The oligodendrocyte, predominantly found in the white matter of the brain, is the cell responsible for the production of myelin. As a general rule, demyelinating diseases result from either attacks on this cell or failure of the cell to regenerate under normal conditions. Consequently, a focal or diffuse loss of myelin occurs. Multiple sclerosis (MS) is the prototypical white matter disease. Many other diseases may mimic its appearance on imaging studies. While not an exhaustive list, this review highlights the important imaging manifestations of these demyelinating diseases that allow more specific diagnosis.

Multiple Sclerosis

Despite the more than 170 years that have passed since the first clinical features of MS were recognized, by Carswell and Cruveilhier in 1837, much of the demyelinating process remains poorly understood. There is a growing body of evidence suggesting that the disease is autoimmune in nature, although genetic factors, i.e., an allele on chromosome 6, have also been identified. Prior infection from Epstein-Barr virus or cytomegalovirus may also play a role. There is a frequent association of MS with many other autoimmune conditions, including Graves’ disease, myasthenia gravis, Crohn’s disease, and systemic lupus erythematosus.

The disease is more prevalent in cooler climates, with an incidence of about 1 per 1,000 in the United States and northern European countries. The vast majority (95%) of afflicted patients are between the ages of 18 and 50 years and it is the second most common disabling disease of young adults. Only acquired immune deficiency syndrome (AIDS) is more common. Most (60%) MS patients are female [1].

Typical clinical presenting symptoms include paresthesia, numbness, diplopia, weakness, gait disturbance, and burning sensations. About 7% of patients present with symptoms related to spinal cord involvement. Hemiparesis, constipation, urinary retention, and incontinence are typical features. Seizure activity occurs in about 5%. Uthoff’s phenomenon, the worsening of symptoms when the patient is exposed to warm temperatures, has long been recognized as a feature of the disease and once was used as a provocative clinical test. MS is very rarely seen in children, especially before puberty. It has been noted that MS patients often experience an exacerbation of symptoms in the first 6 months post-partum. Interestingly, the rate of attacks appears to decrease during the second and third trimester of pregnancy. Detection of oligoclonal gammopathy on cerebrospinal fluid examination is an important laboratory finding but is not always present [2].

Optic neuritis, characterized clinically by retrobulbar pain, a central monocular loss of vision, and an afferent papillary defect (Marcus-Gunn pupil) is especially important as a clinical hallmark for MS. The likelihood of a female patient with optic neuritis having MS either at the time of presentation or sometime in the future is 74%. While the diagnosis is best substantiated by clinical inspection, magnetic resonance imaging (MRI) remains valuable in directing therapy. When two or more MS-like lesions are noted, intravenous corticosteroid therapy is advocated [3].

The clinical criteria (known as the McDonald criteria) required to establish the diagnosis are complex and require strict implementation to be effective [4]. In relapsing-remitting MS, the most common type overall, two distinctly different clinical “attacks” from two different lesions in the central nervous system are required to make the diagnosis. Each attack must last at least 24 h and the onset of the attacks must be separated by at least 30 days [4].

The second most common form of MS is the progressive form, subdivided into primary and secondary subtypes [5]. In the primary progressive form, which affects about 10-15% of the MS patient population, the clinical presentation is marked by a slow onset without the distinct attacks that are typical for the relapsing-remitting form [6]. In the secondary progressive form, the patient presents initially in the relapsing-remitting form with later transformation into progressively worsening disability as a result of individual clinical relapses.

About 10% of MS patients present with a “clinically isolated syndrome”, also known as a “monosymptomatic attack”. Patients with this form have one or two episodes of characteristic symptoms, followed by complete recovery to their neurologic baseline. By its very nature, it is...
clearly an unusual form of MS and some authorities question whether it is truly part of the MS family or a distinct clinicopathologic disease.

Several variants of MS have been identified. An especially aggressive form, known as acute fulminant MS of the Marburg type, manifests with a rapidly progressive neurologic deterioration from severe axonal loss, leading to death within just a few months [7]. Another variant, neuromyelitis optica (NMO), also known as Devic disease, is characterized by both visual and myelopathic symptoms because of simultaneous or sequential involvement of the optic nerve and spinal cord. Recent investigations have identified a specific serum antibody biomarker, NMO-IgG, for the target antigen, aquaporin 4, that distinguishes NMO from MS [8]. It is hypothesized that autoantibodies from peripheral B cells bind to aquaporin 4 along the endothelial surface and activate an inflammatory demyelination and necrosis [9]. Baló concentric sclerosis is a variant form characterized by alternating concentric bands of demyelination and normal myelination, not only histologically but also by MRI [10].

Pathologically, MS is an inflammatory process, with microglial infiltration combined with perivascular cuffing of lymphocytes marking the acute phase of MS plaque formation. In this phase, the oligodendrocyte is most affected by these changes, resulting in the overall loss of myelin. Together with focal hypercellularity, this characterizes the “sclerose en plaque”, as it was originally called by Cruveilhier, which has a predilection for the periventricular zone. When the plaque enters the inactive phase, complete myelin loss and gliosis predominate while the inflammatory changes seen in the acute phase subside. Destruction of axons also ensues, with resultant parenchymal loss and atrophy.

Magnetic resonance imaging is the imaging modality of choice for the evaluation of patients suspected of having MS and is an essential tool in assessing the natural course of the disease as well as the effects of treatment. MRI frequently identifies many lesions that are not suspected from clinical examination [11]. Small focal hyperintense lesions, particularly in a periventricular distribution, with relatively less mass effect for the size of the lesion characterize the disease on T2-weighted images [12]. Many MS lesions are ovoid in shape with their long axis perpendicular to the ventricular wall. This pattern corresponds to the pathway of periventricular white matter vessels and constitutes a pathologic feature referred to as Dawson’s finger [13]. An especially important location for MS plaques is the corpus callosum-septum pellucidum interface. The presence of lesions at this site carries increased specificity for the diagnosis of MS [14]. Fluid-attenuated inversion recovery (FLAIR) imaging is particularly helpful in identifying periventricular lesions, although lesions of the brainstem and cerebellum may be less obvious with this technique [15, 16]. Magnetization transfer imaging, especially on post-contrast imaging, is recommended for its higher contrast-to-noise ratio and has been advocated for the detection of disease in a patient with normal-appearing white matter on pre-contrast imaging [17, 18].

Specific MRI manifestations of the disease have now been recognized as fulfilling the “dissemination in space” and “dissemination in time” components of the clinical McDonald criteria. For dissemination in space, at least three of these four MRI features must be identified: one contrast-enhancing lesion or nine T2-hyperintense lesions if there is no contrast-enhancing lesion; at least one infratentorial lesion; at least one juxtaocular lesion; and at least three periventricular lesions. To fulfill dissemination in time, follow-up MRI after the initial examination is required and must show either a new contrast-enhancing lesion or a new T2 hyperintense lesion that was not evident on the initial study. Follow-up imaging is recommended at 3 months after the initial scan [17].

On initial inspection, the imaging appearance of some large plaques may mimic that of a brain tumor. Closer evaluation will reveal the relative lack of mass effect expected given the size of these “tumefactive” MS plaques, which provides a valuable clue to the correct diagnosis of demyelinating disease [19]. Distinction between plaques in the active phase and plaques in the chronic phase can be made with contrast-enhanced MRI, as active plaques enhance whereas chronic plaques do not [12, 20]. The enhancement correlates with the presence of inflammatory cells [12].

In long-standing disease, cerebral atrophy with prominent ventriculomegaly and sulcal enlargement is commonly noted on MR studies. These features appear to be more common in patients with the secondary progressive form of the disease than in patients with the relapsing-remitting form [21]. Assessment of cerebral atrophy, through subjective measurement of corpus callosum volume or third ventricle width or by computer-aided techniques, correlates better with clinical disability than the number of lesions on T2-weighted images [21, 22]. Advanced MRI techniques are expected to more precisely characterize the nature of the MS plaque and hold the promise of better assessing the effects of therapy. Magnetization transfer imaging has shown differences in magnetization transfer between MS plaques and other white matter lesions, such as those of senesence [23]. On MR spectroscopy, a decreased peak of N-acetyl aspartate (NAA), a decreased NAA:creatinine ratio, and an increased choline:creatine ratio have been seen in active and chronic plaques, although the incidence varies among the different clinical types of the disease. Increased amounts of choline, lipids, lactic acid, and inositol have also been variably reported and highlight the dynamic nature of the MS plaque [24, 25]. Recently, MR perfusion studies have shown regions of decreased perfusion, believed to represent areas of hemodynamic and microvascular abnormality, in areas of normal-appearing white matter on T2-weighted MR images.

In general, spinal cord MS plaques tend to involve one or two vertebral body segments, compared to transverse myelitis, which is usually more diffuse and often extends