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A variety of neurodegenerative pathologies are commonly found in the presence of CTE, adding to the complexity of diagnosis. Further more, the dynamic interplay between RHI and mTBI history is not well understood. While staging criteria for this neuropathologic entity have yet to be established, a consensus meeting to define the neuro pathologic criteria for CTE proposed an algorithm assessing CTE as “low” or “high” in severity. Overall, its contribution, if any, to late-life dementia and parkinsonism in former athletes, soldiers, or others who have sustained repeated concussive injuries is unknown. Research criteria for the clinical diagnosis of CTE have been pro posed. The criteria generally require substantial exposure to RHI, cog nitive impairment (primarily in the domains of episodic memory and executive function) and/or neurobehavioral dysregulation, progressive course, and the absence of an alternative explanation for symptoms. Multiple studies have suggested that these proposed criteria lack speci ficity (i.e., they are frequent in other conditions and non-CTE cases). As such, CTE remains a postmortem diagnosis. Investigations have not observed robust or consistent in vivo brain-related changes associated with years of contact sport/football exposure (a commonly used proxy measure for RHI) using advanced MRI, PET imaging, or blood-based biomarkers. For example, associa tions between years of participation and amyloid deposition or white matter hyperintensity volume have not been observed. Studies of brain morphometry (volumetric and structural changes) and tau deposition have been more variable, though evidence suggests that convention ally employed PET tracers and blood biomarkers may be limited in their specificity for CTE p-tau. Impairment of neuropsychological and neuropsychiatric function is most commonly observed in those with polypathology, particularly amyloid. Taken together, further study is required to better refine the clinical and postmortem diagnostic criteria of CTE, enhance clinicopathologic correlation, and ultimately improve patient care and management. CTE is also discussed in Chap. 435. ■ ■FURTHER READING Brett BL et al: Long-term multidomain patterns of change after trau matic brain injury: A TRACK-TBI LONG Study. Neurol 101:7, 2023. Johnson VE et al: Axonal pathology in traumatic brain injury. Exp Neurol 246:35, 2013. Kowalski R et al: Recovery of consciousness and functional outcome in moderate and severe traumatic brain injury. JAMA Neurol 78:548, 2021. McCrory P et al: Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016. Br J Sports Med 51:838, 2017. Mez J et al: Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. JAMA 318:360, 2017. Nelson L et al: Recovery after mild traumatic brain injury in patients presenting to US level I trauma centers: A Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study. JAMA Neurol 76:1049, 2019. Taylor CA et al: Traumatic brain injury-related emergency depart ment visits, hospitalizations, and deaths—United States, 2007 and 2013. MMWR Surveill Summ 66:1, 2017.

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Multiple Sclerosis Multiple sclerosis (MS) is an autoimmune disease of the central ner vous system (CNS) characterized by chronic inflammation, demyelin ation, gliosis (plaques or scarring), and neuronal loss; the course can be relapsing or progressive. MS plaques typically develop at different

times and in different CNS locations (i.e., MS is said to be disseminated in time and space). One million individuals in the United States, and millions worldwide, are affected. The clinical course is extremely vari able, ranging from a relatively benign condition to a rapidly evolving and incapacitating disease requiring profound lifestyle adjustments. The past decade has seen tremendous progress in understanding basic disease mechanisms underlying MS and in developing highly effec tive therapies especially for the relapsing form of the disease. These advances have dramatically improved the long-term outcome for patients.

■ ■CLINICAL MANIFESTATIONS Onset is typically between 20 and 40 years (slightly later in men than in women), but the disease can present across the lifespan. Women are affected approximately three times more often than men. Early symptoms may be severe or seem so trivial that a patient may not seek medical attention for months or years. On occasion, MS lesions are located exclusively in noneloquent regions of the nervous system, and in such instances, clinical manifestations can be largely or entirely absent. Autopsy series identified MS in some individuals (~0.1% of cases) who were seemingly asymptomatic during life, and magnetic resonance imaging (MRI) scans obtained for unrelated reasons also showed evidence of asymptomatic MS, an incidental finding termed a radiologically isolated syndrome (RIS; see below). CHAPTER 455 Multiple Sclerosis Specific symptoms of MS are varied and reflect the location and severity of lesions within the CNS (Table 455-1). Moreover, neuro logic examination often reveals unexpected findings in addition to the anticipated ones. For example, a patient may present with symptoms in one leg but signs in both. Sensory symptoms include both paresthesias (e.g., tingling, prickling sensations, “pins and needles,” formications, 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 site of the 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. 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) typically precedes or accompanies the visual loss. An afferent pupillary defect (Chap. 34) is usually present. Fundoscopic 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 sarcoidosis or lymphoma. TABLE 455-1 Initial Symptoms of Multiple Sclerosis (MS) PERCENTAGE OF CASES SYMPTOM PERCENTAGE OF CASES SYMPTOM Sensory loss

Lhermitte

Optic neuritis

Pain

Weakness

Dementia

Paresthesias

Visual loss

Diplopia

Facial palsy

Ataxia

Impotence

Vertigo

Myokymia

Paroxysmal attacks

Epilepsy

Bladder

Falling

Source: Data from RJ Swingler, DA Compston: The morbidity of multiple sclerosis. Q J Med 83:325, 1992.

Weakness of the limbs can 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. 26) and is usually accompanied by other pyramidal signs such as spasticity, hyperreflexia, and extensor plantar responses. Occasionally, a tendon reflex may be lost (simulating a peripheral nerve lesion) if an MS lesion disrupts the afferent reflex fibers in the spinal cord (see Fig. 26-2).

Facial weakness due to a lesion in the pons may resemble idiopathic Bell’s palsy (Chap. 452). Unlike Bell’s palsy, facial weakness in MS is usually not associated with ipsilateral loss of taste sensation or retro auricular pain. Spasticity (Chap. 26) is commonly associated with spontaneous and movement-induced muscle spasms, especially in the legs. This can be 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. PART 13 Neurologic Disorders 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 be caused by internuclear ophthalmoplegia (INO) or 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. 34 and V3). 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 horizon tal gaze palsy, (2) a "one and a half" syndrome (horizontal gaze palsy plus an INO), and (3) acquired pendular nystagmus. Ataxia usually manifests as cerebellar tremors (Chap. 450). Ataxia may also involve the head and trunk or the voice, producing a charac teristic cerebellar dysarthria (scanning speech). Vertigo may appear suddenly from a brainstem lesion, superficially resembling acute labyrinthitis (Chap. 24). Hearing loss (Chap. 36) may also occur in MS but is uncommon. ■ ■ANCILLARY SYMPTOMS Paroxysmal symptoms are distinguished by their brief duration (10 s to 2 min), high frequency (5–40 episodes per day), lack of any altera tion of consciousness or change in background electroencephalogram during episodes, and a self-limited course (generally lasting weeks to months). They may be precipitated by hyperventilation or movement. Manifestations can include Lhermitte's symptom; tonic contractions of a limb, face, or trunk (tonic seizures); paroxysmal dysarthria and ataxia; paroxysmal sensory disturbances; and several other less wellcharacterized syndromes. Paroxysmal symptoms probably result from spontaneous discharges arising at the edges of demyelinated plaques and spreading to adjacent white matter tracts. Lhermitte's symptom is an electric shock–like sensation (typically induced by flexion or other movements of the neck) that radiates down the back into the legs. Rarely, it radiates into the arms. It is generally selflimited but may persist for years. Lhermitte's symptom can also occur with other disorders of the cervical spinal cord (e.g., cervical spondylosis). Trigeminal neuralgia, hemifacial spasm, and glossopharyngeal neural gia (Chap. 452) can occur when the demyelinating lesion involves the root entry (or exit) zone of the fifth, seventh, and ninth cranial nerve, respectively. Trigeminal neuralgia (tic douloureux) is a very brief lanci nating facial pain often triggered by an afferent input from the face or teeth. Most cases of trigeminal neuralgia are not MS related; however, atypical features such as onset before age 50 years, bilateral symptoms, objective sensory loss, or nonparoxysmal pain should raise the pos sibility that MS could be responsible. Facial myokymia consists of either persistent rapid flickering con tractions of the facial musculature (especially the lower portion of the orbicularis oculus) or a contraction that slowly spreads across the face. It results from lesions of the corticobulbar tracts or brainstem course of the facial nerve. 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. Such heatrelated symptoms probably result from transient conduction block. Bladder dysfunction is ultimately present in most MS patients. 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 innerva tion). Detrusor hyperreflexia, due to impairment of suprasegmental inhibition, causes urinary frequency, urgency, nocturia, and uncon trolled 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 some patients, especially with advanced disease. Fecal urgency or bowel incontinence is less

common than urinary symptoms but can be socially debilitating. Sexual dysfunction may manifest as decreased libido, impaired geni tal sensation, impotence in men, and diminished vaginal lubrication or adductor spasms in women. Cognitive dysfunction is often mild when present, but 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) or emotional lability (pseudobulbar palsy) was once thought to be characteristic of MS but is actually relatively uncommon. 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. 25) is experienced by most MS patients and 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). DISEASE COURSE In the traditional model of MS, the disease was considered to have three principal clinical forms, designated relapsing-remitting, second ary progressive, and primary progressive. Relapses were thought to be caused by inflammation, while progression was the consequence of neurodegeneration. More recently, these categories were supplanted by a unitary view of the disease, in which inflammation and neurode generation are present in most patients throughout the disease course. The concept that all MS is a single disease is also supported by findings from genetics, epidemiology, immunology, and pathology. Nonethe less, from a clinical perspective, it is still often useful to apply the clas sical subtype scheme to assessment and management of patients.

1. Relapsing-remitting or bout onset MS (RRMS) accounts for 90% of MS cases and is characterized by discrete attacks of neurologic dys function that generally evolve over days to weeks (rarely over hours). In early MS, there is often substantial or complete recovery over the ensuing weeks to months. However, as attacks continue, recovery may be less evident. Between attacks, patients were earlier thought to be neurologically stable; however, it is now clear that most if not all patients with RRMS experience subtle “silent” progression even when relapse-free (Fig. 455-1). The category relapsing MS (RMS) is used to identify all relapsing patients, both RRMS as well as second ary progressive patients who continue to experience attacks.
2. Secondary progressive MS (SPMS) always begins as RRMS. At some point, however, the clinical course changes so that the patient expe riences progressive deterioration in function unassociated with acute attacks. SPMS produces a greater amount of fixed neurologic disability than RRMS. A practical definition for SPMS is a patient who has developed some level of permanent walking disability not due exclusively to relapses. The Extended Disability Status Score (EDSS) is a widely used measure of neurologic impairment in MS

RELAPSING PHASE PREMONITORY PHASE PROGRESSIVE PHASE RIS CIS Relapsing MS Progressive MS NATURAL HISTORY/TRADITIONAL VIEW

EDSS

Relapses MRI Activity –5 –2 Onset

Time (years) A PREMONITORY PHASE Neuroinflammation CURRENT TREATMENT ERA/MODERN VIEW

START HIGH-EFFICACY TREATMENT

EDSS

Relapses MRI Activity –5 –2 Onset

Time (years) B FIGURE 455-1 The clinical course of multiple sclerosis (MS) in the current treatment era. The top half of the figure illustrates the traditional view of the natural history of relapse-onset MS in the pretreatment era. During the relapsing phase, disability accumulation was thought to result from incomplete recovery from relapses, until relapseindependent disability, designated SPMS, supervened. In the bottom half of the figure, the “new” natural history of MS in the current treatment era is shown. With use of highly effective therapies, attacks are abolished in most patients, but insidious progression independent of relapse activity, termed “silent progression,” is now evident during the relapsing phase. CIS, clinically isolated syndrome; EDSS, Extended Disability Status Score; MRI, magnetic resonance imaging; RIS, radiologically isolated syndrome; SPMS, secondary progressive multiple sclerosis. (Table 455-2); an EDSS of 4 or greater, plus a Functional Status Scale (FSS) motor system score of 2 or greater, can support a diagnosis of SPMS. For a patient with RRMS, in the pretreatment era, the risk of developing SPMS was ~3% each year, meaning that the great major ity of RRMS would ultimately evolve into SPMS. However, more recent case series have indicated a much lower rate of evolution to SPMS, estimated at <1% each year, likely due to widespread use of increasingly effective therapies for MS. 3. Primary progressive MS (PPMS) accounts for ~10% of cases. These patients do not experience attacks but rather steadily decline in function from disease onset. Compared to RRMS, the sex distribu tion is more even, the disease begins later in life (mean age ~40 years), and disability develops faster relative to the onset of the first clinical symptom. As noted above, despite these differences PPMS appears

Neuroinflammation Neurodegeneration CHAPTER 455 Multiple Sclerosis MS DISEASE CONTINUUM Neurodegeneration NATURAL HISTORY “Silent Progression” Progression Independent of Relapse Activity (PIRA) OBSERVED COURSE EXPECTED COURSE to represent the same underlying illness as RRMS and SPMS, and some PPMS patients experience relapses over the course of their ill ness. The term active progressive MS is used to categorize progressive MS patients (both SPMS and PPMS) who experience relapses or are found to have new lesions on serial MRI scans. Disability in MS is thought to accumulate as either a consequence of limited recovery following an acute relapse, a process also known as relapse associated worsening (RAW), or from presumed underlying neurodegeneration in the absence of clinical relapse, a process termed progression independent of relapsing activity (PIRA). Although RAW was once thought to be the primary driver of disability accumulation in RRMS, it is now clear that PIRA is the cause of disability accumula tion in RRMS, SPMS, and PPMS. That PIRA events can occur “silently,”

TABLE 455-2 Scoring Systems for Multiple Sclerosis (MS) Expanded Disability Status Scale (EDSS) 0.0 = Normal neurologic examination (all grade 0 in functional status [FS]) 1.0 = No disability, minimal signs in one FS (i.e., grade 1) 1.5 = No disability, minimal signs in more than one FS (more than one grade 1) 2.0 = Minimal disability in one FS (one FS grade 2, others 0 or 1) 2.5 = Minimal disability in two FS (two FS grade 2, others 0 or 1) 3.0 = Moderate disability in one FS (one FS

grade 3, others 0 or 1) or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) although fully ambulatory 3.5 = Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1) 4.0 = Ambulatory without aid or rest for ~500 m 4.5 = Ambulatory without aid or rest for ~300 m 5.0 = Ambulatory without aid or rest for ~200 m PART 13 Neurologic Disorders Functional Status (FS) Score A. Pyramidal functions 0 = Normal 1 = Abnormal signs without disability 2 = Minimal disability 3 = Mild or moderate paraparesis or hemiparesis, or severe monoparesis 4 = Marked paraparesis or hemiparesis, moderate quadriparesis, or monoplegia 5 = Paraplegia, hemiplegia, or marked quadriparesis 6 = Quadriplegia B. Cerebellar functions 0 = Normal 1 = Abnormal signs without disability 2 = Mild ataxia 3 = Moderate truncal or limb ataxia 4 = Severe ataxia all limbs 5 = Unable to perform coordinated movements due to ataxia C. Brainstem functions 0 = Normal 1 = Signs only 2 = Moderate nystagmus or other mild disability 3 = Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves 4 = Marked dysarthria or other marked disability 5 = Inability to swallow or speak D. Sensory functions 0 = Normal 1 = Vibration or figure-writing decrease only, in 1 or 2 limbs 2 = Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in 1 or 2 limbs, or vibratory decrease alone in 3 or 4 limbs 3 = Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in 1 or 2 limbs, or mild decrease in touch or pain, and/or moderate decrease in all proprioceptive tests in 3 or 4 limbs 4 = Marked decrease in touch or pain or loss of proprioception, alone or combined, in 1 or 2 limbs or moderate decrease in touch or pain and/or severe proprioceptive decrease in >2 limbs Source: Adapted from JF Kurtzke: Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 33:1444, 1983. meaning so insidiously that neither the patient nor the provider rec ognizes their occurrence at the time of gradual worsening, raises the important question as to whether there is a meaningful distinction between RRMS and SPMS. If any confirmed PIRA event is considered to be indicative of SPMS, then the SPMS onset begins much earlier in the disease course when patients still experience relapses but have only accumulated relative minor disability. ■ ■EPIDEMIOLOGY Geographic gradients are consistently observed in MS, with the highest prevalence generally found in temperate zones; in tropical regions, the

5.5 = Ambulatory without aid or rest for ~100 m 6.0 = Unilateral assistance required to walk about 100 m with or without resting 6.5 = Constant bilateral assistance required to walk about 20 m without resting 7.0 = Unable to walk beyond about 5 m even with aid; essentially restricted to wheelchair; wheels self and transfers alone 7.5 = Unable to take more than a few steps; restricted to wheelchair; may need aid to transfer 8.0 = Essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms 8.5 = Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions 9.0 = Helpless bed patient; can communicate and eat 9.5 = Totally helpless bed patient; unable to communicate or eat 10.0 = Death due to MS 5 = Loss (essentially) of sensation in 1 or 2 limbs or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head 6 = Sensation essentially lost below the head E. Bowel and bladder functions 0 = Normal 1 = Mild urinary hesitancy, urgency, or retention 2 = Moderate hesitancy, urgency, retention of bowel or bladder, or rare urinary incontinence 3 = Frequent urinary incontinence 4 = In need of almost constant catheterization 5 = Loss of bladder function 6 = Loss of bowel and bladder function F. Visual (or optic) functions 0 = Normal 1 = Scotoma with visual acuity (corrected) better than 20/30 2 = Worse eye with scotoma with

maximal visual acuity (corrected) of 20/30 to 20/59 3 = Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60 to 20/99 4 = Worse eye with marked decrease of fields and maximal acuity (corrected) of 20/100 to 20/200; grade 3 plus maximal acuity of better eye of 20/60 or less 5 = Worse eye with maximal visual acuity (corrected) <20/200; grade 4 plus maximal acuity of better eye of ≤20/60 6 = Grade 5 plus maximal visual acuity of better eye of ≤20/60 G. Cerebral (or mental) functions 0 = Normal 1 = Mood alteration only (does not affect EDSS score) 2 = Mild decrease in mentation 3 = Moderate decrease in mentation 4 = Marked decrease in mentation 5 = Chronic brain syndrome—severe or incompetent prevalence is often 10-fold to 20-fold less. In addition, a north-south gradient was observed in numerous national and regional studies, with decreasing rates as one moves equatorially. The prevalence of MS also increased steadily in several regions around the world over the past half-century, presumably reflecting the impact of some environmental shift, improved diagnosis, and/or a longer lifespan. Moreover, this increase appears to have occurred to a greater degree in women than men and in nonwhite populations. In the United States, there is a slightly higher prevalence in white compared with black individuals, with lower estimates in Hispanics, followed by Asians.

Multiple lines of evidence incriminate a role for infection with the Epstein-Barr virus (EBV) in MS. Individuals who have never been EBV infected (~5% of the population globally) have a very low MS risk, ~20-fold lower than in EBV-positive individuals, and a history of infectious mononucleosis (associated with initial exposure to EBV dur ing adolescence or later in life) increases risk more than twofold higher yet. Higher antibody titers to EBV nuclear antigens were repeatedly associated with MS risk, and studies from longitudinal biobank col lections showed that serologic conversion to EBV is a near-universal prerequisite for development of MS. Following primary EBV infection, a lifelong infection is established in most individuals, with latent EBV exclusively present in very small numbers (~1:10−6) of B lymphocytes. EBV-infected B cells were not consistently identified in the nervous system of MS patients. It is possible that ongoing lytic cycles by very few infected B cells residing within the CNS could produce bursts of inflammation and MS lesions; however, it is more likely that pathology could be triggered by B cell–mediated antigen presentation of EBV peptides that cross-react with MS autoantigens via molecular mimicry (see “Immunology,” below). A history of cigarette smoking is also associated with MS risk. Interestingly, in an animal model of MS, the lung was identified as a critical site for activation of pathogenic T lymphocytes responsible for autoimmune demyelination. Finally, vitamin D deficiency has been repeatedly associated with MS. Immunoregulatory effects of vitamin D could explain these appar ent relationships. Exposure of the skin to ultraviolet B (UVB) radiation from the sun is essential for the biosynthesis of vitamin D, and this endogenous production is the most important source of vitamin D in most individuals. A diet rich in fatty fish represents another source of vitamin D. At higher latitudes, the amount of UVB radiation reach ing the earth’s surface is often insufficient, particularly during winter months, and consequently, low serum levels of vitamin D are frequent in temperate zones. The common practice to avoid direct sun exposure and the widespread use of sunblock would be expected to exacerbate any population-wide vitamin D deficiency. GENETIC CONSIDERATIONS MS aggregates within some families, and adoption, half-sibling, twin, and spousal studies indicate that familial aggregation is primarily due to genetic factors. Importantly, family studies also support a contribution of environment, as fraternal twins of MS patients are at higher risk than nontwin siblings (Table 455-3). Susceptibility to MS is polygenic, with each gene contributing a rela tively small amount to overall risk. The strongest susceptibility signal genome-wide maps to the human

leukocyte antigen (HLA)-DRB1 gene in the class II region of the major histocompatibility complex (MHC) and specifically to HLA-DRB1*1501 (formerly designated DR2), and this association accounts for ~10% of the disease risk. This HLA asso ciation, first described in the early 1970s, suggests that MS, at its core, is an autoimmune disease. Whole-genome association studies have iden tified >230 other MS susceptibility variants, each of which individually has only a very small effect on MS risk. Many of these MS-associated genes have known roles in the adaptive and innate immune system, for example, the genes for the interleukin (IL) 7 receptor (CD127), IL-2 receptor (CD25), and T-cell costimulatory molecule LFA-3 (CD58); some variants also influence susceptibility to other autoimmune dis eases in addition to MS. The variants identified so far all lack specificity TABLE 455-3 Risk of Developing Multiple Sclerosis (MS) 1 in 3 If an identical twin has MS 1 in 15 If a fraternal twin has MS 1 in 25 If a sibling has MS 1 in 50 If a parent or half-sibling has MS 1 in 100 If a first cousin has MS 1 in 1000 If a spouse has MS 1 in 1000 If no one in the family has MS

and sensitivity for MS; thus, at present, they are not useful for diagnosis and have no meaningful effect on the clinical course of MS once it begins. For many years, identification of genes that influence disease expression was elusive, but recently, the first loci for MS severity were identified; unlike risk genes, these variants appear to operate in the nervous system rather than immune system, and one signal reaching genome-wide significance, located in the region of dysferlin and a zinc finger gene (ZNF638), confers a 7-year acceleration of progression to wheelchair-dependent status.

PATHOGENESIS ■ ■PATHOLOGY Demyelination New MS lesions begin with perivenular cuffing by inflammatory mononuclear cells, predominantly T cells and macro phages, which also infiltrate the surrounding white matter. At sites of inflammation, the blood-brain barrier (BBB) is disrupted, but unlike vasculitis, the vessel wall is preserved. At the leading edge of lesions, cytotoxic CD8 cells are found. Involvement of the humoral immune system is also evident; B lymphocytes infiltrate the nervous system, myelin-specific autoantibodies are present on degenerating myelin sheaths, and complement is activated. CHAPTER 455 Multiple Sclerosis Sharply demarcated areas of demyelination are the pathologic hallmark of MS lesions, and evidence of myelin degeneration is found at the earliest time points of tissue injury. Although relative sparing of axons is typical, partial or total axonal destruction can also occur, especially within highly inflammatory lesions. In some lesions, sur viving oligodendrocytes or those that differentiate from precursor cells partially remyelinate the surviving axons, producing so-called shadow plaques. However, in many lesions, oligodendrocyte precursor cells are present but fail to differentiate into mature myelin-producing cells. Therefore, promoting remyelination to protect axons remains an important therapeutic goal. As lesions evolve, there is prominent astro cytic proliferation (gliosis), and the term sclerosis refers to these gliotic plaques that have a rubbery or hardened texture at autopsy. Neurodegeneration Cumulative axonal and neuronal loss is the most important contributor to irreversible neurologic disability and progressive symptoms. With paraplegia due to MS, as many as 70% of axons are ultimately lost from the lateral corticospinal (e.g., motor) tracts. Demyelination can reduce trophic support for axons, redistrib ute ion channels, and destabilize action potential membrane potentials. Axons can adapt initially to these injuries, but over time, distal and retrograde degeneration (“dying-back” axonopathy) occurs. Multiple pathologies appear to contribute to progressive symptoms. Chronic active plaques are preexisting white matter lesions that show evidence of persistent inflammation, progressive axonal loss, and gradual concentric expansion, with large numbers of microglial cells at the leading edge of enlarging lesions without BBB disruption. Also

important is a primary injury to the cerebral cortex. Cortical plaques are frequent in MS but are generally not well visualized by MRI; these can extend upward from adjacent white matter lesions or may be located entirely within the cortex or underneath the pia. Ectopic lymphoid follicles are aggregates of B, T, and plasma cells located in the superficial meninges, especially overlying deep cortical sulci; similar clusters are also present in perivascular spaces. Ectopic lymphoid fol licles are associated with underlying demyelination and neuronal loss in the cerebral cortex, and diffusible factors from these lymphoid cells appear to mediate subpial cortical demyelination and neurodegenera tion. Cux2-positive neurons in layer 2 and 3 of the neocortex appear to be particularly vulnerable. Neuronal and axonal death may result from glutamate-mediated excitotoxicity, oxidative injury, iron accumulation, and/or mitochondrial failure. In relapsing MS, inflammation is characterized by focal perivenular infiltration of lymphocytes and monocytes, BBB disruption, and active demyelination. By contrast, inflammation in progressive MS is more diffuse, with widespread microglial proliferation across large areas of white matter, accompanied by infiltration of CD8 T cells and plasma blasts/plasma cells. Reduced myelin staining and axonal injury (“dirty

white matter”) are associated with these chronic pathologies. Astro gliosis has long been known to be a prominent feature of MS pathol ogy, and activated astrocytes likely contribute directly to neuronal and myelin injury (Chap. 435). Ongoing inflammation occurs behind an intact BBB in many patients with progressive MS, possibly accounting for the failure of immunotherapies not capable of crossing the BBB to benefit patients with progressive MS.

■ ■IMMUNOLOGY An autoimmune response directed against components of CNS myelin, and perhaps other neural elements as well, remains the cornerstone of current concepts of MS pathogenesis. However, specific antigenic targets in MS have never been conclusively identified. B Lymphocytes and Antibodies B cells are centrally involved in the development of demyelinating lesions, as evidenced by the efficacy of B cell–based treatments in all forms of MS (see “Treatment” below). Clonally restricted populations of activated, antigen-experienced, mem ory B cells and plasma cells are present in MS lesions, in meningeal lymphoid follicle-like structures overlying the cerebral cortex, and in cerebrospinal fluid (CSF). They produce the oligoclonal immunoglobu lins and increased antibody synthesis rates in the CSF long useful in the diagnosis of MS. Myelin-specific autoantibodies, some directed against an extracellular myelin protein, myelin oligodendrocyte glyco protein (MOG), have been detected bound to degenerating myelin in MS plaques. However, many more antibodies derived from these B cells appear to be directed against a diverse array of ubiquitous intracellular proteins seemingly unrelated to MS pathogenesis. Furthermore, the specific targets are different in each patient. Therefore, although these highly restricted CNS antibodies are characteristic of MS, their role in disease remains uncertain. PART 13 Neurologic Disorders More likely, the antigen-presenting cell (APC) function of B cells explains their role in MS pathogenesis. Fragments of self-peptides derived from HLA-DR2 proteins themselves were found to bind intact DRB1*1501 molecules on B cells and serve as antigens for presenta tion to T cells. Memory CD4+ T cells derived from CSF responded to these self-peptides bound to DR2 molecules, and in some cases, these self-peptides were cross-reactive with several myelin antigens, as well as proteins derived from EBV, Akkermansia muciniphila (a com mensal gut bacterium associated with dysbiosis in MS patients), and RAS guanyl-releasing protein 2 (RASGRP2), previously found to be a possible T-cell autoantigen in MS. Thus, MS-associated HLA proteins contain fragments that might trigger autoimmunity through molecular mimicry with viral,

*bacterial, or normal host antigens. Autoreactive T Lymphocytes Autoreactive T cells may be trig gered and sustained via B-cell antigen presentation. Myelin basic protein (MBP), an intracellular protein involved in myelin compaction, is an important T-cell antigen in experimental allergic encephalomyelitis (EAE), a laboratory model for MS. Activated MBP-reactive T cells have been identified in the blood, in CSF, and within MS lesions. The MS-associated HLA-DRB1*1501 protein binds with high affinity to a fragment of MBP (spanning amino acids 89–96), potentially stimulat ing T-cell responses to this self-protein. Several different populations of proinflammatory T cells are likely to mediate autoimmunity in MS. T-helper type 1 (TH1) cells producing interferon γ (IFN-γ) are one key effector population; TH1 cytokines, including IL-2, tumor necrosis fac tor (TNF)-α, and IFN-γ, play key roles in activating and maintaining autoimmune responses, and TNF-α and IFN-γ may directly injure oligo dendrocytes or the myelin membrane. B cells from MS patients are also known to be high producers of TNF-α. As noted above, CD8 cytotoxic T cells are present at the active edges of expanding MS lesions, and acti vated CD8 cells also appear to be enriched for reactivity against myelin antigens in MS patients. Microglial Activation Widespread microglial activation is a hall mark of progressive MS pathology. Activated microglia are found in cortical plaques in the absence of macrophage and leukocyte infiltrates. Some cortical plaques are found adjacent to sites of meningeal inflam mation in which tertiary lymphoid follicles are found. As discussed

above, these meningeal lymphoid structures are a hallmark of MS pathology. Microglial activation in MS is thought to be triggered by proinflammatory B and T lymphocytes or in response to tissue injury signals via toll-like receptor signaling. Although once thought to exist in either proinflammatory or anti-inflammatory states, microglia are now understood to have varied and context-dependent transcriptional states. ■ ■PHYSIOLOGY Nerve conduction in myelinated axons occurs in a saltatory manner, with the nerve impulse jumping from one node of Ranvier to the next without depolarization of the axonal membrane underlying the myelin sheath between nodes (Fig. 455-2A). This produces faster conduction velocities (~70 m/s) than the slow velocities (~1 m/s) produced by continuous propagation in unmyelinated nerves. Conduction block occurs when the nerve impulse is unable to traverse the demyelinated segment. This can happen when the resting axon membrane becomes hyperpolarized due to exposure of voltage-dependent potassium chan nels that are normally buried underneath the myelin sheath. A tem porary conduction block often follows a demyelinating event before sodium channels (originally concentrated at the nodes) redistribute along the naked axon (Fig. 455-2B). This redistribution ultimately allows continuous propagation of nerve action potentials through the demyelinated segment. Conduction block may be incomplete, affecting high- but not low-frequency volleys of impulses. Variable conduction block can also occur with raised body temperature or metabolic altera tions. These factors may explain clinical fluctuations that vary from hour to hour or appear with fever or exercise. Conduction slowing occurs when the demyelinated segments of the axonal membrane are reorganized to support continuous (slow) nerve impulse propagation. DIAGNOSIS There is no single diagnostic test for MS. Diagnostic criteria for clini cally definite MS require two or more episodes of symptoms and two or more signs that reflect pathology in anatomically noncontiguous white matter tracts of the CNS (Table 455-4). Symptoms must last for

> “ 24 h and occur as distinct episodes separated by a month or more. In patients who have only one of the two required signs on neurologic examination, the

second may be documented by abnormal tests such as MRI or evoked potentials (EPs). Similarly, in the most recent diagnos tic scheme, the second clinical event (in time) may be supported solely by MRI findings, consisting of either the development of new focal white matter lesions on MRI or the simultaneous presence of both an enhancing lesion and a nonenhancing lesion in an asymptomatic loca tion. In patients whose course is progressive from onset for ≥6 months Saltatory nerve impulse Myelin sheath Axon Node of Ranvier Na+ channels A Continuous nerve impulse Myelin sheath Myelin sheath Axon Na+ channels B FIGURE 455-2 Nerve conduction in myelinated and demyelinated axons. A. Saltatory nerve conduction in myelinated axons occurs with the nerve impulse jumping from one node of Ranvier to the next. Sodium channels (shown as breaks in the solid black line) are concentrated at the nodes where axonal depolarization occurs. B. Following demyelination, additional sodium channels are redistributed along the axon itself, thereby allowing continuous propagation of the nerve action potential despite the absence of myelin.

TABLE 455-4 Diagnostic Criteria for Multiple Sclerosis (MS) CLINICAL PRESENTATION ADDITIONAL DATA NEEDED FOR MS DIAGNOSIS 2 or more attacks; objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack None 2 or more attacks; objective clinical evidence of 1 lesion Dissemination in space, demonstrated by ≥1 T2 lesion on MRI in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) OR • Await a further clinical attack implicating a different CNS site 1 attack; objective clinical evidence of 2 or more lesions Dissemination in time, demonstrated by • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time OR • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan OR • Await a second clinical attack 1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome) Dissemination in space and time, demonstrated by: For dissemination in space • ≥1 T2 lesion in at least 2 out of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) OR • Await a second clinical attack implicating a different CNS site AND • For dissemination in time • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time OR • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan OR • Await a second clinical attack Insidious neurologic progression suggestive of MS (PPMS) 1 year of disease progression (retrospectively or prospectively determined) PLUS 2 out of the 3 following criteria: • Evidence for dissemination in space in the brain based on ≥1 T2+ lesions in the MS-characteristic periventricular, juxtacortical, or infratentorial regions • Evidence for dissemination in space in the spinal cord based on ≥2 T2+ lesions in the cord • Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index) Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PPMS, primary progressive multiple sclerosis. Source: Reproduced with permission from AJ Thompson et al: Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 17:162, 2018. without superimposed relapses, documentation of intrathecal IgG synthesis may be used to support a diagnosis of PPMS. DIAGNOSTIC TESTS ■ ■MAGNETIC RESONANCE IMAGING MRI has revolutionized the diagnosis and management of MS

(Fig. 455-3); characteristic abnormalities are found in >95% of patients, although the majority of lesions visualized by MRI are

asymptomatic. An increase in vascular permeability from a breakdown of the BBB is detected by leakage of intravenous gadolinium (Gd) into the parenchyma. Such leakage occurs early in the development of an MS lesion and serves as a marker of inflammation. Gd enhancement typically persists for <1 month, and the residual MS plaque remains visible indefinitely as a focal area of hyperintensity (a lesion) on T2-weighted images. Lesions are frequently oriented perpendicular to the ventricular surface, corresponding to a pattern of perivenous demyelination (Dawson's fingers; Fig. 455-3B). Lesions are multifocal within the brain, brainstem, and spinal cord. Lesions >6 mm located in the corpus callosum, periventricular white matter, brainstem, cerebel lum, or spinal cord are particularly helpful diagnostically. Also useful diagnostically is a central vein sign within plaques visualized with susceptibility-weighted (such as T2*) sequences (Chap. 434). Criteria for the use of MRI in diagnosis of MS are shown in Table 455-4.

Serial MRI studies in RRMS reveal that bursts of focal inflamma tory disease activity occur far more frequently than would have been predicted by the frequency of relapses. Thus, early in MS, most disease activity is clinically silent. CHAPTER 455 The total volume of T2-weighted signal abnormality (the "burden of disease") shows a significant (albeit weak) correlation with clinical disability. Quantitative measures of brain and especially spinal cord atrophy provide evidence of diffuse tissue injury and correlate more strongly with measures of disability or progressive MS. Serial MRI studies also indicate that progressive brain atrophy occurs even in very early MS and continues throughout the disease course. Approximately one-third of T2-weighted lesions appear as hypointense lesions (black holes) on T1-weighted imaging. Black holes are markers of irreversible demyelination and axonal loss, although even this measure depends on the timing of the image acquisition (e.g., most acute Gd-enhancing T2 lesions are T1 dark, and in chronic lesions, there is progressive T1 darkening over time). Multiple Sclerosis ■ ■CEREBROSPINAL FLUID CSF changes in MS include a mononuclear cell pleocytosis and an increased level of intrathecally synthesized IgG. The total CSF protein is usually normal or only mildly elevated. Various formulas distinguish intrathecally synthesized IgG from IgG that entered the CNS passively from the serum. The CSF IgG index expresses the ratio of IgG to albumin in the CSF divided by the same ratio in the serum. The IgG synthesis rate uses serum and CSF IgG and albumin measurements to calculate the rate of CNS IgG synthesis. The measurement of oligoclo nal bands (OCBs) by agarose gel electrophoresis of the CSF assesses intrathecal production of specific IgG clones separated by differences in charge. Two or more discrete OCBs, not present in a paired serum sample, are found in >90% of patients with MS. OCBs may be absent at the onset of MS, and in individual patients, the number of bands may increase over time. A mild CSF pleocytosis (>5 cells/μL) is present in ~25% of cases, usually in young patients with RMS. A pleocytosis of >75 cells/μL, the presence of polymorphonuclear leukocytes, or a protein concentration

> 1 g/L (>100 mg/dL) in CSF should raise concern that the patient may not have MS. Because of its utility to rule in and also rule out MS, CSF examination is highly recommended as part of the routine MS workup, and especially when the diagnosis is uncertain. ■ ■EVOKED POTENTIALS EP testing assesses function in

> afferent (visual, auditory, and somato sensory) or efferent (motor) CNS pathways. EPs use computer averag ing to measure CNS electric potentials evoked by repetitive stimulation of selected peripheral nerves or of the brain. These tests provide the most information when the pathways studied are clinically uninvolved. For example, in a patient with a relapsing spinal cord syndrome with sensory deficits in the legs, an abnormal somatosensory EP following posterior tibial nerve stimulation provides little new information. By contrast, an abnormal visual EP in this circumstance would permit a diagnosis of clinically definite MS (Table 455-4). Abnormalities on one or more EP modalities occur in 80–90% of MS patients. EP abnormali ties are not specific to MS, although a marked delay in the latency of a

PART 13 Neurologic Disorders specific EP component (as opposed to a reduced amplitude or distorted wave shape) suggests demyelination. DIFFERENTIAL DIAGNOSIS The possibility of an alternative diagnosis should always be considered (Table 455-5), particularly when (1) symptoms are localized exclu sively to the posterior fossa, craniocervical junction, or spinal cord; (2) the patient is <15 or >60 years of age; (3) the clinical course is pro gressive from onset; (4) the patient has never experienced visual, sen sory, or bladder symptoms; or (5) laboratory findings (e.g., MRI, CSF, or EPs) are atypical. Similarly, symptoms that are uncommon or rare in MS (e.g., aphasia, parkinsonism, chorea, isolated dementia, severe muscular atrophy, peripheral neuropathy, episodic loss of conscious ness, fever, headache, seizures, or coma) favor an alternative diagnosis. Diagnosis can be particularly difficult in patients with a rapid or explo sive (stroke-like) onset or those with mild symptoms and a normal neurologic examination. Rarely, intense inflammation and swelling may produce a mass lesion that mimics a primary or metastatic tumor. Disorders possibly mistaken for MS include neuromyelitis optica (NMO) and the more recently identified myelin oligodendrocyte protein-associated disease (MOGAD) and glial fibrillary acid pro tein (GFAP) disorders (Chap. 456); these should be considered in patients who present with bilateral and/or severe optic neuritis or severe transverse myelitis. With hyperacute or postinfectious presenta tions, another consideration is acute disseminated encephalomyelitis (ADEM; Chap. 456). Other possibilities include Sjögren’s syndrome, sarcoidosis, vascular disorders (antiphospholipid syndrome and vas culitis), rarely CNS lymphoma, and still more rarely infections such as syphilis or Lyme disease. The specific tests required to exclude alternative diagnoses will vary with each clinical situation; however, an erythrocyte sedimentation rate, serum B12 level, antinuclear antibodies, and treponemal antibody should probably be obtained in all patients with suspected MS. TREATMENT Therapy for MS can be divided into several categories: (1) treatment of acute attacks, (2) treatment with disease-modifying agents that reduce the biologic activity of MS, and (3) symptomatic therapy. Treatments that promote remyelination or neural repair do not currently exist, but several promising approaches are being actively investigated. A B C D FIGURE 455-3 Magnetic resonance imaging findings in multiple sclerosis (MS). A. Axial first-echo image from T2-weighted sequence demonstrates multiple bright signal abnormalities in white matter, typical for MS. B. Sagittal T2-weighted fluid-attenuated inversion recovery (FLAIR) image in which the high signal of cerebrospinal fluid (CSF) has been suppressed. CSF appears dark, whereas areas of brain edema or demyelination appear high in signal, as shown here in the corpus callosum (arrows). Lesions in the anterior corpus callosum are frequent in MS and rare in vascular disease. C. Sagittal

T2-weighted fast spin echo image of the thoracic spine demonstrates a fusiform high-signal-intensity lesion in the midthoracic spinal cord. D. Sagittal T1-weighted image obtained after the intravenous administration of gadolinium diethylene triamine pentaacetic acid (DTPA) reveals focal areas of blood-brain barrier disruption, identified as high-signal-intensity regions (arrows).

TABLE 455-5 Disorders That Can Mimic Multiple Sclerosis (MS) Acute disseminated encephalomyelitis (ADEM) Antiphospholipid antibody syndrome Behçet's disease Cerebral autosomal-dominant arteriopathy, subcortical infarcts, and leukoencephalopathy (CADASIL) Congenital leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy) Glial Fibrillary Acidic Protein (GFAP) Autoimmunity Human immunodeficiency virus (HIV) infection Ischemic optic neuropathy (arteritic and nonarteritic) Lyme disease Mitochondrial encephalopathy with lactic acidosis and stroke (MELAS) Myelin oligodendrocyte glycoprotein-associated disease (MOGAD) Neoplasms (e.g., lymphoma, glioma, meningioma) Neuromyelitis optica Sarcoidosis Sjögren's syndrome Stroke and ischemic cerebrovascular disease Syphilis Systemic lupus erythematosus and related collagen vascular disorders Tropical spastic paraparesis (HTLV-1/2 infection) Vascular malformations (especially spinal dural AV fistulas) Vasculitis (primary CNS or other) Vitamin B12 deficiency Abbreviations: AV, arteriovenous; CNS, central nervous system; HTLV, human T-cell lymphotropic virus. As noted above, the EDSS is a widely used measure of neurologic impairment in MS (Table 455-2). Most patients with EDSS scores <3.5 walk normally and are generally not disabled; by contrast, patients with EDSS scores >4.0 have progressive MS (SPMS or PPMS), are gaitimpaired, and often are occupationally disabled. ■ ■ACUTE ATTACKS OR INITIAL DEMYELINATING EPISODES When patients experience acute deterioration, it is important to consider whether this change reflects new disease activity or a "pseu doexacerbation" resulting from an increase in ambient temperature, fever, or an infection. When the clinical change is thought to reflect a pseudoexacerbation, glucocorticoid treatment is inappropriate. Gluco corticoids are used to manage first attacks and exacerbations that are moderate to severe in severity. They provide short-term clinical benefit by reducing the degree and duration of attacks. Whether treatment provides any long-term benefit on the course of the illness is less clear. Therefore, mild attacks are often not treated. Physical and occupational therapy can help with mobility and manual dexterity. Glucocorticoid treatment is usually administered as intravenous methylprednisolone, 500–1000 mg/d for 3–5 days, either without a taper or followed by a course of oral prednisone beginning at a dose of 60–80 mg/d and gradually tapered over 2 weeks. Orally administered methylprednisolone, prednisone, or dexamethasone (in equivalent dosages) can be substituted for the intravenous portion of the therapy. Outpatient treatment is almost always possible. Side effects of short-term glucocorticoid therapy include fluid retention, potassium loss, weight gain, gastric disturbances, acne, and emotional lability. Concurrent use of a low-salt, potassium-rich diet and avoidance of potassium-wasting diuretics are advisable. Lithium carbonate (300 mg orally bid) may help manage emotional lability and insomnia associated with glucocorticoid therapy. Patients with a history of peptic ulcer disease may require cimetidine (400 mg bid) or ranitidine (150 mg bid). Proton pump inhibitors such as pantoprazole (40 mg orally bid) may reduce the likelihood of gastritis, especially when large doses are administered orally. Plasma exchange (five to seven exchanges: 40–60 mL/kg per exchange, every other day for 14 days)

may benefit patients with fulminant attacks of demyelination that are unresponsive to glucocorticoids.

■ ■DISEASE-MODIFYING THERAPIES FOR MS RMS More than a dozen immunomodulatory and immunosuppres sive agents are in use for treatment of RMS (Table 455-6). In phase 3 clinical trials, each was shown to reduce the frequency of clinical relapses and evolution of new brain MRI lesions. Each can also be used in SPMS patients who continue to experience attacks, both because SPMS can be difficult to distinguish from RRMS and because the available clinical trials, although not all definitive, suggest that such patients may sometimes derive therapeutic benefit. Moreover, regula tors now consider patients with recent relapses to be a “relapsing form of MS” (i.e., RMS), regardless of whether these patients previously had progressive disability independent from relapses. It is important to note that the relative efficacy of the different agents has not been directly tested in head-to-head studies and that cross-trial comparisons are inaccurate. However, given the increasingly complex landscape of therapeutics for MS, for convenience, the presentation of these agents was divided by an estimate of their relative (high, moderate, or modest) perceived level of efficacy. These are meant to serve as a general guide, with the caveat that considerable variance exists in practice patterns, as well as availability of these agents, in different parts of the world. CHAPTER 455 Multiple Sclerosis Therapy should be initiated in all patients diagnosed with RMS and those presenting with a first demyelinating event who are at high risk for MS (sometimes termed as a clinically isolated syndrome [CIS]). We favor use of the most highly effective disease-modifying therapies as first-line options for most patients. This recommendation is based on evidence from long-term prospective trials and real-world data indicating that initial treatment with highly effective agents provides outstanding control against relapsing disease, maximum protection against relapse-independent progression, and long-term outcomes, and is safe. We typically begin with an anti-CD20 B-cell-targeting drug (ocrelizumab, ofatumumab, or ublituximab) or, if these approved treat ments are unavailable, with rituximab or a biosimilar. In JCV-negative patients, we begin with the cell-trafficking inhibitor natalizumab. AntiCD20 agents are particularly attractive given their high level of efficacy, relative ease of use, favorable safety profile, and absence of rebound fol lowing discontinuation. For patients who prefer oral treatment, either an S1P modulator or a fumarate is also reasonable for first-line therapy. First-line treatment with high-efficacy therapy has supplanted the alternative approach in which a treatment of modest or moderate effectiveness was first used and therapy advanced to a more effec tive agent when breakthrough disease (evident clinically or by MRI) occurred. Older first-generation therapies, such as IFN-βor glatiramer acetate, are often continued in patients who are doing well on these agents but are less commonly used today for patients with new-onset MS. Irrespective of the agent used, a change in therapy may be required in patients with suboptimal responses, such as those experiencing relapses and/or active MRI scans while on treatment, or for adverse events that may be drug-related. Pregnancy-related management is discussed later in this chapter. Some patients, especially those with a mild initial RRMS course— e.g., a normal examination or minimal impairment (EDSS ≤2.5) and low disease activity by MRI—may initially decline therapy with a potent immunosuppressive drug. In these situations, either an oral (fumarates, S1P modulators, or teriflunomide) or injectable (IFN-β or glatiramer acetate) agent can be considered. The injectable agents (IFN-β and glatiramer acetate) have a superb long-term track record for safety but have a high nuisance factor due to the need for frequent injections, as well as bothersome side effects that reduce adherence. As noted above, multiple lines of evidence indicate that institution of effective therapy can improve the long-term outcome of MS, includ ing a prolongation of the time to reach disability outcomes (e.g., SPMS and requiring assistance to ambulate) and reduction in MS-related mortality. These benefits seem most conspicuous when treatment is begun early in the relapsing stage of the illness. It may be reasonable to delay initiating treatment in some patients

with (1) normal neurologic

TABLE 455-6 Disease-Modifying Therapies for Multiple Sclerosis CATEGORY AND MECHANISM OF ACTION GENERIC NAME (TRADE NAME) DOSE AND INTERVAL CHARACTERISTICS COMMENTS (USE, ADVERSE EFFECTS, ETC.) Highly Effective Anti-CD20 B cell MAbs: Depletes B lymphocytes, especially motile B cells in peripheral blood; B cells in lymphoid organs variably protected; plasma cells preserved Ocrelizumab (Ocrevus) 600-mg infusion q6 months (first dose given as two 300-mg infusions 14 days apart) Ofatumumab (Kesimpta) 20-mg subcutaneous injections monthly (after 3 weekly 20-mg loading doses) Ublituximab (Briumvi) 450-mg infusion q6 months (first dose given as 150-mg, followed 14 days later by 450-mg, infusions) Rituximab (Rituxan and biosimilars) 1000-mg infusion q6 months (dose used in phase 2 trial in RMS); some clinicians use 500 mg IV q6 months PART 13 Neurologic Disorders Natalizumab (Tysabri) 300-mg monthly infusion Humanized Hypersensitivity Rxns (<10%) including anaphylaxis; NAbs in ~6%; major risk is PML (0.4%); can be given safely only if serum antibodies to JC virus are absent (~50% of patients); repeat testing q6 months with ongoing treatment; risk of rebound disease activity after cessation Anti-α4 subunit of α4β1 integrin (adhesion molecule) MAb: Prevents lymphocytes from binding to endothelial cells and entering the CNS Anti-CD52 MAb: Depletes lymphocytes and monocytes Alemtuzumab (Lemtrada) 12 mg/m2 infusion for 5 consecutive days; a second 3-day course administered 1 year later Moderately Effective Sphingosine-1-phosphate (S1P) modulators: Prevents egress of lymphocytes from secondary lymphoid organs Pretreatment CBC, LFTs, ECG, eye exam required; vaccinate for VZV in seronegative patients Fingolimod (Gilenya) 0.5 mg oral once daily Binds to S1P1, S1P3, S1P4, and S1P5 receptors Ozanimod (Zeposia) 1 mg oral once daily S1P1- and S1P5-selective inhibitor (cardiac receptors are mostly S1P3 and only weakly engaged by ozanimod) Ponesimod (Ponvory) 20 mg oral once daily S1P1-selective modulator Up-titration regimen used to begin treatment; initial dose requires 4-h cardiac monitoring for patients with heart rate <55 beats/min Siponimod (Mayzent) Based on CYP2C9 genotype. 1 mg oral daily for pts with CYP2C9 1/*3 or 2/*3 Dose reduced in patients with the CYP2C9 *3/*3 genotype (<0.5% of the population) due to substantially elevated drug levels Fumarate: Immunomodulator; reduces proinflammatory and increases regulatory cytokines; inhibits degradation of Nrf2, increasing natural antioxidants Dimethyl fumarate (Tecfidera) 240 mg oral twice daily (halfdose for first 7 days) Diroximel fumarate (Vumerity) 262 mg oral twice daily Metabolized to active compound monomethyl fumarate 2-Chlorodeoxyadenosine: Lymphocytotoxic; possibly followed by reconstitution by nonpathogenic immune cells Cladribine (Mavenclad) Weight-based oral dosing (3.5 mg/kg) divided over 4–5 days, repeated 23–27 days later; a second identical course is administered 1 year later

Humanized ADCC > complement Infusion reactions usually mild; outstanding efficacy and safety in longterm RMS extension trials; also approved for PPMS Fully human Complement > ADCC Advantage of home-based treatment; only very minor injection- related reactions Chimeric ADCC > Complement Chimeric Complement > ADCC Formally tested only in preliminary (phase 2) study Long-lasting benefits but serious risks limit use; approval in United States only for patients who have failed at least two other drugs Multiple autoimmune complications including thyroid (~25%) and ITP (1–3%), malignancies, infection risk Heart block or bradycardia can occur with first dose; a 6-h period of initial observation with ECG monitoring required; LFT abnormalities, macular edema; rare VZV or cryptococcal infections; risk of rebound disease activity after cessation for all agents in this class Up-titration regimen used to begin treatment; first-dose monitoring not required for most patients S1P1- and S1P5-selective modulator Approved for SPMS with active disease (relapses or

new focal MRI lesions); firstdose monitoring only for patients with sinus bradycardia, heart block, or prior myocardial infarction or heart failure Metabolized to active compound monomethyl fumarate Gastrointestinal side effects, flushing; these may improve over time; monitor for LFT abnormalities and for lymphopenia (which can persist after drug cessation); rare PML cases Similar side effect profile as dimethyl fumarate Purine analogue prodrug phosphorylated in lymphocytes and incorporated into DNA, triggering apoptosis; long-lasting Long-lasting benefits but use limited by risks of malignancy, teratogenicity, and infection including PML (Continued)

TABLE 455-6 Disease-Modifying Therapies for Multiple Sclerosis CATEGORY AND MECHANISM OF ACTION GENERIC NAME (TRADE NAME) DOSE AND INTERVAL CHARACTERISTICS COMMENTS (USE, ADVERSE EFFECTS, ETC.) Modestly Effective Glatiramer acetate: Immunomodulator; reduces proinflammatory and increases regulatory cytokines; induces antigen-specific suppressor T cells; binds MHC molecules Glatiramer acetate (Copaxone) Subcutaneous injection 20 mg daily, or alternatively, 40 mg three times weekly Intramuscular injections 30 mg once weekly With all IFN preparations: flu-like symptoms (fever, chills, myalgias) common; managed with NSAIDs; mild lab abnormalities (LFTs, lymphopenia); rare cases of severe hepatotoxicity Interferon-β-1a (Rebif) Interferon (IFN)-β: Immunomodulator; reduces proinflammatory and increases regulatory cytokines; interferes with antigen presentation, T-cell proliferation, lymphocyte trafficking Interferon-β-1a (Avonex) Subcutaneous injections 44 mg three times per week Subcutaneous injections 250 mg every other day Interferon-β-1b (Betaseron or Extavia) Pegylated interferon-β-1a (Plegridy) Subcutaneous injections 125 mg every 14 days Teriflunomide: Antiinflammatory; limits proliferation of rapidly dividing B and T lymphocytes Teriflunomide (Aubagio) 14 mg oral daily Inhibits mitochondrial enzyme dihydro-orotate dehydrogenase involved in de novo pyrimidine synthesis; cytostatic rather than cytotoxic Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; CBC, complete blood count; CNS, central nervous system; ECG, electrocardiogram; ITP, immune thrombocytopenia; LFT, liver function test; MAbs, monoclonal antibodies; MHC, major histocompatibility complex; MRI, magnetic resonance imaging; NAb, neutralizing antibody; NSAID, nonsteroidal anti-inflammatory drug; PML, progressive multifocal leukoencephalopathy; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; Rxn, reaction; SPMS, secondary progressive multiple sclerosis; VZV, varicella-zoster virus. examinations, (2) a single attack or a low attack frequency, and (3) a low burden of disease as assessed by brain MRI. Untreated patients, however, should be followed closely with periodic brain MRI scans; the need for therapy is reassessed if scans reveal evidence of ongoing, subclinical disease. Finally, vitamin D deficiency should be corrected in all patients with MS, and generally this requires oral supplementa tion with vitamin D3, 4000 IU daily. Several clinical trials showed that supplementation with vitamin D in relapsing MS patients reduces MRI measures of disease activity and may also reduce the relapse frequency in patients actively treated with either IFN or glatiramer acetate. SPMS For patients with active SPMS, either ocrelizumab or siponi mod is a reasonable first-line option. Ocrelizumab is approved for active SPMS despite not having been specifically studied in this patient population. Siponimod in a single pivotal study reduced the risk of progression in SPMS; however, subgroup analysis showed that patients with a relapse in the 2 years prior to treatment and those with contrastenhancing lesions on brain MRI received the most therapeutic benefit. Regulatory bodies also approved cladribine and ponesimod for active SPMS despite neither having been specifically studied in this MS subgroup. PPMS Ocrelizumab was shown to reduce progression of clinical disability in PPMS by 25% and also improve other clinical and MRI markers of inflammatory and degenerative disease activity. Although the magnitude of the effect in PPMS is

lower than in RMS, for the average patient with PPMS, these data translate to the expectation that >7 years of wheelchair-independent function is gained on aver age. Ocrelizumab is the only agent convincingly shown to modify the course of PPMS. ■ ■OTHER OFF-LABEL TREATMENT OPTIONS Autologous hematopoietic stem cell transplantation appears to be highly effective in reducing relapses and may improve disability in relapsing MS. It appears to be largely ineffective for patients with progressive MS. Stem cell transplantation also carries significant risk, however, includ ing toxicities from chemotherapy-conditioning regimens. Ongoing clinical trials should help to better position this procedure with respect to available pharmacologic interventions.

(Continued) Synthetic random polypeptide of four amino acids (l-glutamic acid, l-lysine, l-alanine, Well tolerated; injection site reactions; ~15% of patients experience one (or less often more than one) episode of flushing, chest tightness, dyspnea, palpitations, anxiety l-tyrosine) Neutralizing antibodies in 2–10% (can decrease over time with all IFN preparations) Neutralizing antibodies in 15–25% Neutralizing antibodies in 30–40% CHAPTER 455 Pegylation increases half-life; neutralizing antibodies in <1% Hair thinning, gastrointestinal toxicity (nausea and diarrhea), rarely toxic epidermal necrolysis or Stevens-Johnson syndrome; long-lasting teratogenicity (elimination protocol with cholestyramine or activated charcoal) Multiple Sclerosis Intravenous immunoglobulin (IVIg), administered in monthly pulses (up to 1 g/kg) for up to 2 years, appears to reduce annual exacerbation rates. However, its use is limited because of its high cost, questions about optimal dose, and uncertainty about any impact on long-term disability. It can be considered when the risks of immunosuppression preclude use of other MS agents. Numerous clinical trials of promising experimental therapies are currently underway. These include studies testing higher doses of ocrelizumab; Bruton’s tyrosine kinase (BTK) inhibitors to selec tively deplete B cells, plasma cells, and microglia; CD19-targeted chimeric antigen receptor (CAR) T cells; and molecules to promote remyelination. THERAPIES TO AVOID Many purported treatments for MS have never been subjected to sci entific scrutiny. These include dietary therapies (e.g., the Swank diet, the Paleo diet, the Wahls diet), megadose vitamins, calcium orotate, bee stings, cow colostrum, hyperbaric oxygen, procarin (a combination of histamine and caffeine), chelation, acupuncture, acupressure, various Chinese herbal remedies, and removal of mercury-amalgam tooth fill ings, among others. Although infections with EBV, human herpesvirus (HHV) 6, or other agents are plausibly involved in MS, treatment with antiviral agents or antibiotics is not recommended. A chronic cere brospinal insufficiency (CCSVI) was proposed as a cause of MS, and surgical intervention with vascular repair was recommended; however, multiple studies failed to confirm the initial claims. A double-blind trial of high-dose biotin to improve disability in progressive forms of MS also found no benefit. Patients should avoid costly or potentially hazardous unproven treatments, many of which also lack biologic plausibility. SYMPTOMATIC THERAPIES For all patients, it is important to encourage attention to a healthy life style, including maintaining an optimistic outlook, a healthy diet, and regular exercise as tolerated (swimming is often well-tolerated because of the cooling effect of cold water). It is reasonable also to correct vitamin D deficiency with oral vitamin D and consider dietary supple mentation with long-chain fatty acids (such as omega-3 oil tablets) due to their mild immunomodulatory effects.

Bladder dysfunction management is best guided by urodynamic testing because symptoms correlate poorly with the specific patho physiology, which can also change over time as the disease evolves. The underlying cause can be bladder hyperreflexia, atony, or dyssynergia between the detrusor and the external sphincter muscle.

Detrusor hyperreflexia can be initially managed with evening fluid restriction or frequent voluntary voiding. If these methods fail, beta-3 adrenergic agonists such mirabegron (25–50 mg/d) and vibegron (75 mg/d) that relax bladder smooth muscle should be tried. Beta-3 adrenergic agonists are preferred over anticholinergic agents such as oxybutynin (5–15 mg/d), propantheline bromide (10–15 mg/d), tolterodine tartrate (2–4 mg/d), or solifenacin (5–10 mg/d) because anticholinergic side effects can worsen other MS symptoms includ ing cognitive dysfunction. Co-administration of pseudoephedrine (30–60 mg) with anticholinergics is sometimes beneficial. Detrusor muscle injections of botulinum toxin (e.g., onabotulinumtoxinA 200 IU) can be useful when anticholinergics are ineffective or produce side effects such as cognitive dysfunction or fatigue. PART 13 Neurologic Disorders An atonic bladder due to loss of reflex bladder wall contraction may respond to bethanechol (30–150 mg/d), and detrusor/sphincter dyssyn ergia may respond to phenoxybenzamine (10–20 mg/d) or terazosin hydrochloride (1–20 mg/d). However, both conditions often require catheterization. Urinary tract infections should be treated promptly. Patients with postvoid residual urine volumes >200 mL are predisposed to infec tions. Prevention by urine acidification (with cranberry juice or vitamin C) inhibits some bacteria. Prophylactic administration of anti biotics is sometimes necessary but may lead to colonization by resistant organisms. Intermittent catheterization may help to prevent recurrent infections and reduce overflow incontinence. Treatment of constipation includes high-fiber diets and fluids. Natu ral or other laxatives may help. Fecal incontinence may respond to a reduction in dietary fiber. Spasticity and spasms may improve with physical therapy, regular exercise, and stretching. Avoidance of triggers (e.g., infections, fecal impactions, bed sores) is extremely important. Effective medications include baclofen (20–120 mg/d), diazepam (2–40 mg/d), tizanidine (8–32 mg/d), dantrolene (25–400 mg/d), and cyclobenzaprine hydro chloride (10–60 mg/d). For severe spasticity, a baclofen pump (deliver ing medication directly into the CSF) can provide substantial relief. Weakness can sometimes be improved with the use of potassium channel blockers such as 4-aminopyridine (20 mg/d) and 3,4-diaminopyridine (40–80 mg/d), particularly in the setting where lowerextremity weakness interferes with the patient’s ability to ambulate. Extended-release 4-aminopyridine (10 mg twice daily) can be obtained either as dalfampridine (Ampyra) or through a compounding phar macy. The principal concern with the use of these agents is the possibil ity of inducing seizures at high doses. Ataxia/tremor is often intractable. Clonazepam (0.5–2 mg/d), primi done (50–250 mg/d), propranolol (40–200 mg/d), or ondansetron (8–16 mg/d) may help. Wrist weights occasionally reduce tremor in the arm or hand. Thalamotomy and deep-brain stimulation have been tried with mixed success. Pain is treated with anticonvulsants (gabapentin [300–3600 mg/d]; pregabalin [50–300 mg/d]; carbamazepine [100–1000 mg/d]; phenytoin [300–600 mg/d]); tricyclic antidepressants (amitrip tyline [25–100 mg/d], nortriptyline [25–100 mg/d], desipramine [100–300 mg/d]); serotonin-norepinephrine reuptake inhibitors (duloxetine [20–120 mg/d] or venlafaxine [75–225 mg/d]); or anti arrhythmics (mexiletine, 300–900 mg/d). If these approaches fail, patients should be referred to a comprehensive pain-management program. Depression should be actively treated. Useful drugs include the selective serotonin reuptake inhibitors (escitalopram [10–20 mg/d], fluoxetine [20–80 mg/d], or sertraline [50–200 mg/d]), tricyclic antide pressants (amitriptyline [25–150 mg/d], nortriptyline [25–150 mg/d], or desipramine [100–300 mg/d]) and mixed norepinephrine/sero tonin reuptake inhibitors (duloxetine [20–120 mg/d] or venlafaxine [75–225 mg/d]).

Fatigue may improve with assistive devices, help in the home, or suc cessful management of spasticity. Careful attention to medications that could contribute to fatigue is often helpful. For

example, patients who require anticholinergic medication for nocturia may benefit from dos ing at bedtime only. Excessive daytime somnolence caused by MS may respond to methylphenidate (5–25 mg/d), modafinil (100–400 mg/d), or armodafinil (150–250 mg/d). Cognitive problems may respond marginally to lisdexamfetamine (40 mg/d). Paroxysmal symptoms respond dramatically to low-dose anticonvul sants (acetazolamide [200–600 mg/d], carbamazepine [50–400 mg/d], phenytoin [50–300 mg/d], or gabapentin [600–1800 mg/d]). Heat sensitivity may respond to heat avoidance, air-conditioning, or cooling garments. Sexual dysfunction may be helped by lubricants to aid in genital stimulation and sexual arousal. Management of pain, spasticity, fatigue, and bladder/bowel dysfunction may also help. Sildenafil (50–100 mg), tadalafil (5–20 mg), or vardenafil (5–20 mg), taken 1–2 h before sex, are standard treatments for erectile dysfunction. PROGNOSIS Historically, most patients with MS ultimately experienced progres sive neurologic disability. In older studies conducted before diseasemodifying therapies for MS were available, 15 years after onset, only 20% of patients had no functional limitation, and between one-third and one-half of RMS patients progressed to SPMS and required assis tance with ambulation; furthermore, 25 years after onset, ~80% of MS patients reached this level of disability. Long-term studies from the early treatment era indicated clearly that prognosis had improved substantially, with a two- to threefold slowing of transition from RMS to SPMS. And currently with high-efficacy therapy widely available, the prognosis continues to improve; relapses are largely eliminated and relapse-independent progression has been further slowed. For example, the ocrelizumab extension trials revealed that after 10 years of continuous treatment, nearly 80% of patients with RMS experienced no disease worsening and more patients had improved than worsened, and in PPMS, more than one-third had experienced no worsening and more than 80% were still ambulatory. As noted above, the long-term course may improve further as highly efficacious agents are increas ingly employed early in the disease course. However, many patients with progressive MS still continue to worsen despite best available ther apy, and for these patients, more effective therapies are sorely needed. Natural history studies from the pretreatment era indicated that certain clinical features suggest a more favorable prognosis. These include ON or sensory symptoms at onset; fewer than two relapses in the first year of illness; and minimal impairment after 5 years. Predic tors of an early aggressive course of the illness include an older age at symptom onset, male gender, greater disability, and the appearance of motor signs during the first year of the illness. Importantly, some MS patients, estimated at <10%, have a benign variant of MS and never develop neurologic disability even when untreated. ■ ■PREGNANCY-RELATED ISSUES Pregnant MS patients experience fewer attacks during gestation (especially in the last trimester) but more attacks in the first 3 months postpartum. When considering the pregnancy year as a whole (i.e., 9 months of pregnancy plus 3 months postpartum), the overall disease course is unaffected. Disease-modifying therapy is generally discontin ued during pregnancy, and special care needs to be taken with agents (natalizumab and the S1P drugs) that have risk of rebound disease activity following discontinuation. Replacement of these agents with an anti-CD20 B-cell therapy such as ocrelizumab before conception appears to mitigate this risk and also provide long-lasting protection that extends throughout the pregnancy and immediate postpartum period. Intravenously administered B-cell therapies also provide an attractive management option for many patients contemplating preg nancy, and our practice is to advise patients to stop receiving infusions 3–4 months prior to attempting to conceive. Earlier studies raised con cerns that drugs used for fertility treatments might worsen MS disease

A B C D FIGURE 455-4 Magnetic resonance imaging findings in variants of MS. A and B. Acute tumefactive MS. In A, a sagittal T2-weighted fluid-attenuated inversion recovery (FLAIR) image of a large solitary right parieto-occipital white matter lesion is shown, with effacement of overlying cortical sulci consistent with mass effect. In B, T1-weighted image obtained after the intravenous administration of gadolinium diethylene triamine pentaacetic acid (DTPA) reveals a large serpiginous area of blood-brain barrier disruption consistent with acute inflammation. C and D. Balo's concentric sclerosis. In C, an axial T2-weighted sequence shows multiple areas of abnormal ovoid bright signal in the supratentorial white matter bilaterally; some lesions reveal concentric layers, typical of Balo's concentric sclerosis. In D, T1-weighted magnetic resonance images after gadolinium demonstrate abnormal enhancement of all lesions with some lesions demonstrating concentric ring enhancement. activity, but more recent studies indicate that these produce little if any additional risk. CLINICAL VARIANTS OF MS Acute or fulminant MS (Marburg's variant) is an aggressive demy elinating process that in some cases progresses inexorably to death within 1–2 years. Typically, there are no remissions. Marburg's vari ant does not seem to follow infection or vaccination, and it is unclear whether this syndrome represents an extreme form of MS or another disease altogether. When an acute demyelinating syndrome pres ents as a solitary expansile lesion, a brain tumor is often suspected (Fig. 455-4A, B). Such cases are designated tumefactive MS, and a brain biopsy may be required to establish the diagnosis. Balo's con centric sclerosis is another fulminant demyelinating syndrome char acterized by concentric brain or spinal cord lesions with alternating spheres of demyelination and remyelination (Fig. 455-4C, D). For these fulminant demyelinating states, no controlled trials of therapy exist; high-dose glucocorticoids and plasma exchange are often used, with uncertain benefit. ■ ■FURTHER READING Absinta M et al: Mechanisms underlying progression in multiple scle rosis. Curr Opin Neurol 33:277, 2020.

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