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Review Article

Medical Progress

MULTIPLE SCLEROSIS

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MORE than 100 years has passed since Charcot, Carswell, Cruveilhier, and others described the clinical and pathological characteristics of multiple sclerosis.[1] This enigmatic, relapsing, and often eventually progressive disorder of the white matter of the central nervous system continues to challenge investigators trying to understand the pathogenesis of the disease and prevent its progression.[2] There are 250,000 to 350,000 patients with multiple sclerosis in the United States.[3] Multiple sclerosis typically begins in early adulthood and has a variable prognosis. Fifty percent of patients will need help walking within 15 years after the onset of disease.[4] Advanced magnetic resonance imaging (MRI) and spectroscopy may allow clinicians to follow the pathological progression of the disease and monitor the response to treatment. Recent progress has occurred in understanding the cause, the genetic components, and the pathologic process of multiple sclerosis. The short-term clinical and MRI manifestations of disease activity have been reduced by new therapies, although the degree of presumed long-term benefit from these treatments will require further study.

CLINICAL COURSE AND DIAGNOSIS

A patient's presenting symptoms and the temporal evolution of the clinical findings may suggest the correct diagnosis. In relapsing–remitting multiple sclerosis — the type present in 80 percent of patients — symptoms and signs typically evolve over a period of several days, stabilize, and then often improve, spontaneously or in response to corticosteroids, within weeks. Relapsing–remitting multiple sclerosis typically begins in the second or third decade of life and has a female predominance of approximately 2:1. The tendency for corticosteroids to speed recovery from relapses often diminishes with time. Persistent signs of central nervous system dysfunction may develop after a relapse, and the disease may progress between relapses (secondary progressive multiple sclerosis). Twenty percent of affected patients have primary progressive multiple sclerosis, which is characterized by a gradually progressive clinical course and a similar incidence among men and women.

Relapsing–remitting multiple sclerosis typically starts with sensory disturbances, unilateral optic neuritis, diplopia (internuclear ophthalmoplegia), Lhermitte's sign (trunk and limb paresthesias evoked by neck flexion), limb weakness, clumsiness, gait ataxia, and neurogenic bladder and bowel symptoms. Many patients describe fatigue that is worse in the afternoon and is accompanied by physiologic increases in body temperature. The onset of symptoms post partum and symptomatic worsening with increases in body temperature (Uhthoff's symptom) and pseudoexacerbations with fever suggest the diagnosis. Some patients have recurring, brief, stereotypical phenomena (paroxysmal pain or paresthesias, trigeminal neuralgia, episodic clumsiness or dysarthria, and tonic limb posturing) that are highly suggestive of multiple sclerosis.

Prominent cortical signs (aphasia, apraxia, recurrent seizures, visual-field loss, and early dementia) and extrapyramidal phenomena (chorea and rigidity) only rarely dominate the clinical picture. Eventually, cognitive impairment, depression, emotional lability, dysarthria, dysphagia, vertigo, progressive quadriparesis and sensory loss, ataxic tremors, pain, sexual dysfunction, spasticity, and other manifestations of central nervous system dysfunction may become troublesome. Patients who have primary progressive multiple sclerosis often present with a slowly evolving upper-motor-neuron syndrome of the legs ("chronic progressive myelopathy"). Typically, this variant worsens gradually, and quadriparesis, cognitive decline, visual loss, brain-stem syndromes, and cerebellar, bowel, bladder, and sexual dysfunction may develop.

The diagnosis is based on established clinical and, when necessary, laboratory criteria.[5] Advances in cerebrospinal fluid analysis and MRI, in particular, have simplified the diagnostic process (Fig. 1).[6] The relapsing forms are considered clinically definite when neurologic dysfunction becomes "disseminated in space and time." Primary progressive multiple sclerosis may be suggested clinically by a progressive course that lasts longer than six months, but laboratory studies to obtain supportive evidence and efforts to exclude

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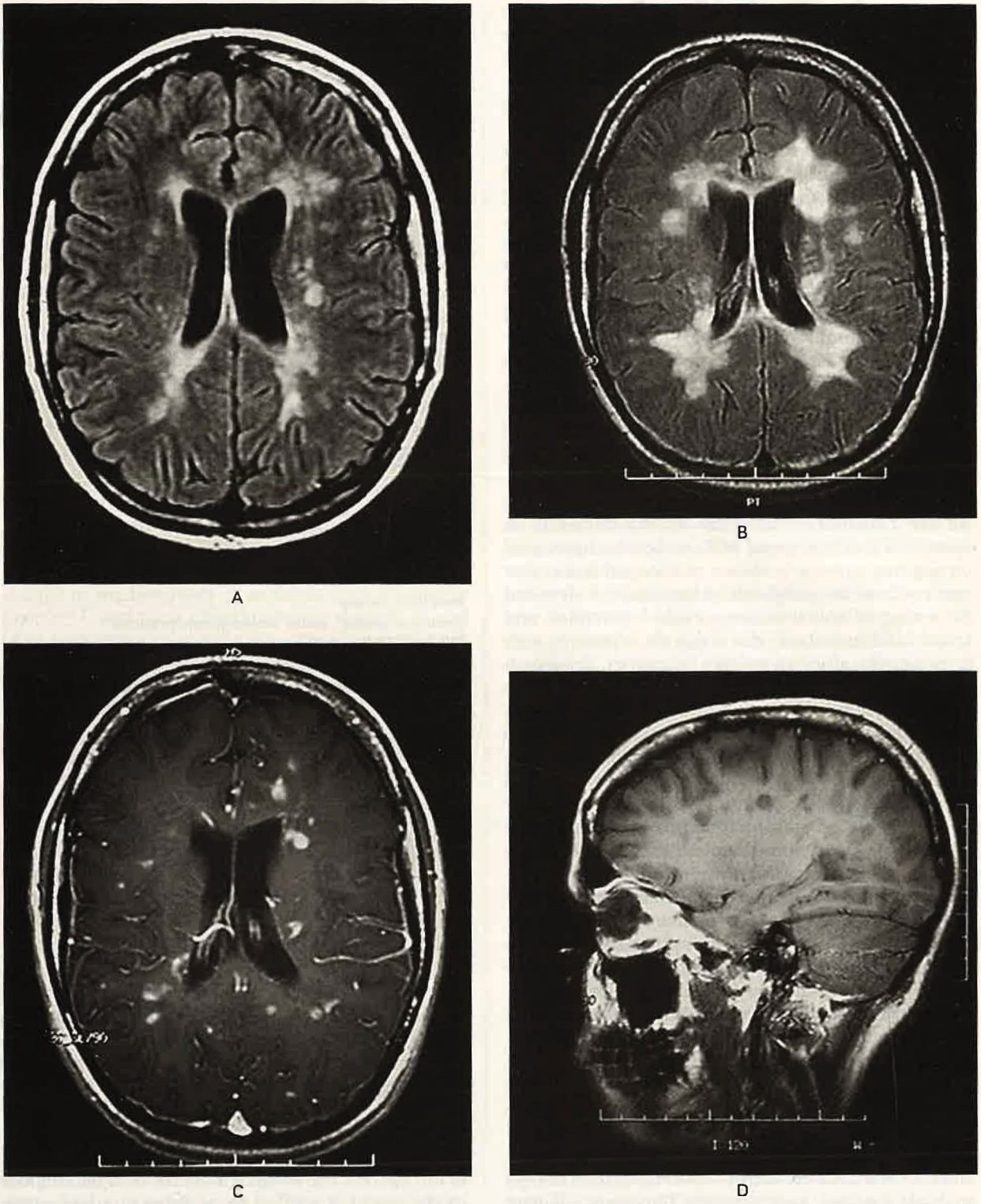

Figure 1. MRI Scans of the Brain of a 25-Year-Old Woman with Relapsing–Remitting Multiple Sclerosis.

An axial FLAIR (fluid-attenuated inversion recovery) image shows multiple ovoid and confluent hyperintense lesions in the periventricular white matter (Panel A). Nine months later, the number and size of the lesions have substantially increased (Panel B). After the administration of gadolinium, many of the lesions demonstrate ring or peripheral enhancement, indicating the breakdown of the blood–brain barrier (Panel C). In Panel D, a parasagittal T_1-weighted MRI scan shows multiple regions in which the signal is diminished (referred to as "black holes") in the periventricular white matter and corpus callosum. These regions correspond to the chronic lesions of multiple sclerosis.

other, potentially treatable illnesses are advised; for example, structural or metabolic myelopathy can be identified by appropriate laboratory studies, including spinal MRI (Table 1). On MRI, findings of multifocal lesions of various ages, especially those involving the periventricular white matter, brain stem, cerebellum, and spinal cord white matter, support the clinical impression. The presence of gadolinium-enhancing lesions on MRI indicates current sites of presumed inflammatory demyelination (active lesions).

When there is diagnostic uncertainty, repeated MRI after several months may provide evidence that the lesions are "disseminated in time." Cerebrospinal fluid analysis often shows increased intrathecal synthesis of immunoglobulins of restricted specificity (oligoclonal bands may be present, or the synthesis of IgG may be increased), with moderate lymphocytic pleocytosis (almost invariably there are fewer than 50 mononuclear cells). Physiologic evidence of subclinical dysfunction of the optic nerves and spinal cord (changes in visual evoked responses and somatosensory evoked potentials) may provide support for the conclusion that there is "dissemination in space."[7] Therefore, spinal MRI and evoked-potential testing may provide evidence of a second lesion that can confirm the diagnosis. Abnormalities detected by testing of somatosensory evoked potentials and spinal MRI may clarify the diagnosis in patients with optic neuritis alone or isolated brain-stem abnormalities and in those suspected of having unifocal cerebral multiple sclerosis on the basis of MRI. If positive, abnormalities detected by tests of visual evoked responses may support the diagnosis of multiple sclerosis in patients with isolated brain-stem or spinal cord lesions.

The course of multiple sclerosis in an individual patient is largely unpredictable. Patients who have a so-called clinically isolated syndrome (e.g., optic neuritis, brain-stem dysfunction, or incomplete transverse myelitis) as their first event have a greater risk of both recurrent events (thereby confirming the diagnosis of clinically definite multiple sclerosis) and disability within a decade if changes are seen in clinically asymptomatic regions on MRI of the brain.[8] The presence of oligoclonal bands in cerebrospinal fluid slightly increases the risk of recurrent disease.[9]

Studies of the natural history of the disease have provided important prognostic information that is useful for counseling patients and planning clinical trials.[4,10,11] Ten percent of patients do well for more than 20 years and are thus considered to have benign multiple sclerosis. Approximately 70 percent will have secondary progression.[4] Frequent relapses in the first two years, a progressive course from the onset, male sex, and early, permanent motor or cerebellar findings are independently, but imperfectly, predictive of a more severe clinical course. Women and patients with predominantly sensory symptoms and optic neuritis have a more favorable prognosis. Life expectancy may be shortened slightly; in rare cases, patients with fulminant disease die within months after the onset of multiple sclerosis. Suicide remains a risk, even for young patients with mild symptoms.[12]

TABLE 1. DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS.

Metabolic disorders
Disorders of B_{12} metabolism*
Leukodystrophies
Autoimmune diseases
Sjögren's syndrome, systemic lupus erythematosus, Behçet's disease, sarcoidosis, chronic inflammatory demyelinating polyradiculopathy associated with central nervous system demyelination, antiphospholipid-antibody syndrome
Infections†
HIV-associated myelopathy* and HTLV-1–associated myelopathy,* Lyme disease, meningovascular syphilis, Eales' disease
Vascular disorders
Spinal dural arteriovenous fistula*
Cavernous hemangiomata
Central nervous system vasculitis, including retinocochlear cerebral vasculitis
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
Genetic syndromes
Hereditary ataxias and hereditary paraplegias*
Leber's optic atrophy and other mitochondrial cytopathies
Lesions of the posterior fossa and spinal cord
Arnold–Chiari malformation, nonhereditary ataxias
Spondylotic and other myelopathies*
Psychiatric disorders
Conversion reaction, malingering
Neoplastic diseases
Spinal cord tumors,* central nervous system lymphoma
Paraneoplastic disorders
Variants of multiple sclerosis‡
Optic neuritis; isolated brain-stem syndromes; transverse myelitis; acute disseminated encephalomyelitis, Marburg disease; neuromyelitis optica

*This disorder or group of disorders is of particular relevance in the differential diagnosis of progressive myelopathy and primary progressive multiple sclerosis.

†HIV denotes human immunodeficiency virus, and HTLV-1 human T-cell lymphotropic virus type 1.

‡In many patients with these variants, clinically definite multiple sclerosis develops or the course is indistinguishable from that of multiple sclerosis.

EPIDEMIOLOGIC FEATURES

The prevalence of multiple sclerosis varies considerably around the world.[13] Kurtzke classified regions of the world according to prevalence: a low prevalence was considered less than 5 cases per 100,000 persons, an intermediate prevalence was 5 to 30 per 100,000 persons, and a high prevalence was more than 30 per 100,000 persons.[14] The prevalence is highest in northern Europe, southern Australia, and the middle part of North America. There has been

a trend toward an increasing prevalence and incidence, particularly in southern Europe.[15,16] Even in areas with uniform methods of ascertainment and high prevalence, such as Olmsted County, Minnesota, the incidence has increased from 2 to 6 per 100,000 during the past century.[17] However, the incidence has actually declined in some,[18,19] but not all,[20] areas of northern Europe. Stable or declining rates have been reported most often in regions with high prevalence and incidence. The extent to which the observed increases in incidence are explained by an enhanced awareness of the disease and improved diagnostic techniques is uncertain. There is a large reservoir of mild cases, the recognition of which may depend heavily on the zeal and resources of the investigator.

The reasons for the variation in the prevalence and incidence of multiple sclerosis worldwide are not understood. Environmental and genetic explanations have been offered, and both factors probably have a role. The occurrence of rapid shifts in the incidence of multiple sclerosis, if not artifactual, is an argument for an environmental influence, as is the equivocal, but suggestive, evidence of the clustering of cases in terms of both geography and time and of epidemics, especially on the Faroe Islands.[21] The apparent change in the frequency of multiple sclerosis among people[22,23] and their offspring[24] who migrate to and from high-prevalence areas is another factor that has been presented to support the existence of an environmental factor. However, each of these relations has potential confounders that preclude the drawing of a definite conclusion regarding the importance of environmental factors.[25] The nature of putative environmental factors remains unclear in numerous case–control studies. Studies that show that the incidence of multiple sclerosis among the adopted children of patients with multiple sclerosis is not higher than expected seem to argue against the possibility that a transmissible factor is primarily responsible for the increased risk of the disease among relatives and instead suggest that genetic factors may be responsible.[26]

GENETIC FACTORS

Evidence that genetic factors have a substantial effect on susceptibility to multiple sclerosis is unequivocal. The concordance rate of 31 percent among monozygotic twins is approximately six times the rate among dizygotic twins (5 percent).[27] The absolute risk of the disease in a first-degree relative of a patient with multiple sclerosis is less than 5 percent; however, the risk in such relatives is 20 to 40 times the risk in the general population.[28] Since 1973, it has been recognized that the presence of the HLA-DR2 allele substantially increases the risk of multiple sclerosis.[29] This effect has been found in all populations, with the exception of that in Sardinia.[30] The magnitude of the relative risk depends on the frequency of the HLA-DR2 allele in the general population. Given the high frequency of this allele in the population, the risk attributable to the HLA-DR2 allele is considerable. Populations with a high frequency of the allele (e.g., those in Scotland) have the highest risk of multiple sclerosis.

The mode of transmission of genetic susceptibility to multiple sclerosis is complex. Most cases are sporadic, despite the clear excess risk among the relatives of patients. Investigators have used the usual genetic approaches to identify genes associated with an increased risk of multiple sclerosis.

Studies of candidate genes have targeted individual genes with microsatellite markers with use of association and linkage strategies. For some genetic regions, such as the HLA region on chromosome 6, it has been difficult to identify the specific polymorphism that predisposes persons to the disease, given the high degree of linkage disequilibrium at that locus. Candidate-gene studies were followed by four studies in which the entire genome was scanned.[31-34] Regions of interest have been identified, although none have been linked to the disease with certainty. Considering the rather large number of patients evaluated in such studies, one might conclude tentatively that no single gene, except possibly those for HLA antigens,[35] exerts a strong effect.

Further refinement of the linkage map is in progress.[36] Whether this approach will prove powerful enough to identify genes with a relatively weak effect is difficult to predict. To enhance the detection of genes with a weak effect, investigators have begun to use strategies involving linkage-disequilibrium mapping and transmission-disequilibrium testing. In these approaches, putative causative alleles or marker alleles and haplotypes are assessed to determine whether they are associated with the disease at a population level or whether they are associated with a higher-than-expected rate of transmission of disease from heterozygous parents to their children. This effort will involve a major expenditure of resources to achieve genome-wide coverage. The development of novel analytic techniques for these types of genetic data sets makes such an undertaking feasible.[37]

The severity and course of multiple sclerosis may also be influenced by genetic factors. Epidemiologic evidence to support this premise comes from studies examining the rate of concordance for measures that describe and quantitate variations in the course of disease, including the age at onset, the proportion of patients in whom the disease progresses, and the extent of disability over time.[38] HLA-DR and DQ polymorphisms are not associated with the course and severity of multiple sclerosis, despite their substantial contribution to disease susceptibility.[39] Recently, variants of the interleukin-1β–receptor and interleukin-1–receptor antagonist genes,[40] immunoglobulin Fc receptor genes,[41] and apolipoprotein E gene[42] have been associated with the course of the disease, but these findings await confirmation.

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