms, but only rarely will such conditions be followed by other neurologic problems. The first symptom of MS in 16 to 30 percent of patients is ON. Follow-up of patients with isolated ON shows that about 50 percent go on to develop clinical MS. The interval between the ON and development of MS can be as long as 35 years, although most cases (75 to 90 percent) will be evident in 10 years. Isolated ON can be seen in multiplex families with MS, suggesting that clin-

TABLE 1. Initial Symptoms, Clinical Course, and Predominant Clinical Category in 461 MS Patients*

Symptom	FREQUENCY				TOTAL	
	WOMEN (n = 279)		MEN (n = 182)		(n = 461)	
	NO.	%	NO.	%	NO.	%
Visual loss in one eye	54	18	24	13	78	17
Double vision	27	10	35	19	62	13
Disturbance of balance and gait	38	14	45	25	83	18
Sensory disturbance in limbs	72	26	79	43	151	33
Sensory disturbance in face	10	4	6	3	16	3
Acute myelitis syndrome	20	7	6	3	26	6
Lhermitte's symptom	7	3	6	3	13	3
Pain	5	2	3	2	8	2
Progressive weakness	27	9	18	8	45	10
Clinical course						
Relapsing and remitting	164	59	93	51	257	56
Chronic progressive	67	24	60	33	127	28
Combined	66	24	29	16	95	21
Benign	39	14	16	9	55	12
Predominant clinical category						
Spinal	128	46	134	74	262	57
Cerebellar	23	8	35	19	58	13
Cerebral	11	4	7	4	18	4

*These patients satisfied the criteria for clinically definite MS of Schumacher and colleagues and were seen at the MS clinic, University of Western Ontario, London, between 1972 and 1976.¹⁰

TABLE 2. High-Risk Factors in MS

Racial background	Caucasian, North European, British Isles
Sex	Female
Age	20 to 40
Residence before age 15 years	Above 37th parallel
Family history of MS	Sibs > parents > others

ical isolated ON may represent a single episode of MS. Thirteen percent of ON patients can eventually be shown to have a non-MS cause, such as Leber's disease or ischemia. Most patients with MS and ON have a complete recovery over a period of weeks or months, although occasionally the visual loss is permanent. Those patients who recover may have a completely normal physical examination at a time when visual evoked potentials show a prolonged latency. The reverse corollary to this is that patients with

TABLE 3. Clinical Prognostic Indicators at Time of Initial Presentation*

BETTER PROGNOSIS	WORSE PROGNOSIS
Female	Male
Younger (<30)	Older (>35)
Acute onset with remission	Chronic progressive
Initial symptoms sensory	Motor or coordination disturbance

*Data derived from an analysis of the MS clinic population. University of Western Ontario.¹⁰

definite optic atrophy on funduscopic examination many times retain normal visual acuity or may even never have had a symptom suggestive of acute ON. Visual defects other than typical ON can be seen in MS, such as hemianopsias or quadrantanopsias, but these are too rare to be considered reliable initial symptoms.

Internuclear Ophthalmoplegia

Patients with an acute bilateral INO will have horizontal double vision on lateral gaze in either direction, with minimal or no diplopia in primary gaze. These symptoms suggest bilateral ocular paresis without displacement of the eyes in the primary position. This history in a young adult can be used as evidence of a brainstem lesion even without medical documentation. The lesion in a bilateral INO is located in the medial longitudinal fasciculus in the dorsal medial pons or midbrain. An acute bilateral INO in a young adult is almost pathognomonic of MS. The only possible alternative causes are metastatic cancer, arteriovenous malformation, and, occasionally, lupus erythematosus. Lupus can cause an INO although it is typically unilateral, as in other vascular ophthalmop-

plegias. Diplopia is seen as an initial symptom in 13 percent of MS patients.

Tic Douloureux (Trigeminal Neuralgia)

Sharp and lancinating pain in the face or jaw occurring in flurries, frequently provoked by touching a "trigger" point, and without concomitant sensory loss, is typical of tic douloureux. When tic begins in a person younger than the age of 40 years, and other organic lesions of the trigeminal nerve have been ruled out, it is frequently caused by MS. Jensen and colleagues¹² noted 22 patients with MS of 900 with tic. The symptoms and signs of MS preceded the facial pain in 19 of the 22 patients (86 percent), whereas two had trigeminal neuralgia for 4 or 5 years before the onset of MS. Sixteen patients were classified as having typical trigeminal neuralgia, whereas six had atypical facial pain. The tic was bilateral in seven patients. Thus, the prevalence of MS in these 900 patients with tic was 2.4 percent. This association was 20 to 50 times higher than the expected frequency of MS in a control Danish population. The frequency of bilateral trigeminal neuralgia was much higher in MS than in idiopathic tic. When tic douloureux occurs as an isolated symptom in a young person, the diagnosis of MS cannot be made, but a history of typical tic in a young adult who goes on to develop a second typical MS symptom or sign can be used as evidence for dissemination in space.

Lhermitte's Symptom

Lhermitte described a symptom of tingling down the back and into the legs that had an electric shocklike quality produced by flexion of the neck.¹³ This has been called Lhermitte's sign for many years. It is not a sign, and it apparently was first reported by Babinski, who described the symptom in patients with spinal contusion. Lhermitte later

pointed out that it was seen frequently in MS. The original description was of a pain resembling an electric shock. It was described as uncomfortable but not really painful, closely resembling those sensations produced by an electric current. It was described as always occurring when the patient flexed the neck forward placing the chin on the chest. It could radiate into the upper limbs, down the back, or into the legs.

Even though the original description was by Babinski, it was also described in a thesis by Ribeton. Lhermitte and his colleague were insistent that this symptom indicated damage to spinal cord and not damage to nerve roots. Recent observations support this concept. The distortion of the spinal cord associated with neck flexion must induce electrical changes that are perceived as a buzzing or electric shock sensation.

In MS this symptom is not always associated with flexion of the neck. Occasionally flexion of the dorsal spine (trunk) or simply a jar to the spine or walking over uneven ground can produce the same symptoms. The condition can occasionally become very disabling, even in patients with no other neurologic deficit.

In clinical practice most of the patients with this symptom have MS, although it is not specific. Kanchandani and Howe¹⁴ point out that Lhermitte's symptom is not pathognomonic for MS. They report observing it in one of 11 patients with subacute combined degeneration of the spinal cord caused by vitamin B₁₂ deficiency. It occurs rarely in other condition, such as neck trauma, radiation myelitis, herniated cervical disc, cervical spondylosis, syringomyelia, and spinal cord tumor. In one series of 140 MS patients it was noted in one-third and occurred in the first episode in 16 percent. A patient with a long-standing typical Lhermitte's symptom who develops an ON has clear-cut signs of dissemination in time and space.

Lhermitte's symptom is unlikely to be caused by hysteria. It is a reliable indicator of cervical cord disease and, as mentioned

by Lhermitte, is frequently observed in MS if care is taken to elicit a proper history. It is seen as the initial symptom of MS in between 5 and 16 percent of patients.

Acute Transverse Myelitis

Approximately 7 percent of patients who have on admission a complete, acute transverse myelitis (ATM) will develop MS later on. Incomplete cord syndromes commonly herald the advent of MS, especially if children and the elderly are excluded. Lipton and Teasdall¹⁵ followed 34 adult patients with ATM of unknown cause. Five patients died during the first 4 months of the illness. Follow-up information was obtained from the remaining 29 patients 5 to 42 years after onset. Postmortem examination was available in three. During follow-up, a clinical diagnosis of MS was made in only one patient. Altrochi¹⁶ noted that only 4 of 67 patients with ATM developed MS during follow-up. Ropper and Poskanzer¹⁷ followed 52 patients with ATM for an average of 5 years. They observed seven patients (13.5 percent) who developed clinical MS during that period. Nonetheless, three of the patients who developed MS were included in the series despite the fact that they had visual symptoms before the ATM and had temporal pallor or optic atrophy on examination at the time of the ATM. If those three patients with preexisting neurologic symptoms or signs are excluded, the incidence of MS in their follow-up of ATM drops to 7.7 percent. Berman and associates¹⁸ studied 62 Israeli Jews with ATM and observed only one who developed MS during the follow-up period. In their 747 patients with MS, none had started with ATM. All these studies suggest that complete and severe ATM is an unusual initial symptom in MS.

Incomplete acute transverse cord syndromes are much more frequently encountered in MS. Sensory levels are often seen in the acute phase, but it is rare to note a persistent sharp sensory level. In a patient with

a second neurologic episode, a history of subacute or acute onset of sensory loss and weakness in both lower extremities with recovery strongly suggests MS. Clear-cut clinical documentation of the observations at these times may not be available. A combined motor-sensory disturbance with a suggestion of a sensory level occurring acutely in a young adult with rapid recovery is so typical, although not frequent, that this can be considered a reliable past symptom for the diagnosis of MS. A common story is that the patient might have been diagnosed as having hysterical paraplegia, and this suspicion seemed to have been confirmed by rapid spontaneous recovery following psychiatric hospitalization. This history in a young adult who later develops symptoms and signs of brainstem, cerebral, or cerebellar disease can reliably be used to satisfy the requirements for dissemination in space.

The Sensory Useless Hand

This is a characteristic but uncommon symptom of MS. It usually begins with the acute or subacute onset of paresthesia and numbness in a single upper extremity and a decreased ability to use the hand properly. Men often report that they can no longer use that hand to identify coins in their pocket. The same may be true of women trying to search for objects in their purse. Handwriting is usually impaired as well. The most severely affected patients will have an absolutely useless extremity caused by a loss in sensory feedback control. They will have reduced or absent vibratory sense, two-point discrimination, and joint position sense. They may also give a history of spontaneous uncontrolled movements of the hand (pseudathetosis). These patients, if tested carefully at the time, can be shown to have normal strength, normal deep tendon reflexes, and normal crude sensation. This symptom most likely represents a plaque in the lateral portion of the posterior columns of the cord. This is another symptom so typ-

ical of MS that if it has occurred in a young adult, without pain and with recovery, it can be used reliably to show dissemination in space even without documentation. It can last as long as 9 months and still remit.

Miscellaneous Symptoms Associated with MS

Other symptoms that are seen frequently in MS must be considered unreliable for documenting dissemination in time and space purely on historical grounds. These symptoms are diplopia only in one direction of gaze, the vague onset of binocular or monocular blurring of vision, urinary urgency, frequency, or incontinence, vertigo that occurs alone without other symptoms, non-specific "numbness" in one or more limbs, and various types of radicular or generalized pain. Many of these symptoms occur in MS but are not typical enough to be used on an unsupported historical basis as evidence for dissemination in space. Rarely, a single large lesion, or even a concentration of small lesions in one cerebral hemisphere, may produce a clinical picture resembling brain tumor, including signs of increased intracranial pressure, papilledema, contralateral hemiparesis, electroencephalographic (EEG) focus, and ventricular shift. Headaches occur in a minority of patients, but it is difficult, since headaches are so common, to ascribe them to MS.

Pain and Phantom Limb Phenomenon

Even though MS is usually considered a painless disease, pain is experienced by as many as 20 percent of patients at some time during their clinical course. The pain can be radicular and simulate root compression. Occasionally patients have tabetic-like pains or a thalamic pain syndrome. "Zoster-like" radicular pains around the thorax are also noted and are sometimes associated with sensory loss, but usually are not. Similar to

the peripheral nerve signs noted later, they are probably caused by a lesion in the CNS at the point of entry of the sensory root.

Another pain frequently observed in MS is a deep-seated symmetrical and distal throbbing and burning sensation. This type of pain is usually, but not always, associated with physical observations of posterior column sensory loss. It can be difficult to manage.

Mayeux and Benson¹⁹ described a patient with typical MS who complained of a supernumerary phantom limb during an exacerbation. On the basis of physical observations, they attributed this exacerbation, including the phantom illusion, to a lesion of the anterior lateral aspect of the cervical spinal cord. These pain symptoms suggest MS plaques involving the dorsal root entry zone. However, the patient who has MS is subject to the usual aches and pains of any other person and is particularly liable to back pain because of musculoskeletal instability. Often, close examination has revealed that the pain does not originate in the CNS but is caused by such ailments as bursitis, arthritis, or osteochondritis. Persistent, nagging low back discomfort is a frequent complaint that probably results from long-standing asymmetric musculoskeletal spasm in the paraspinal area in patients with gait disturbance, weakness, or spasticity. Such patients often have lumbar scoliosis that may need orthopedic attention. Patients confined to wheelchairs also frequently have these complaints.

Painful Tonic Spasms

A small proportion of patients with MS develop paroxysmal motor symptoms suggestive of a basal ganglia disturbance. These usually take the form of painful tonic contractions of all the muscles in a limb with slow superimposed athetoid movements. They can last anywhere from a few seconds to a couple of minutes. They may occur frequently, many times a day, over a period of

several weeks and then disappear. When the spasms go away, they are likely never to return. Fortunately, these painful tonic spasms respond very well to anticonvulsants or intravenous diazepam. The neurologist can reassure the patient that even though they are frightening and dramatic, these spasms are benign and likely to stop spontaneously without residual occurrence. Occasionally, the spasms can involve both the arm and leg on the same side and be so persistent as to mimic paroxysmal choreoathetosis.

Other Paroxysmal Symptoms

Up to 5 percent of patients with MS have seizures. Some of these seizures are obviously focal and are caused by subcortical lesions. They are usually easily controlled with anticonvulsants. The history of an isolated seizure cannot be used as an indication for previously existing cerebral disease in order to satisfy the criteria for dissemination in space.

Elia and Dean²⁰ reviewed 24,000 case notes from patients with MS in the west midland region of England. They observed 27 patients who had both MS and seizures. Twenty-seven EEGs were obtained from 16 patients. Nine of the traces were considered to be within normal limits, four showed lateralizing focal features in the form of slow waves and spikes, and 14 showed bilateral abnormalities with diffuse nonspecific slowing. Of interest is the fact that of these 27 patients, 21 had psychiatric symptoms severe enough to warrant consulting a psychiatrist. The authors pointed out that the incidence of epilepsy among MS patients varies in published reports from 0.5 to more than 10 percent, compared with the estimate by Lennox in 1960 of 0.3 to 0.5 percent epilepsy among the general population. Taking the higher number (0.5 percent), this would mean that of the 24,000 patients with MS, 12 would be expected to have epilepsy. Twenty-seven (1.1 percent) is more than double the expected number. Despite this,

the authors concluded that the statistical evidence was not enough to support the assumption of a causal relationship between the two diseases. Our own experience has been that 5 percent of our MS population has had seizures. We have been unable to identify a specific cause for seizures other than MS in any of these patients.

Paroxysmal sensory symptoms can occur and are most intriguing. Sudden loss of vision in one eye can last for seconds or minutes. This probably reflects a metabolic disturbance influencing conduction in previously demyelinated optic nerve fibers. Paroxysmal and diffuse numbness and tingling similar to the sensation seen in Lhermitte's symptom are also noted. They occasionally affect the whole body and may progress in a steady and stereotyped fashion. As in the paroxysmal motor symptoms, these can occur frequently during the day, but once the episode is over it usually does not recur. The mechanism for these symptoms is entirely unknown.

MS patients may also have paroxysmal attacks of dysarthria, ataxia, diplopia, sensory loss, weakness, or itching.²¹ The evanescent character of these symptoms often causes patients with MS to be diagnosed as hysterical. The marked sensitivity of the demyelinated nerve fiber to metabolic and physiologic changes probably explains many of these symptoms.

Osterman²² reports three patients with MS who had paroxysmal itching. Yamamoto and associates²³ also described itching. Osterman's patients had no other systemic diseases, allergy, drug reaction, or emotional stress related to their itching. The attacks started and ended abruptly, lasting from several seconds to several minutes, and occurred five to six times a day, frequently beginning during sleep. The itching involved the face, trunk, and extremities and was often symmetrical and segmental. The attack would sometimes start when the patient began to move. Superficial sensory disturbances were present in the affected areas in all patients;

the paroxysmal itching changed to trigeminal neuralgia in one patient, whereas continuous pain changed to paroxysmal itching in another. Paroxysmal itching can appear as the first and only symptom at the onset of MS. It was a predictive symptom of exacerbation in one of the three patients.

PHYSICAL EXAMINATION

Special features most pertinent to MS will be discussed in an attempt to highlight those features of the examination that are most typical of MS or those that can be quite subtle but still highly suggestive of MS.

Visual Symptoms

(These are covered in Chapters 5 and 6.)

Other Cranial Nerve Abnormalities

Lesions of the third, fifth, and seventh nerves occur in MS. These nerves are involved in their intra-axial course. This is particularly true of the seventh nerve and may result in what appears to be a peripheral facial palsy. Taste, however, is almost never affected.

In an acute relapse of MS the descending root of the fifth cranial nerve may be involved, resulting in the production of unilateral facial numbness, paresthesia, or pain. Paroxysmal unilateral facial pain indistinguishable from trigeminal neuralgia occurs in approximately 1 to 2.5 percent of cases. Conversely, in a series of 124 patients with trigeminal neuralgia, ten patients with MS were observed.²⁴ The onset of typical trigeminal neuralgia in a patient younger than the age of 40 years should raise the suspicion of MS (see before).

Pseudobulbar palsy, with its associated dysarthria, dysphagia, and emotional instability, may result from lesions in the supranuclear corticobulbar tracts. Hemifacial spasm or facial myokymia often not associated with

facial weakness is an infrequent but characteristic symptom.²⁵ Spontaneous rhythmic discharges can be demonstrated by electromyography (EMG). These involuntary facial movements have been thought to be secondary to irritation of the motor neurons of the facial nerve.

Vertigo has been noted in 30 to 50 percent of MS patients at some time during their illness and as an initial symptom in from 5 to 12 percent.²⁶ It is believed to be caused by damage to neurons in or near the interconnections in the vestibular complex. Lesions of the cochlear-trapezoid interconnections and the lateral lemnisci may produce deafness or severe tinnitus, which are virtually always bilateral, but this is seldom observed. Although some investigators have claimed that sophisticated audiologic tests will reveal a significant incidence of hearing impairment in MS, clinical experience suggests that deafness caused by MS is quite rare.

Cognitive Deficits and Depression

Psychologic parameters in MS are discussed in a separate chapter. There is a complex interrelationship between stress factors, depression, and cognitive deficits caused by MS hemispheric lesions.

A major factor is the necessary emotional adjustment. This adjustment often takes 2 or 3 years, and some patients are never able to adjust emotionally to having a chronic progressive incurable disorder. It is also believed, although it is difficult to prove, that emotional stress can act as a trigger for the onset of symptoms, the production of new symptoms, or the exaggeration of old symptoms.⁸

Matthews²⁷ has reported three patients in whom the first manifestation of MS was an acute psychiatric problem with subsequent complete remission. In the first two, after remission of the acute psychiatric symptoms, typical signs and symptoms of MS developed, leading to diagnosis in retrospect. In the third patient, abnormal visual evoked potentials and computed tomography (CT)

scanning were strongly suggestive of MS at the outset. Matthews points out that MS must be considered among the causes of acute mental symptoms in previously healthy young adults.

We have had personal experience in observing at least four patients who developed a manic-depressive psychosis before the symptoms of MS were noted. Whether the two conditions are related is uncertain. This is another situation in which nuclear magnetic resonance scanning may be helpful.

Goodstein and Ferrell²⁸ report three patients hospitalized for recurrent emotional disorders with a predominance of depressive symptoms. In each case no precipitant for depression was identified, no previous neurologic diagnosis was entertained, and repeated efforts at psychotherapy were unsuccessful. The episodic nature of the symptoms and poor response to treatment that is usually effective created a high index of suspicion for CNS disease. A diagnosis of MS was based on subtle neurologic signs, elevation of gamma globulin in the cerebrospinal fluid (CSF), and abnormalities on neuropsychologic testing.

Olmos-Lau and associates²⁹ have described a case of MS contaminated by a striking motor aphasia. In their review of the literature, they noted 14 additional cases with well-documented aphasia in patients with an equally well-established diagnosis of MS. As a manifestation of MS, aphasia is extremely rare, being absent in many large series, although some authors have noted an incidence of 1 to 3 percent.

Tabira and colleagues³⁰ have noted cortical deafness in a patient with MS. The patient recovered completely from total deafness after going through stages of auditory agnosia and pure word deafness. The audiologic and neurophysiologic studies suggested lesions in the subcortical white matter.

Discriminatory Sensation

Loss of those sensations believed to be carried in the posterior columns of the cord is

typical of MS. The most subtle abnormality may be impairment of two-point discrimination in the fingertips. With more severe lesions, this can progress to loss of vibratory sense and then joint position sense. Occasionally there is loss of joint position sense without a concomitant loss of vibratory sense, but this is quite unusual. In the upper extremities, two-point discrimination can be used as a reliable screening test for discriminatory sensation loss. This test also has the advantage of being semiquantitative. The distance between the two points can be seen to fluctuate, with worsening and improvement of the condition. Two-point discrimination is reliable only in the fingertips and the lips. Normal discrimination is less than 5mm. There are many normal persons who can discriminate easily down to 2 or 3mm, but an overall normal should be considered 5mm. Changes between 5 and 10mm in the fingertips are to be considered abnormal. Asymmetries of 1mm even below the 5mm threshold are also considered abnormal. Loss of discrimination beyond 10mm is difficult to quantitate.

Occasionally in MS loss of these sensations may not involve the entire hand. The fourth and fifth fingers can be quite severely affected at a time when the first three fingers are normal, although the reverse distribution is unusual.

Vibratory sense should be tested with a 128Hz tuning fork. It should be first tested on the most distal portion of the extremity. With progressive loss of vibratory sense, the loss will be detectable more and more proximally on the limb. Comparison of the decay of vibratory sense between the patient and the examiner is a reliable method of quantitation of vibratory sense loss. If the examiner can feel the vibration for seconds longer than the patient, this should be considered a clear-cut abnormality, unless the same difference is noted when testing the forehead.

The method of testing joint position sense is important. Again the most distal portion of the extremities should be tested first. Position sense should always be tested over only

one joint, and the easiest to test is the second interphalangeal joint. In a normal person very fine movements can be appreciated. When testing for position sense, it is essential to make sure that the patient understands exactly what is being done, since otherwise the data obtained may be in error. If the patient first observes the movement of the joint under visual inspection, it is then much easier to get reliable results with the eyes closed. The patient should be asked to identify the direction and time of onset of the movement. A normal person should be able to detect movements of one or two degrees. Identification of the direction of movement is much more reliable than the identification of the position of the digit or limb following the movement. Abnormalities in proprioception can be confirmed by identifying the phenomenon of pseudoathetosis or a positive Romberg test.

Deep Tendon Reflexes

A typical observation in MS is of exaggerated deep tendon reflexes. Hyperreflexia is extremely common and is often not pathologic. Transient clonus can also be present bilaterally and not be abnormal in a very tense person. Frequently, the reflexes in MS are asymmetrically increased, and often there are quantitatively normal deep tendon reflexes with a definite asymmetry from side to side. If these asymmetries are reproducible in several different examining positions, they must be considered valid observations. There is nothing definite under these circumstances to indicate whether the abnormality is on the more active or less active side. This decision should be made using associated observations.

It is common in MS to see depressed or absent deep tendon reflexes. These altered reflexes are probably caused by lesions at the root entry zone into the spinal cord on the sensory side and must be considered a sensory disturbance. The reflexes most frequently noted to be absent in MS are the biceps (C5), brachioradialis (C6), and triceps

(C7). In a series of 145 patients, one or more tendon reflexes were absent in 30 percent.⁸

The syndrome of the "inverted" brachioradialis reflex can be seen. In this the biceps or brachioradialis reflex, or both, will be absent at the same time that the triceps reflex is exaggerated. Tapping the brachioradialis reflex may result in an actual extension of the arm or at least very active flexion of the fingers. This indicates a defect in the C5 or C6 segment of the reflex with an exaggerated reflex below that level. This reflex exaggeration below the level suggests that the corticospinal tract is damaged, possibly at the same level as the absent reflex. An unusual but characteristic finding in MS is an "inverted" triceps reflex. This is an absent triceps reflex with a hyperactive biceps and brachioradialis. Tapping the triceps reflex results in flexion of the arm. This indicates immediately that there are two lesions, one at the C7 level root entry zone causing the absent reflex, and one higher than the C5 segment involving the pyramidal tract that causes the hyperactive reflexes. This one sign can indicate dissemination in space. Muscle atrophy caused by disuse as well as absent deep tendon reflexes may occur in persons with prolonged spastic paralysis who have developed contractures. In addition, secondary peripheral neuropathies due to nutritional deficiency or compression occur frequently in MS and account for many of these observations.

Interpreting absent, diminished, or easily fatigued abdominal reflexes is difficult. The abdomen must be free of surgical scars in a relatively young person who is not obese or whose abdominal musculature has not been stretched by several pregnancies. Absences of abdominal reflexes, especially if unilateral, may then be considered significant.

Motor and Coordination Signs

Most MS patients will have abnormalities in the motor systems, largely in the pyramidal tract. It requires great clinical skill to judge

clumsiness in the arms. Detecting definite cerebellar abnormalities in a patient with predominantly pyramidal tract disturbances is difficult but important. Extreme caution must be used before assigning clumsy, rapid alternating movements to a cerebellar lesion if there are pyramidal or posterior column conditions present. Clumsiness can be caused by even minor pyramidal or posterior column defects. Only the truly side-to-side, sometimes irregular intention tremor can be used as a cerebellar localizing observation under these circumstances.

Cerebellar tremor must be clearly differentiated from essential or parkinsonian tremor. A few "beats" of regular tremor at the end of the finger-to-nose maneuver is often erroneously interpreted as being of cerebellar origin. This may be only a manifestation of benign essential tremor superimposed upon movement. The very rhythmic "rubral" tremor can be seen very characteristically in MS. This is most likely due to a lesion in the cerebellar outflow pathways. The tremor can be seen at what appears to be rest, but is in reality an intention tremor that seems to be produced by the intent to move.

Dysarthria must be clearly differentiated from the hesitant speech of the mildly aphasic. Many patients with MS have monotonous, scanning speech. They can also have very slurred speech caused by spasticity, cerebellar lesions, a combination of the two, or even by pronounced facial weakness.

Care must be taken in interpreting certain signs of gait disturbance. These may result from cerebellar lesions, loss of position sense, motor weakness, or any combination of these. It therefore makes sense to examine all other elements of sensory and motor function before examining coordination and gait. Deep tendon reflexes should be examined for evidence of spasticity, the sensory system for evidence of impaired discriminatory sensation or proprioception, and strength in order to detect weakness, before testing coordination and gait. Systematic knowl-

edge of the strength and sensory deficits will permit more accurate interpretation of apparent abnormalities in coordination. In this way a premature and inappropriate diagnosis of a cerebellar lesion may be eliminated.

Peripheral Nerve Signs and Amyotrophy

Even though MS is a disease of the CNS and primarily of the white matter, physical evidence of gray matter, peripheral nerve involvement, or both is often noted. These signs are probably observed because acute lesions in MS can involve gray matter and can be associated with anterior horn cell loss. At the same time, peripheral nerve fibers can be involved either before their exit from or after their entry into the CNS. For that reason segmental sensory loss, loss of deep tendon reflexes, and muscle atrophy are noted in MS, although these observations are not typical.

Neurogenic muscle atrophy is not usually considered compatible with purely white matter disease in the CNS. Even though Charcot described muscle atrophy in MS, it is not considered typical. Despite that, we see a number of patients who have either transient or permanent loss of muscle bulk. This is often associated with fasciculations and other active signs of denervation. Hand atrophy typical of amyotrophic lateral sclerosis can be seen, although it is not common. During the acute phase of rapidly progressive spinal relapses, it is possible to find fasciculations and widespread minor degrees of muscle atrophy. Many times this will recover, suggesting that it is only a temporary disturbance of function in anterior horn cells and not associated with anterior horn cell death.

Fisher and coworkers³¹ studied nine patients clinically and electrophysiologically. All of these patients had atrophy of intrinsic muscles of the hand. These patients were discovered in a group of 150 MS patients, none of whom were severely disabled, with an average duration between 2 and 15 years.

They noted atrophy of the muscles of the thenar eminence, the interossei, and particularly the first dorsal interosseus. Wasting was severe in two and mild to moderate in seven. In six patients it was unilateral. The EMG studies, including standard motor sensory and F wave conduction in addition to needle examinations, were entirely sensory and F wave conduction in addition to needle examinations, were entirely normal in eight of the nine patients. One patient had mild reduction of the radial nerve sensory amplitudes. Somatosensory evoked potentials showed prolonged interwave latencies or dispersion of potentials only in the central somatosensory system in eight patients, the ninth being normal. They concluded, without offering any explanation, that the atrophy of intrinsic hand muscles in MS was due to "central lesions." They did suggest, however, that atrophy may have been caused by "relative disuse of the hands" weakened by loss of corticospinal and other central control mechanisms.

We have had personal experience with widespread neurogenic atrophy in several patients with MS. One of these was a young man who during an exacerbation developed severe neurogenic wasting in both legs confirmed by muscle biopsy. After recovery from the exacerbation, he began to recover bulk in his legs, but they never returned to full normal-muscle bulk. We have also seen a number of patients with acute spinal cord exacerbations who had widespread fasciculations and EMG evidence of denervation. Exactly what mechanism is operating in these patients is unclear.

When muscle atrophy is seen in MS, the first diagnostic consideration should be nerve entrapment. Wasting in the hands is much more likely to be due to an ulnar nerve entrapment than it is to the MS process itself. Some recent investigators have claimed evidence of direct peripheral nerve involvement in MS.^{32,33} This is yet to be clearly substantiated and confirmed. The important point is that muscle atrophy must not be

considered to be incompatible with the diagnosis of MS.

Facial sensory loss is often suggestive of a trigeminal lesion, a third or, rarely, a sixth nerve palsy, or a peripheral seventh nerve palsy in MS. These abnormalities are probably produced by peripheral motor or sensory fibers being involved during their course in the CNS. A subtle change also suggesting central motor neuron involvement is facial myokymia. Occasionally, one can see signs of aberrant reinnervation, such as interfacial synkinesis or jaw movement synchronized with eye closure.

Temperature-Related Changes

A full discussion of this will be undertaken in the chapter covering the hot bath test. Changes in ambient temperature or endogenous temperature can be associated with marked increases in symptoms and signs. Exercise on a hot day can produce blindness in a patient with otherwise normal vision. Other symptoms, such as ataxia, weakness, or diplopia, can also be greatly exaggerated by heat or exercise. When these are the presenting symptoms, the diagnosis can be difficult, since there will be no abnormal neurologic observations at rest.

Fatigue

Fatigue can sometimes be so marked as to mimic that seen in myasthenia gravis. For example, repeated contraction of the muscles for ankle dorsiflexion can be followed by almost total paralysis of these muscles after only three or four tries. One explanation for this is that in the laboratory rapid stimulation of demyelinated fibers can result in temporary conduction block. This is probably caused by a loss of the usual safety factor for maintenance of conduction in demyelinated fibers.

Patten and colleagues³⁴ studied three patients with the kind of easy fatigability seen

in myasthenia gravis. In each case abnormal decrements to repetitive stimulation were demonstrated by EMG. Treatment with ephedrine or anticholinesterase drugs increased the patient's functional capacity while improving the EMG abnormality. It was thought that these patients represented an overlap syndrome in which the clinical and laboratory features of both MS and MG could coexist in the same patient. In some patients, however, EMG study does not produce evidence to support this connection. We have personally observed several patients in whom myasthenia and MS have coexisted or existed at different times. This is a very intriguing association between two putative autoimmune neurologic diseases and can probably be explained by the tendency for patients with organ-specific autoimmune diseases to have multiple immune abnormalities.

A generalized sense of fatigue is probably the most disabling single symptom in MS. Many patients who are relatively normal in terms of neurologic observations can be completely disabled by an overall and generalized sense of fatigue. The mechanism of this generalized fatigue is unknown. Perhaps it relates to the phenomena seen with rapid stimulation of demyelinated fibers, temperature changes, or both. Even though fatigue is typical of MS, it cannot be considered as characteristic or specific in making a diagnosis.

Extrapyramidal Involvement

Extrapyramidal involvement is extremely rare but does occur. Some patients during the course of exacerbation developed severe dystonic syndromes that can last for several weeks. The tonic spasm seen in MS can also mimic paroxysmal choreoathetosis. We have seen one patient who developed a syndrome similar to paroxysmal choreoathetosis in whom an appropriate enhancing lesion was seen in the head of the caudate nucleus on the contralateral side.

Hysterical Symptoms

Patients with MS are likely to develop hysterical symptoms. Patients with a chronic neurologic disorder, such as MS, in which the frequency and severity of exacerbations cannot be predicted become tense and introspective. They may then become suggestible, and hysterical symptoms often occur under these circumstances.

Caplan and Nadelson³⁵ described the difficulty of separating the organic and hysterical components of illness, particularly in patients with MS. They report four MS patients who had additional major hysterical disabilities. Hysterical visual loss, tunnel vision, hemiparesis, paraparesis, and sensory loss are common. These hysterical relapses must be carefully distinguished from true organic ones. Unfortunately this is not always possible. The usual tests for hysteria, such as consistency, reproducibility, and anatomic distribution, should be used, but these are not always helpful.

FREQUENTLY ENCOUNTERED CLINICAL SYNDROMES

Even though the distribution of lesions in MS is widespread and many times random, certain areas are more frequently involved than others. In a single patient the areas affected may be restricted entirely to one neurologic system or anatomic region. For this reason, predominantly cerebral, ocular, brainstem, cerebellar, or spinal syndromes can be noted (Table 1). It is difficult to make an accurate diagnosis in these situations. In such cases laboratory studies are most helpful.

Cerebral MS

Even though cerebral MS is seen in fewer than 5 percent of the patients, it is a major clinical problem.³⁶ Young persons who begin with cerebral symptoms early in the disease many times remain predominantly ce-

rebral. This is a most disabling and tragic form of MS. Surveys have shown that subtle cerebral symptoms are present in a majority of patients after 10 to 15 years of disease. These can range from emotional lability to pseudobulbar affect, decrease in the ability to form new memories, or frank dementia. The use of CT scans has helped considerably in identifying the multiplicity of lesions in the cerebrum, and nuclear magnetic resonance imaging should be even more helpful. The chapter on imaging techniques covers the interpretation of these lesions in detail.

Visual MS

Even though it is unusual for permanent visual failure to develop in MS, patients are occasionally seen with visual involvement as the primary disabling factor. These patients should always be investigated and reinvestigated for treatable lesions that might be compromising the visual system. In these patients the visual involvement can be symmetrical, but it is usually not. The development of slowly progressive visual failure is very unusual for MS, and MS should never be diagnosed until rigid criteria for dissemination in space have been satisfied. In addition, one should never hesitate to reinvestigate in order to rule out compressive lesions that might be treatable.

Cerebellar MS

Cerebellar MS is another most distressing and very disabling subcategory. Patients with chronic progressive cerebellar syndrome due to MS probably are the most disabled of all. Small lesions in the cerebellar pathways can cause major physical disabilities. The onset of chronic progressive ataxia and intention tremor is a poor prognostic sign.

Chronic Spinal MS

Thirty percent of patients have a chronic progressive course from the outset, and the

great majority of these are chronic spinal. This is usually a combined motor-sensory disturbance that affects all limbs, but predominantly the lower extremities. All such patients should have myelography performed at least once and often several times in order to rule out compressive lesions if no clinical or paraclinical lesions can be identified above the neck. Occasionally patients with spinal cord arteriovenous malformations, thoracic disc, or intramedullary tumors can progress in such a way as to mimic spinal MS. This possibility should always be kept in mind.

Ungar, and associates³⁷ reviewed 672 patients with myelopathy admitted to the Columbia-Presbyterian Medical Center. Group 1 (520 patients, 77.3 percent) had a familial disorder, a history, or other neurologic signs to make the diagnosis obvious on admission by history, examination, or x-ray. Only 14 were diagnosed as having MS (2.69 percent). In group 2, (108 patients, 16.2 percent) the diagnosis was reached after more extensive investigation. In 78 of these patients causes other than MS were noted. On the basis of additional signs 13 patients were diagnosed as having probable MS and 17 were considered to have possible MS on the basis of elevated CSF gamma globulin. In group 3 (44 patients, 6.5 percent) no cause for the spastic paraparesis could be found and diagnostic considerations included amyotrophic lateral sclerosis and MS. The cause of the myelopathy was thought to be MS in 28 percent.

Paty and coworkers³⁸ investigated 72 patients with chronic progressive myelopathy (CPM) for changes that would help in the diagnosis of MS. The mean age of onset was 42 years, the mean duration was 10 years, and the mean Kurtzke Disability Status Scale Rating was 4.5. Oligoclonal banding was seen in 32 patients (44 percent), pattern visual evoked potentials were abnormal in 32 (44 percent), and blink reflex latencies were abnormal in 40 (56 percent). At least one of these studies was abnormal in 61 patients (85 percent) and at least two in 48 (66 percent). The CT scan was abnormal in 38 (55

percent), 36 with atrophy and three with low-density or enhancing lesions. Double dose-delayed CT scans were not done. This study suggested that at least 44 percent of patients with CPM might have MS on the basis of oligoclonal banding in the CSF. Physiologic tests suggesting diffuse or disseminated disease brought the total that might be MS to 85 percent. Only autopsy follow-up can tell the exact diagnostic accuracy of these studies in this syndrome.

In an acute relapse of spinal MS myelography may show swelling of the cord that simulates a tumor.³⁹ In the case of acute spinal symptoms associated with enlargement of the cord in a young adult MS must be considered. If the swelling results from inflammation, it will subside. Swelling caused by an intrinsic spinal cord tumor should either remain the same or become worse over a period of time. Therefore demonstrating an enlarged cord in a young adult should not be considered diagnostic of intramedullary tumor. Follow-up studies should be done in order to differentiate tumor from acute inflammation as seen in MS or acute transverse myelitis.

It must be stressed that the acute or subacute onset of spinal symptoms and signs in a young adult should initiate a concerted effort to discover evidence of lesions elsewhere in the nervous system by means of reliable, noninvasive procedures. Unless these are observed, myelography must be carried out.

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