Cleveland Clinic Quarterly

Volume 34 January 1967 No. 1

Multiple sclerosis—an enigma

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The accurate diagnosis of multiple sclerosis may be one of the easiest in medicine to make in some instances, but on other occasions it may be one of the most difficult. Literally volumes have been written about this disease, in regard to etiology, symptoms, and treatment; yet, concerning most of these aspects there is little total agreement among clinicians. However, nearly everyone is willing to admit that no one really knows what constitutes multiple sclerosis as a clinical entity; no one knows the cause of it; and, thus far, there is no really satisfactory treatment for this condition.

Multiple sclerosis or, as it is sometimes designated, *disseminated sclerosis, insular sclerosis,* or Charcot's term *sclérose en plaques,*[1] was first recognized and described by Carswell[2] (1838) and Cruveilhier[3] (1829–1842).

According to Greenfield,[1] Charcot is credited with being the first physician to recognize the pathologic features of this disorder and, his report of the triad of the clinical manifestations of the disease—intention tremor, scanning speech, and nystagmus—has been referred to by most clinicians who have written about multiple sclerosis.

Observations concerning multiple sclerosis, which have accumulated from a neurologic practice at the Cleveland Clinic, make me realize how difficult a problem is this fairly common neurologic entity. Unfortunately, the term *disseminated sclerosis* has in many instances become a sort of clinical catchall to include many disorders the clinician is unable to establish as clear-cut entities. Someday in the future the complex condition of multiple sclerosis as now described may no longer be recognized. With advances in neurochemistry and perhaps better diagnostic aids it is conceivable that this condition will be separated into discrete and concise entities. For this reason I believe that it is well to point out some of the diagnostic pitfalls and to attempt to identify a number of conditions that often are misdiagnosed as multiple sclerosis.

The term *multiple sclerosis* probably should be used only for conditions in which the clinical history includes evidence of exacerbations and remissions affecting the motor, the cerebellar, and the sensory systems. Likewise, there should be evidence of involvement of these systems at some time during the course of the disease. Disseminated sclerosis is essentially a disorder of the white matter of the nervous system, as are other types of demyelinating derangements such as diffuse sclerosis (Schilder's disease), neuromyelitis optica, and diffuse myelitis. For the most part, demyelination in multiple sclerosis occurs without destruction of the axons; in other words, whatever the process may be, the chief area of vulnerability in the nervous system is the myelin sheath or the myelin covering of the axons.

Etiology. The cause of multiple sclerosis is not known. The etiologic possibilities have ranged from spirochetal involvement to psychoneurosis. The most recent and probably the most plausible theory thus far proposed is that disseminated sclerosis may be the result of an autoimmune disorder, wherein for some (unknown) reason the individual's nervous system becomes sensitized (in some manner), thus causing the destruction of myelin. This pathologic mechanism has been reproduced for the most part in animals, and is designated as experimental, allergic encephalomyelitis.

Disseminated sclerosis is primarily a disease entity occurring in persons living in the temperate climates, and may have some relationship to the amount of sunlight in a specific region. According to a recent sunshine map, the territory on the southern border of the Great Lakes and that in the State of Washington have the lowest amount of sunshine of any regions in the United States. Likewise, the incidence of multiple sclerosis in the above-mentioned geographic areas is higher than in other areas of the United States. Some of my colleagues in neurology, practicing in the warmer climes such as Texas, report that it is almost a special occasion when they see a case of multiple sclerosis developing in a native of that particular region.

Age, sex, and race distribution. Multiple sclerosis is essentially a disease of young persons, the majority of these patients first seeking medical attention between the ages of 20 and 40 years. However, I have seen patients in whom this condition was first recognized in the sixth or seventh decade of life, and one 14-year-old boy in whom the disease presented a typical clinical picture. In my experience, the later the onset of multiple sclerosis the better the prognosis.

Most textbooks state that multiple sclerosis occurs equally often in the two sexes but in my practice the disease has been more prevalent in women than in men. The incidence is less in Negroes than in Caucasians.

Symptoms. Historically, some of the most characteristic symptoms of disseminated sclerosis are blurred or double vision of a transient nature; subjective sensory disturbance, such as a feeling of numbness and/or tingling in

one or several extremities, again of a transient nature; weakness, and particularly fatigability. In advanced cases the history often indicates bladder or bowel disturbance. The symptoms vary, being characterized by urgency, incontinence, hesitancy or difficulty in voiding or defecating.

With few exceptions, pain is unusual in most persons having multiple sclerosis. If pain is prominent in the individual's complaints, the physician's suspicion of disseminated sclerosis should be immediately lessened. Exceptions to this generality concerning pain, are trigeminal neuralgia and the occasional sensation of a tight band about the trunk or chest or possibly even the sensation of tightness about or in one or more of the extremities. In my experience, headache has rarely if ever been a part of the symptom complex of multiple sclerosis.

Pain as a part of the misleading symptom complex is exemplified by the case of a 35-year-old woman whose original complaints were visual disturbance. I have followed the course of this patient's condition for seven years. Periodically she has had bouts of retrobulbar neuritis with definite scotomata, and at times paresthesias of the extremities and some unsteadiness in walking. These symptoms and findings suggest the possibility of a demyelinating disorder. About two years ago she began to experience severe backache as well as sharp pains shooting into the extremities. At this time, fortunately, the original diagnosis of multiple sclerosis was reappraised. It was only after three tests for lupus erythematosus that lupus erythematosus was diagnosed. If the old view is followed that "all conditions should be put under one umbrella," I think it is most likely that this woman has lupus erythematosus, which also is a disease causing a variety of symptoms and signs.

Rarely, vertigo may be a manifestation of disseminated sclerosis. One notable example occurred in a young man who, upon getting out of his car, was suddenly seized with an attack of vertigo and fell to the sidewalk. Subsequently, the typical syndrome of disseminated sclerosis developed in this man. Caution must be exercised in the diagnosis of the condition of the 25- to 35-year-old mother of several children who seeks medical attention because of a sensation of numbness and tingling in one or more extremities and in whom only minor or no abnormalities can be demonstrated objectively by examination. The history may suggest marital problems and fear of additional pregnancies. Consequently, the great tendency is to label such a woman as a neurotic. It is indeed embarrassing to diagnose such a condition as a neurosis, to give the patient mild sedation and to reassure her, only to have her return a few months later with the same complaints plus nystagmus, weakness of one or more extremities, and evidence of long-tract involvement of the spinal cord! The differential diagnosis between hysteria and disseminated sclerosis is often extremely difficult. Much has been written about this particular problem and such astute observers as Gowers[4] and

Oppenheim[5] have pointed out that multiple sclerosis is frequently mistaken for hysteria. It has been reported by Langworthy and his colleagues[6-9] that there may well be a relationship between multiple sclerosis and hysteria. It is their opinion that the basic hysterical personality structure of certain individuals with disseminated sclerosis is manifest long before there is evidence of the neurologic disease.

Neurologic signs. The neurologic signs of multiple sclerosis are protean. Abnormalities of the gait are extremely common and these are characterized usually by ataxia—the individual walking on a wide base—often further complicated by various degrees of muscle spasticity. As far as the cranial nerves are concerned, optic disk pallor is seen in a large percentage of persons with this disorder, and nystagmus is one of its important clinical signs. Nystagmus may vary in type from a plain horizontal nystagmus on lateral-gaze testing, to a horizontal nystagmus with a rotatory component, or to a nystagmus that is present primarily in the abducting eye or that elicited by upward vertical gaze. One of the most typical kinds of nystagmus in disseminated sclerosis is that associated with internuclear opthalmoplegia or the medial longitudinal fasciculus (MLF) syndrome. While it is possible for conditions other than a demyelinating process to produce lesions of the medial longitudinal fasciculus, multiple sclerosis is by far the most common cause of internuclear opthalmoplegia. Hence, if one can elicit this type of nystagmus—that in which the abducting eye is more affected than the adducting eye—suspicion should immediately be increased concerning the possibility of disseminated sclerosis.

Cogan[10] states:

> Bilateral internuclear ophthalmoplegia wherein both eyes are involved is most frequently seen, by far, with multiple sclerosis but some cases have been reported following epidemics of encephalitis lethargica and it is not uncommon as a complication of diverse lesions of the brain stem (tumors, Wernicke's encephalopathy, syringobulbia and so forth). Nevertheless, when bilateral internuclear ophthalmoplegia is present alone or when it is the most conspicuous abnormality, the underlying condition is almost invariably multiple sclerosis.*

Cogan[10] states further:

> Conversely, the most common ocular motor manifestation of multiple sclerosis is internuclear ophthalmoplegia. Only rarely is it combined with the ocular sensory manifestation (retrobulbar neuritis) of multiple sclerosis.*

My experience is in agreement with Cogan's comments that rarely does pallor of the optic disks and internuclear ophthalmoplegia occur in the

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* *From Cogan, David G., NEUROLOGY OF THE OCULAR MUSCLES, 2d Ed., 1956, pages 87 and 88. Courtesy of the author and Charles C Thomas, Publisher, Springfield, Illinois.*

same individual. This raises the question of why some portions of the nervous system should be more vulnerable than others in one patient and not another.

Other significantly suggestive signs of disseminated sclerosis are an increase of the deep tendon reflexes and extensor plantar responses, or Babinski signs.

The cerebellar system is often affected, so patients with disseminated sclerosis may have considerable difficulty in performing coordinated movements. Some of the important tests for cerebellar dysfunction are the finger-to-nose test, the heel-to-knee test, rapid and alternating movements of the hands, and the rebound phenomenon.

Many authors stress absence or diminished activity of the abdominal reflexes as being a sign of multiple sclerosis. In my opinion, the abdominal reflexes are an unreliable guide, since childbearing in women, obesity, and operative scars may alter normal abdominal reflex activity.

Differential diagnosis. Drug intoxication has been mistaken for disseminated sclerosis. Ataxia, nystagmus, and incoordination may be prominent findings in drug intoxication. Hence, should the history not be too suggestive of a demyelinating process, and the clinical signs be marginal except for ataxia, nystagmus, and perhaps some slurred speech, the possibilities of an intoxication should be considered. I have seen several examples of this state, especially due to phenobarbital, and, as could be expected, as soon as the patients were hospitalized and administration of the medication was stopped, the signs and symptoms regressed rapidly.

Syringomyelia and syringobulbia may be mistaken for multiple sclerosis. Here again, if a careful history is obtained, the chances are that there would be little to suggest a demyelinating process. Sensory testing indicating dissociation of sensation—particularly diminished or absence of pain and temperature recognition, and preservation of light touch, vibratory and position sense—should assist greatly in differentiating syringomyelia from disseminated sclerosis.

Tumors, both intracranially and within the spinal canal, may cause symptoms and signs suggesting multiple sclerosis. I have seen two patients who had verified tumors of the foramen magnum whose presenting complaints were suggestive of disseminated sclerosis.

Ten years ago a 61-year-old woman was admitted to the Cleveland Clinic Hospital with a referral diagnosis of multiple sclerosis. She was unable to walk, and examination revealed paraplegia, hyperactive deep tendon reflexes in the lower extremities, bilateral Babinski signs, and bladder dysfunction. The disorder was of from one to two years' duration and the history indicated a remissive type of disturbance, because several months after the onset of weakness the condition improved with a physical therapy regimen, only

to worsen subsequently. There was no evidence of involvement of the cranial nerves nor of the upper extremities. These findings immediately raised the question as to whether or not something other than a demyelinating disorder was present, and a lumbar puncture was done. Analysis of the cerebrospinal fluid revealed a protein content of 138 mg per 100 ml. (In my experience, cerebrospinal fluid protein levels of more than 75 to 80 mg per 100 ml should arouse suspicion of conditions other than those of typical disseminated sclerosis.) There was likewise a first-zone colloidal gold curve. Subsequently, myelography revealed an obstruction at the level of the first thoracic vertebra, and removal of a meningioma resulted in an 80 to 90 percent return of function in the lower extremities. Here, even though the history was somewhat suggestive, the lack of clinical findings in the cranial nerves or upper extremities raised doubts regarding the referral diagnosis of disseminated sclerosis.

Treatment. As might be expected from the fact that the etiology is not known, there has been no really worthwhile treatment outlined for disseminated sclerosis. In this regard, probably more treatments have been suggested than possible etiologic factors; and, as yet, no one form of therapy is satisfactory. On the basis that multiple sclerosis may be an autoimmune disorder, and that there is pathologic evidence of loosening of tissue structure around areas of plaque formation in the central nervous system (suggesting the possibility of edema), I have resorted to adrenocorticotropic hormone (ACTH) as a therapeutic agent.

ACTH seems to be of help in acute cases; but it is wise not to become overly optimistic about these results inasmuch as this condition may run an up- and down-hill course in its early phases even without treatment. Consequently, there is some question as to the effectiveness of ACTH or of steroids. Even though I recognize full well the possible clinical course of multiple sclerosis, I prefer not to be a therapeutic nihilist and, consequently, have used ACTH whenever possible in suspected cases of this disorder. Although ACTH is not specific treatment for multiple sclerosis it is most difficult not to become enthusiastic regarding such therapy when symptoms, and, less often signs, improve within a matter of some hours or a few days after the initiation of such treatment.

In any treatment for this disorder it is most important to follow one of the basic therapeutic principles, namely, the earlier the treatment the better the result. I think that it is not at all unreasonable to suspect that once an individual's nervous system becomes literally studded with sclerotic plaques, probably no amount of ACTH or of steroids is going to help to reverse the basic pathologic lesion or to improve the physiologic activity of the nervous system. However, if treatment can be instituted essentially near the onset of the disorder, ACTH may shorten the course of that particular exacerbation,

and prolonged use of ACTH may reduce the possibility of further exacerbations.

SUMMARY AND CONCLUSION

In summary, a typical case of multiple sclerosis from my observations would be characterized as follows: A 25- to 30-year-old, white woman who has resided in a temperate climate throughout most of her life, has a history of exacerbations and remissions either of blurred or of double vision, and/or transient episodes of numbness and paresthesias of the extremities. At some time during the course of her illness she has had weakness of one leg or both legs, has manifested an ataxic gait with possible spasticity; has nystagmus or temporal pallor of one or both optic disks; has hyperactive deep tendon reflexes; has Babinski signs; and incoordination of either one of the upper or lower, or both upper and both lower extremities. As the malady has progressed, bladder and bowel sphincter control has likewise been subject to dysfunction. In spite of eventual rather widespread derangement of the nervous system, she is likely to live to an age of 60 years or older, although eventually confined to a wheelchair or bed and, for the most part, will complain little and not be unduly concerned about her unfortunate lot in life.

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