Evidence supports a role of one, or more likely several, of the following mechanisms in progressive MS. Axonal and neuronal death may result from glutamate-mediated excitotoxicity, oxidative injury, iron accumulation, and/or mitochondrial failure either occurring as a consequence of free-radical damage or due to accumulation of deletions in mitochondrial DNA.

## CLINICAL MANIFESTATIONS

The onset of MS may be abrupt or insidious. Symptoms may be severe or seem so trivial that a patient may not seek medical attention for months or years. Indeed, at autopsy, approximately 0.1% of individuals who were asymptomatic during life will be found, unexpectedly, to have pathologic evidence of MS. Similarly, in the modern era, an MRI scan obtained for an unrelated reason may show evidence of asymptomatic MS. Symptoms of MS are extremely varied and depend on the location and severity of lesions within the CNS **(Table 458-2)**. Examination often reveals evidence of neurologic dysfunction, often in asymptomatic locations. For example, a patient may present with symptoms in one leg but signs in both.

*Weakness of the limbs* may manifest as loss of strength, speed, or dexterity, as fatigue, or as a disturbance of gait. Exercise-induced weakness is a characteristic symptom of MS. The weakness is of the upper motor neuron type **(Chap. 30)** and is usually accompanied by other pyramidal signs such as spasticity, hyperreflexia, and Babinski signs. Occasionally a tendon reflex may be lost (simulating a lower motor neuron lesion) if an MS lesion disrupts the afferent reflex fibers in the spinal cord **(see Fig. 30-2)**.

*Spasticity* **(Chap. 30)** is commonly associated with spontaneous and movement-induced muscle spasms. More than 30% of MS patients have moderate to severe spasticity, especially in the legs. This is often accompanied by painful spasms interfering with ambulation, work, or self-care. Occasionally spasticity provides support for the body weight during ambulation, and in these cases, treatment of spasticity may actually do more harm than good.

*Optic neuritis* (ON) presents as diminished visual acuity, dimness, or decreased color perception (desaturation) in the central field of vision. These symptoms can be mild or may progress to severe visual loss. Rarely, there is complete loss of light perception. Visual symptoms are generally monocular but may be bilateral. Periorbital pain (aggravated by eye movement) often precedes or accompanies the visual loss. An afferent pupillary defect **(Chap. 39)** is usually present. Funduscopic examination may be normal or reveal optic disc swelling (papillitis). Pallor of the optic disc (optic atrophy) commonly follows ON. Uveitis is uncommon and should raise the possibility of alternative diagnoses such as sarcoid or lymphoma.

*Visual blurring* in MS may result from ON or diplopia (double vision); if the symptom resolves when either eye is covered, the cause is diplopia.

*Diplopia* may result from internuclear ophthalmoplegia (INO) or from palsy of the sixth cranial nerve (rarely the third or fourth). An INO consists of impaired adduction of one eye due to a lesion in the ipsilateral medial longitudinal fasciculus **(Chaps. 41e and 42)**.

**TABLE 458-2 INITIAL SYMPTOMS OF MS**

| Symptom | Percentage of Cases | Symptom | Percentage of Cases |
|---|---|---|---|
| Sensory loss | 37 | Lhermitte | 3 |
| Optic neuritis | 36 | Pain | 3 |
| Weakness | 35 | Dementia | 2 |
| Paresthesias | 24 | Visual loss | 2 |
| Diplopia | 15 | Facial palsy | 1 |
| Ataxia | 11 | Impotence | 1 |
| Vertigo | 6 | Myokymia | 1 |
| Paroxysmal attacks | 4 | Epilepsy | 1 |
| Bladder | 4 | Falling | 1 |

***Source:*** After WB Matthews et al: *McAlpine's Multiple Sclerosis.* New York, Churchill Livingstone, 1991.

Prominent nystagmus is often observed in the abducting eye, along with a small skew deviation. A bilateral INO is particularly suggestive of MS. Other common gaze disturbances in MS include (1) a horizontal gaze palsy, (2) a "one and a half" syndrome (horizontal gaze palsy plus an INO), and (3) acquired pendular nystagmus.

*Sensory symptoms* are varied and include both paresthesias (e.g., tingling, prickling sensations, formications, "pins and needles," or painful burning) and hypesthesia (e.g., reduced sensation, numbness, or a "dead" feeling). Unpleasant sensations (e.g., feelings that body parts are swollen, wet, raw, or tightly wrapped) are also common. Sensory impairment of the trunk and legs below a horizontal line on the torso (a sensory level) indicates that the spinal cord is the origin of the sensory disturbance. It is often accompanied by a bandlike sensation of tightness around the torso. Pain is a common symptom of MS, experienced by >50% of patients. Pain can occur anywhere on the body and can change locations over time.

*Ataxia* usually manifests as cerebellar tremors **(Chap. 450)**. Ataxia may also involve the head and trunk or the voice, producing a characteristic cerebellar dysarthria (scanning speech).

*Bladder dysfunction* is present in >90% of MS patients, and in a third of patients, dysfunction results in weekly or more frequent episodes of incontinence. During normal reflex voiding, relaxation of the bladder sphincter (α-adrenergic innervation) is coordinated with contraction of the detrusor muscle in the bladder wall (muscarinic cholinergic innervation). *Detrusor hyperreflexia*, due to impairment of suprasegmental inhibition, causes urinary frequency, urgency, nocturia, and uncontrolled bladder emptying. *Detrusor sphincter dyssynergia*, due to loss of synchronization between detrusor and sphincter muscles, causes difficulty in initiating and/or stopping the urinary stream, producing hesitancy, urinary retention, overflow incontinence, and recurrent infection.

*Constipation* occurs in >30% of patients. Fecal urgency or *bowel incontinence* is less common (<15%) but can be socially debilitating.

*Cognitive dysfunction* can include memory loss; impaired attention; difficulties in executive functioning, memory, and problem solving; slowed information processing; and problems shifting between cognitive tasks. Euphoria (elevated mood) was once thought to be characteristic of MS but is actually uncommon, occurring in <20% of patients. Cognitive dysfunction sufficient to impair activities of daily living is rare.

*Depression*, experienced by approximately half of patients, can be reactive, endogenous, or part of the illness itself and can contribute to fatigue.

*Fatigue* **(Chap. 29)** is experienced by 90% of patients; this symptom is the most common reason for work-related disability in MS. Fatigue can be exacerbated by elevated temperatures, depression, expending exceptional effort to accomplish basic activities of daily living, or sleep disturbances (e.g., from frequent nocturnal awakenings to urinate).

*Sexual dysfunction* may manifest as decreased libido, impaired genital sensation, impotence in men, and diminished vaginal lubrication or adductor spasms in women.

*Facial weakness* due to a lesion in the pons may resemble idiopathic Bell's palsy **(Chap. 455)**. Unlike Bell's palsy, facial weakness in MS is usually not associated with ipsilateral loss of taste sensation or retroauricular pain.

*Vertigo* may appear suddenly from a brainstem lesion, superficially resembling acute labyrinthitis **(Chap. 28)**. *Hearing loss* **(Chap. 43)** may also occur in MS but is uncommon.

**Ancillary Symptoms** *Heat sensitivity* refers to neurologic symptoms produced by an elevation of the body's core temperature. For example, unilateral visual blurring may occur during a hot shower or with physical exercise (*Uhthoff's symptom*). It is also common for MS symptoms to worsen transiently, sometimes dramatically, during febrile illnesses (see "Acute Attacks or Initial Demyelinating Episodes," below). Such heat-related symptoms probably result from transient conduction block (see above).

*Lhermitte's symptom* is an electric shock–like sensation (typically induced by flexion or other movements of the neck) that radiates down