

MULTIPLE SCLEROSIS

The diagnosis of multiple sclerosis (MS), just as that of most other neurologic disorders, is based primarily on the neurologic history, findings on neurologic examination and, lesser extent, results of special examinations. Since the initial delineation of MS as a distinct clinical and pathologic entity by Charcot in the past century, the diagnosis has been based on symptoms and objective evidence of white matter lesions of the central nervous system disseminated both temporally and spatially, with onset for all patients is in the second half of the third decade of life. The disease has a peculiar geographic distribution, being more prevalent in northern, temperate latitudes and less frequent in tropical and subtropical regions of the world.

Epidemiologic studies of MS make this disease compatible with genetic as well as with a variety of known and unknown environmental etiologic factors, and the current pathogenetic hypothesis suggests a significant dysregulation of immunologic mechanisms, probably triggered by a viral exposure early in life. It should be pointed out that as of now no single virus has yet been identified as the most likely culprit.

Disturbances of sensation, motor disorders, gait difficulties and monocular loss of vision are the most common symptoms in multiple sclerosis at the time of initial examination, to the point that in their absence, and in the absence of a clear course of remissions and exacerbation, and in the presence of an entirely normal cerebrospinal fluid examination, the diagnosis of MS should be considered at least doubtful. The combination of symptoms and sign in established case can be quite varied and can mimic any syndrome attributable to central nervous system white matter disease. Symptoms and signs attributable to gray matter disease, such as seizures, aphasia, apraxia etc. are quite unusual, at least initially.

Although the diagnosis of MS is ultimately a clinical one, advances in laboratory, neurophysiologic and neuroimaging techniques have aided in the diagnosis of this disorder. At the current stage of our knowledge, however, no diagnostic test can be considered 100% specific.

Approximately 75% of all patient manifest a course of the disease characterized by remissions and exacerbations and approximately 25% have a chronically progressive course from the very onset of the disease. A very small percentage of patients have a rapidly fulminating course leading to death in only a few months. The emergence of new diagnostic techniques and our increasing diagnostic acumen may reveal in the future that what we now call MS may represent only the tip of an iceberg and that there may be a huge number of benign monosymptomatic or asymptomatic cases in the population at large which are as yet undiagnosed or not diagnosable.

It should again be emphasized that results of cerebrospinal fluid (CSF) studies and other test may be abnormal for various reasons; hence, these are not specific for MS.

- **CEREBROSPINAL FLUID** - The CSF protein concentration is increased in approximately a fourth of the patients. Mild increase CSF leukocyte count, usually less than 20 /ml, can occur. Cell counts greater than 25 /ml are seen in less than 1% of patients with MS, usually in association with active diseases. The frequent increase in gamma-globulin (60 to 75 % of patients with MS) has been known since the early 1940's. A very sensitive test pointing to active disease is an IgG index higher than 0.7. Myelin basic protein can be found in the CSF in MS and in a variety of other conditions

accompanied by primary or secondary demyelination. Oligoclonal bands in the CSF are significant only when they are not present in the serum.

- **EVOKED STUDIES** - An evoked potential is the electric response to stimulation of a sensory pathway, recorded through surface electrodes, amplified, and subjected to signal averaging. Electrophysiologic testing facilitates the detection, and often the localization, of lesions affecting central sensory pathways. With these techniques, the presence of lesions in patients with unusual symptoms and equivocal deficits can be identified when the clinical picture suggests only one lesion.
- An abnormal evoked potential is not specific for MS; therefore, it must be interpreted in the context of the clinical picture. Electromyographic and nerve conduction tests pointing to peripheral nerve or muscle diseases should steer away from the diagnosis of a primary CNS demyelinating process.
- **IMAGING STUDIES**
 - **MAGNETIC RESONANCE IMAGING** - Magnetic resonance imaging (MRI) currently is the preferred imaging technique for obtaining evidence in support of a diagnosis of MS. The typical abnormalities on NM most commonly are located in the supratentorial white matter, especially in the periventricular region. They may appear as multiple discrete lesions, or they may coalesce to form more homogeneous borders surrounding the ventricles. These abnormalities have a location similar to that of the demyelinating lesions observed at autopsy. Less commonly, lesions can be detected in the cerebellum and in the brainstem.
 - **COMPUTED TOMOGRAPHY (CT)** - While CT is not as sensitive as NM in the detection of abnormalities in MS, it nevertheless may demonstrate a wide variety of findings. Cerebral atrophy is the most common and least specific abnormality. Hypodense lesions before administration of contrast agent may be present in periventricular and deep white matter and, uncommonly, in the posterior fossa. Enhancement seems to correlate with acute disruption of the blood-brain barrier, and the areas of abnormal enhancement can be abolished by treatment with corticosteroids.
- **DIFFERENTIAL DIAGNOSIS** - Numerous disorders can potentially mimic MS. Conditions to be ruled out include collagen vascular disorders, sarcoidosis, acute disseminated encephalomyelitis, Behcet's disease, cerebrovascular occlusive disease, meningovascular syphilis, paraneoplastic disorders. Other conditions to be considered are hereditary spinocerebellar ataxias, subacute combined degeneration of the spinal cord (Vitamin B12 deficiency), progressive spastic paraparesis secondary to retrovirus infection (HTLV I), primary CNS lymphomas, arterio-venous malformations of the brainstem and spinal cord, Arnold-Chiari malformation. Psychiatric disorders almost always enter in the differential diagnosis early in the course of the disease.
- **MANAGEMENT** - The clinical therapeutic trials are all aimed at altering the patients' immune system, inasmuch as the demyelination in MS is thought to be immune mediated. Some authors recommend the intravenous use of ACTH, or methylprednisolone for moderate to severe exacerbations, and oral administration of prednisone for mild exacerbation of MS. Low dose maintenance treatment with steroids should have no place

in the therapeutic armamentarium of MS. The results of treatment of chronic progressive MS, whether slow or rapid in its course, is dismal. We consider azathioprine, cyclophosphamide, cyclosporine, lymphatic irradiation and plasmapheresis as experimental treatment modalities without important therapeutic effect.

Case studies

A 36 year-old laborer, born and raised in Brazil, has been living in Southern Louisiana for the past two years working as a fisherman. Over the past several months he has been developing a gradually progressive weakness and numbness of both lower extremities, problems with balance and coordination, and urinary retention. On neurological examination you find increased DTR's 3+ in upper extremities and 4+ in lower extremities with ankle clonus and bilateral Hoffman reflex and Babinski. Cranial nerves are normal.

- a. Where is likely to be the lesion?
- b. Discuss a comprehensive differential diagnosis.
- c. Select three diagnostic tests, which would most likely narrow down your differential diagnosis.

A 57 year-old Caucasian female house wife, obese, known hypertensive, and insulin dependent diabetic for the past 15 years, has developed weakness and numbness in the lower extremities over the past several months. The primary care physician has obtained a MRI of the brain without Gadolinium contrast. The radiology report indicates that on the T-2 weighted images there are "few punctate lesions bilaterally in the supratentorial white matter, at the subcortical level and in the basal ganglia bilaterally, compatible with the diagnosis of multiple sclerosis". The primary care physician, during a casual conversation in the cafeteria, requests your opinion on the case without giving you any details on the neurologic examination and wants to know which other diagnosis tests you would request.

- a. How would you handle this 'over the coffee' consultation?
- b. Which would you expect to be the most likely findings on neurologic examination?
- c. Which is the one diagnostic test most likely to be helpful in confirming your diagnostic impression?

A 32 year-old female, born and raised in Fargo, ND, who has been working in New Orleans for the past three years as a sales manager in a Department store, has a history of having had a right optic neuropathy seven years ago with complete recovery of function without any treatment. Four years ago she experienced a foot drop on the left treated as a common peroneal palsy and improved after treatment by a chiropractor. A few months ago she developed urinary incontinence and right-sided hemiparesis without speech or language impairment. The only diagnostic test obtained was a CT scan of the brain, which was reported as normal and was put on two week course of oral prednisone, 60 mg daily, followed by 20 mg daily for the past three months and has experienced partial improvement. She has put on more than 20 lbs and has recently been found out to have type II diabetes. She was never seen by a neurologist but has been seeing a psychologist for marital problems, and at the suggestion of her psychologist she comes to you for assessment and appropriate diagnostic and therapeutic management.

- a. Provide for a brief critical review of the case.
- b. How would you have handled this case?
- c. How are you going to manage it now?

