MULTIPLE SCLEROSIS (MS)

Multiple sclerosis is characterized by disseminated patches of demyelination in the brain and spinal cord. Common symptoms include visual and oculomotor abnormalities, paresthesias, weakness, spasticity, urinary dysfunction, and mild cognitive impairment. Typically, neurologic deficits are multiple, with remissions and exacerbations gradually producing disability. Diagnosis is by history of remissions and exacerbations plus clinical signs, test results, lesions seen on MRI, or other criteria (depending on symptoms) to objectively demonstrate ≥ 2 separate neurologic abnormalities. Treatment includes corticosteroids for acute exacerbations, immunomodulatory drugs to prevent exacerbations, and supportive measures.

Multiple sclerosis (MS) is believed to involve an immunologic mechanism. One postulated cause is infection by a latent virus (possibly a human herpesvirus such as Epstein-Barr virus), which, when activated, triggers a secondary immune response. An increased incidence among certain families and presence of human leukocyte antigen (HLA) allotypes (HLA-DR2) suggests genetic susceptibility. MS is more common among people who spend their first 15 yr of life in temperate climates (1/2000) than in those who spend them in the tropics (1/10,000). One explanation is that lower levels of vitamin D are associated with an increased risk of MS, and vitamin D levels correlate with the degree of sun exposure, which is lower in temperate climates. Cigarette smoking also appears to increase risk. Age at onset ranges from 15 to 60 yr, typically 20 to 40 yr; women are affected somewhat more often.

Neuromyelitis optica (Devic disease), previously considered a variant of MS, is now recognized as a separate disorder.

Pathophysiology

Localized areas of demyelination (plaques) occur, with destruction of oligodendroglia, perivascular inflammation, and chemical changes in lipid and protein constituents of myelin in and around the plaques. Axonal damage is possible, but cell bodies and axons tend to be relatively preserved. Fibrous gliosis develops in plaques that are disseminated throughout the CNS, primarily in white matter, particularly in the lateral and posterior columns (especially in the cervical regions), optic nerves, and periventricular areas. Tracts in the midbrain, pons, and cerebellum are also affected. Gray matter in the cerebrum and spinal cord can be affected but to a much lesser degree.

Symptoms and Signs

MS is characterized by varied CNS deficits, with remissions and recurring exacerbations. Exacerbations average about 3/yr, but frequency varies greatly. Although multiple sclerosis may progress and regress unpredictably, there are typical patterns of progression:

- Relapsing-remitting pattern: Exacerbations alternate with remissions, when partial or full recovery occurs or symptoms are stable. Remissions may last months or years. Exacerbations can occur spontaneously or can be triggered by an infection such as influenza.
- Primary progressive pattern: The disease progresses gradually with no remissions, although there may be temporary plateaus during which the disease does not progress. Unlike in the relapsing-remitting pattern, there are no clear exacerbations.
- Secondary progressive pattern: This pattern begins with relapses alternating with remissions, followed by gradual progression of the disease.
- Progressive relapsing pattern: The disease progresses gradually, but progression is interrupted by sudden, clear relapses. This pattern is rare.

The most common initial symptoms are the following:

- Paresthesias in one or more extremities, in the trunk, or on one side of the face
- Weakness or clumsiness of a leg or hand
- Visual disturbances (eg, partial loss of vision and pain in one eye due to retrobulbar optic neuritis, diplopia due to ocular palsy, scotomas)

Other common early symptoms include slight stiffness or unusual fatigability of a limb, minor gait disturbances, difficulty with bladder control, vertigo, and mild affective disturbances; all usually indicate scattered CNS involvement and may be subtle. Excess heat (eg, warm weather, a hot bath, fever) may temporarily exacerbate symptoms and signs.

Mild cognitive impairment is common. Apathy, poor judgment, or inattention may occur. Affective disturbances, including emotional lability, euphoria, or, most commonly, depression, are common. Depression may be reactive or partly due to cerebral lesions of MS. A few patients have seizures.

Cranial nerves

Unilateral or asymmetric optic neuritis and bilateral internuclear ophthalmoplegia are typical. Optic neuritis causes loss of vision (ranging from scotomas to blindness), eye pain, and sometimes abnormal visual fields, a swollen optic disk, or a partial or complete afferent pupillary defect.

Internuclear ophthalmoplegia results if there is a lesion in the medial longitudinal fasciculus connecting the 3rd, 4th, and 6th nerve nuclei. During horizontal gaze, adduction of one eye is decreased, with nystagmus of the other (abducting) eye; convergence is intact.

Rapid, small-amplitude eye oscillations in straight-ahead (primary) gaze (pendular nystagmus) are uncommon but characteristic of MS. Vertigo is common. Intermittent unilateral facial numbness or pain (resembling trigeminal neuralgia), palsy, or spasm may occur. Mild dysarthria may occur, caused by bulbar weakness, cerebellar damage, or disturbance of cortical control. Other cranial nerve deficits are unusual but may occur secondary to brain stem injury.

Motor

Weakness is common. It usually reflects corticospinal tract damage in the spinal cord, affects the lower extremities preferentially, and is bilateral and spastic. Deep tendon reflexes (eg, knee and ankle jerks) are usually increased, and an extensor plantar response (Babinski's sign) and clonus are often present. Spastic paraparesis produces a stiff, imbalanced gait; in advanced cases, it may confine patients to a wheelchair. Painful flexor spasms in response to sensory stimuli (eg, bedclothes) may occur late. Cerebral or cervical spinal cord lesions may result in hemiparesis, which sometimes is the presenting symptom.

Cerebellar

In advanced MS, cerebellar ataxia plus spasticity may be severely disabling; other cerebellar manifestations include slurred speech, scanning speech (slow enunciation with a tendency to hesitate at the beginning of a word or syllable), and Charcot's triad (intention tremor, scanning speech, and nystagmus).

Sensory

Paresthesias and partial loss of any type of sensation are common and often localized (eg, to one or both hands or legs). Various painful sensory disturbances (eg, burning or electric shocklike pains) can occur spontaneously or in response to touch, especially if the spinal cord is affected.

An example is Lhermitte's sign, an electric shocklike pain that radiates down the spine or into the legs when the neck is flexed. Objective sensory changes tend to be transient and difficult to demonstrate.

Spinal cord

Involvement commonly causes bladder dysfunction (eg, urinary urgency or hesitancy, partial retention of urine, mild urinary incontinence). Constipation, erectile dysfunction in men, and genital anesthesia in women may occur. Frank urinary and fecal incontinence may occur in advanced MS.

Progressive myelopathy, a variant of MS, causes spinal cord motor weakness but no other deficits.

Diagnosis

- Clinical criteria
- Brain and spinal MRI
- Sometimes CSF IgG levels and evoked potentials

MS is suspected in patients with optic neuritis, internuclear ophthalmoplegia, or other symptoms that suggest MS, particularly if deficits are multifocal or intermittent. Most diagnostic criteria for MS require a history of exacerbations and remissions plus objective demonstration by examination or testing of ≥ 2 separate neurologic abnormalities. Brain and spinal MRI is done. MRI plus clinical findings may be diagnostic, but if they are inconclusive, additional testing may be necessary to objectively demonstrate separate neurologic abnormalities. Such testing usually begins with CSF analysis and, if necessary, includes evoked potentials.

MRI is the most sensitive imaging test for MS and can exclude other treatable disorders that may mimic MS, such as nondemyelinating lesions at the junction of the spinal cord and medulla (eg, subarachnoid cyst, foramen magnum tumors). Gadolinium-contrast enhancement can distinguish actively inflamed from older plaques. Alternatively, contrast-enhanced CT can be done. The sensitivity of MRI and CT is increased by giving twice the dose of contrast agent (which is standard practice) and delaying scanning (double-dose delayed scanning).

CSF examination, including opening pressure, cell count and differential, protein, glucose, Ig, oligoclonal bands, and usually myelin basic protein and albumin, is done. IgG is usually increased as a percentage of CSF components, such as protein (normally < 11%) or CSF albumin (normally < 27%). IgG levels correlate with disease severity. Oligoclonal bands can usually be detected by agarose electrophoresis of CSF. Myelin basic protein may be elevated during active demyelination. CSF lymphocyte count and protein content may be slightly increased.

Other tests include evoked potentials, which are often more sensitive for MS than symptoms or signs. Visual evoked responses are sensitive and particularly helpful in patients with no confirmed cranial lesions (eg, those with lesions only in the spinal cord). Somatosensory evoked potentials and brain stem auditory evoked potentials are sometimes also measured. Sometimes systemic disorders (eg, SLE) and infections (eg, Lyme disease) can mimic MS and should be excluded with specific blood tests. Blood tests to measure an IgG antibody specific for neuromyelitis optica (NMO-IgG) may be done to differentiate that disorder from MS.

Prognosis

The course is highly varied and unpredictable. In most patients, especially when MS begins with optic neuritis, remissions can last months to > 10 yr. However, some patients, particularly men with onset in middle age, have frequent exacerbations and are rapidly incapacitated. Cigarette smoking may accelerate the course. Life span is shortened only in very severe cases.

Treatment

- Corticosteroids for acute exacerbations
- Immunomodulators to prevent exacerbations

- Baclofen or tizanidine for spasticity
- Gabapentin or tricyclic antidepressants for pain
- Supportive care

Goals include shortening acute exacerbations, decreasing frequency of exacerbations, and relieving symptoms; maintaining the patient's ability to walk is particularly important.

Acute exacerbations that cause objective deficits sufficient to impair function (eg, loss of vision, strength, or coordination) are treated with brief courses of corticosteroids (eg, prednisone 60 to 100 mg po once/day tapered over 2 to 3 wk, methylprednisolone 500 to 1000 mg IV once/day for 3 to 5 days). Some evidence indicates that IV corticosteroids shorten acute exacerbations, slow progression, and improve MRI measures of disease. Immunomodulatory therapy, such as interferons (IFNs) or glatiramer, decreases the frequency of acute exacerbations and delays eventual disability. Typical regimens include IFN-β1b 8 million IU sc every other day, IFN-β1a 6 million IU (30 μg) IM weekly, and IFN-β1a 44 μg sc 3 times weekly. Common adverse effects of IFNs include flu-like symptoms and depression (which tend to decrease over time), development of neutralizing antibodies after months of therapy, and cytopenias. Glatiramer acetate 20 mg sc once/day may be used.

The immunosuppressant mitoxantrone, 12 mg/m^2 q 3 mo for 24 mo, may be helpful, particularly for progressive MS that is refractory to other treatments. Natalizumab, an anti-α_4 integrin antibody, inhibits passage of leukocytes across the blood-brain barrier; given as a monthly infusion, it reduces number of exacerbations and new brain lesions but may increase the risk of progressive multifocal leukoencephalopathy. If immunomodulatory drugs are ineffective, monthly IV immune globulin may help.

Immunosuppressants other than mitoxantrone (eg, methotrexate, azathioprine, mycophenolate, cyclophosphamide, cladribine) have been used for more severe, progressive MS but are controversial. Plasma exchange and hematopoietic stem cell transplantation may be somewhat useful for severe, intractable disease.

Other treatments can be used to control specific symptoms:

- Spasticity is treated with escalating doses of baclofen 10 to 20 mg po tid to qid or tizanidine 4 to 8 mg po tid. Gait training and range-of-motion exercises can help weak, spastic limbs.
- Painful paresthesias are usually treated with gabapentin 100 to 600 mg po tid; alternatives include tricyclic antidepressants (eg, amitriptyline 25 to 75 mg po at bedtime, desipramine 25 to 100 mg po at bedtime if amitriptyline has intolerable anticholinergic effects), carbamazepine 200 mg po tid, and opioids.
- Depression is treated with counseling and antidepressants.
- Bladder dysfunction is treated based on its underlying mechanism.
- Fatigue can be treated with amantadine 100 mg po tid or modafinil 100 to 300 mg po once/day.

Encouragement and reassurance help. Regular exercise (eg, stationary biking, treadmill, swimming, stretching) is recommended, even for patients with advanced MS, because it conditions the heart and muscles, reduces spasticity, prevents contractures, and has psychologic benefits. Vitamin D supplements (800 to 1000 units daily) may decrease the risk of disease progression. Vitamin D also reduces the risk of osteoporosis, particularly in patients at increased risk because mobility is decreased or they take corticosteroids. Patients should maintain as normal and active a life as possible but should avoid overwork, fatigue, and exposure to excess heat. Cigarette smoking should be stopped. Vaccination does not appear to increase risk of exacerbations. Debilitated patients require measures to prevent pressure ulcers and UTIs; intermittent urinary self-catheterization may be necessary.

SYRINGOMYELIA (SYRINX)

A syrinx is a fluid-filled cavity within the spinal cord (syringomyelia) or brain stem (syringobulbia). Predisposing factors include craniocervical junction abnormalities, spinal cord trauma, and spinal cord tumors. Symptoms include flaccid weakness of the hands and arms and deficits in pain and temperature sensation in a capelike distribution over the back and neck; light touch and position and vibration sensation are not affected. Diagnosis is by MRI. Treatment includes correction of the cause and surgical procedures to drain the syrinx or otherwise open CSF flow.

Syrinxes usually result from lesions that partially obstruct CSF flow. At least $^1/_2$ of syrinxes occur in patients with congenital abnormalities of the craniocervical junction (eg, herniation of cerebellar tissue into the spinal canal, called Chiari malformation), brain (eg, encephalocele), or spinal cord (eg, myelomeningocele). For unknown reasons, these congenital abnormalities often expand during the teen or young adult years. A syrinx can also develop in patients who have a spinal cord tumor, scarring due to previous spinal trauma, or no known predisposing factors. About 30% of people with a spinal cord tumor eventually develop a syrinx.

Syringomyelia is a paramedian, usually irregular, longitudinal cavity. It commonly begins in the cervical area but may extend downward along the entire length of the spinal cord. Syringobulbia, which is rare, usually occurs as a slitlike gap within the lower brain stem and may disrupt or compress the lower cranial nerves or ascending sensory or descending motor pathways.

Symptoms and Signs

Symptoms usually begin insidiously between adolescence and age 45. Syringomyelia develops in the center of the spinal cord, causing a central cord syndrome. Pain and temperature sensory deficits occur early but may not be recognized for years. The first abnormality recognized may be a painless burn or cut. Syringomyelia typically causes weakness, atrophy, and often fasciculations and hyporeflexia of the hands and arms; a deficit in pain and temperature sensation in a capelike distribution over the shoulders, arms and back is characteristic. Light touch and position and vibration sensation are not affected. Later, spastic leg weakness develops. Deficits may be asymmetric.

Syringobulbia may cause vertigo, nystagmus, unilateral or bilateral loss of facial sensation, lingual atrophy and weakness, dysarthria, dysphagia, hoarseness, and sometimes peripheral sensory or motor deficits due to medullary compression.

Diagnosis and Treatment

A syrinx is suggested by an unexplained central cord syndrome or other characteristic neurologic deficits, particularly pain and temperature sensory deficits in a capelike distribution. MRI of the entire spinal cord and brain is done. Gadolinium enhancement is useful for detecting any associated tumor.

Underlying problems (eg, craniocervical junction abnormalities, postoperative scarring, spinal tumors) are corrected when possible. Surgical decompression of the foramen magnum and upper cervical cord is the only useful treatment, but surgery usually cannot reverse severe neurologic deterioration.

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

ALS (Lou Gehrig disease, Charcot's syndrome) is the most common MND. Patients present with random, asymmetric symptoms, consisting of cramps, weakness, and muscle atrophy of the hands (most commonly) or feet. Fasciculations, spasticity, hyperactive deep tendon reflexes, extensor plantar reflexes, clumsiness, stiffness of movement, weight loss, fatigue, and difficulty controlling facial expression and tongue movements soon follow. Other symptoms include hoarseness, dysphagia, slurred speech, and a tendency to choke on liquids. Late in the disorder, inappropriate, involuntary, and uncontrollable excesses of laughter or crying (pseudobulbar affect) occur. Sensory systems,

consciousness, cognition, voluntary eye movements, sexual function, and urinary and anal sphincters are usually spared. Death is usually caused by failure of the respiratory muscles; 50% of patients die within 3 yr of onset, 20% live 5 yr, and 10% live 10 yr. Survival > 30 yr is rare.

Progressive bulbar palsy

The muscles innervated by cranial nerves and corticobulbar tracts are predominantly affected, causing progressive difficulty with chewing, swallowing, and talking; nasal voice; reduced gag reflex; fasciculations and weak movement of the facial muscles and tongue; and weak palatal movement. A pseudobulbar affect, with emotional lability, may occur if the corticobulbar tract is affected. Patients with dysphagia have a very poor prognosis; respiratory complications due to aspiration frequently result in death within 1 to 3 yr.

Primary lateral sclerosis and progressive pseudobulbar palsy

Muscle stiffness and signs of distal motor weakness gradually increase, affecting the limbs in primary lateral sclerosis and the lower cranial nerves in progressive pseudobulbar palsy. Fasciculations and muscle atrophy may follow many years later. These disorders usually take several years to produce total disability.

Diagnosis

Diagnosis is suggested by progressive, generalized motor weakness without significant sensory abnormalities. Other neurologic disorders that cause pure muscle weakness include disorders of neuromuscular transmission and various myopathies. Acquired causes of pure motor weakness include noninflammatory myopathies, polymyositis, dermatomyositis, thyroid and adrenal disorders, electrolyte abnormalities (hypokalemia, hypercalcemia, hypophosphatemia), and various infections (eg, syphilis, Lyme disease, hepatitis C).

When cranial nerves are affected, a secondary treatable cause is less likely. Upper and lower motor neuron signs plus weakness in facial muscles strongly suggest ALS.

Electrodiagnostic tests should be done to check for evidence of disorders of neuromuscular transmission or demyelination. Such evidence is not present in MNDs; nerve conduction velocities are usually normal until late in the disease process. Needle electromyography (EMG) is the most useful test, showing fibrillations, positive waves, fasciculations, and sometimes giant motor units, even in unaffected limbs.

Brain MRI is required. MRI of the cervical spine is indicated when there is no clinical or EMG evidence of cranial nerve motor weakness.

Laboratory tests are done to identify treatable disorders. Tests include CBC, electrolytes, creatine phosphokinase, thyroid tests, serum and urine protein electrophoresis with immunofixation for monoclonal antibodies, anti-myelin-associated glycoprotein (MAG) antibodies, and a 24-h urine collection to check for heavy metals in patients who may have been exposed to them. A lumbar puncture should be done; elevated WBCs or protein levels strongly suggest an alternative diagnosis.

Serum Venereal Disease Research Laboratories (VDRL) tests, ESR, and measurement of certain antibodies (rheumatoid factor, Lyme titer, HIV, hepatitis C virus, antinuclear [ANA], anti-Hu paraneoplastic) are indicated only if suggested by risk factors or history. Genetic testing (eg, superoxide dismutase gene mutation) and enzyme measurements (eg, hexosaminidase A) should not be done unless patients are interested in genetic counseling; disorders detected by these tests have no known treatment.

Treatment

There is no specific treatment. However, an antiglutamate drug, riluzole 50 mg po bid, prolongs life in patients with bulbar-variant ALS. A multidisciplinary team approach helps patients cope with progressive neurologic disability. Physical therapy may help maintain muscle function. Occupational therapists can recommend adaptive braces and walking devices to help with activities of daily living. Speech and language therapists may provide alternative communication devices. Patients with pharyngeal weakness should be fed with extreme care and may require percutaneous endoscopic gastrostomy. Pulmonary specialists are crucial as respiratory weakness develops; they may recommend noninvasive respiratory support (eg, bilevel positive airway pressure) or tracheostomy and full ventilatory support.

Baclofen may help reduce spasticity; quinine or phenytoin may help decrease cramps. A strong anticholinergic drug (eg, glycopyrrolate, amitriptyline, benztropine, trihexyphenidyl, transdermal hyoscine, atropine) may be used to decrease saliva production. Amitriptyline and fluvoxamine are options for managing pseudobulbar affect. Pain in late stages of these disorders may require opioids and benzodiazepines. Surgery to improve swallowing has had limited success in patients with progressive bulbar palsy.

Early in the disorder, health care practitioners must talk frankly with patients, family members, and caregivers to determine the level of intervention acceptable. These decisions should be reviewed and confirmed at various stages of the disorder.