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# Neuroimaging of Multiple Sclerosis, Acute Disseminated Encephalomyelitis, and Other Demyelinating Diseases

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## Introduction

Demyelinating diseases are characterized by acquired damage to normally constituted myelin sheaths as a consequence of a great variety of different insults.[1] According to the etiology, demyelinating disorders are classified as primary and include multiple sclerosis (MS) and neuromyelitis optica (NMO) or as secondary and include allergic acute disseminated encephalomyelitis (ADEM), viral progressive multifocal leukoencephalopathy (PML), human immunodeficiency virus infection, and subacute sclerosing panencephalitis; vascular Binswanger disease and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); postanoxic encephalopathy; posterior reversible encephalopathy syndrome; central pontine myelinolysis; Marchiafava-Bignami disease; Wernicke encephalopathy; toxic lesions due to methanol, ethylene glycol, toluene, carbon monoxide, or organic mercury; lesions due to radiation; and disseminated necrotizing leukoencephalopathy.[1]

In this review article, the main clinical and pathologic aspects and the basic features of the diagnosis of MS and NMO have been discussed. Special focus is devoted to the McDonald magnetic resonance imaging (MRI) diagnostic criteria for MS.[2-4] Amongst the secondary demyelinating diseases, ADEM and PML have been described in detail. The increased risk of PML in patients with MS treated with recently Food and Drug Administration–approved immunomodulating agents requires the identification of early clinical and radiological features so as to avoid severe outcomes in terms of disability and mortality. Finally, a general overview of the most common diseases to consider in the differential diagnosis of MS and other demyelinating diseases is presented.

## Multiple Sclerosis

MS is a disabling disease of the central nervous system (CNS) with an autoimmune pathogenesis leading to areas of inflammatory demyelination and various degrees of widespread neuroaxonal damage.[5] The etiology of MS is unknown but the interplay of several genetic and environmental factors is likely to contribute to the development of the disease. It occurs in young adults, with a low prevalence in children (3%-5%) and in adults older than 50 years (9%). It is more common in women (with a ratio of 2:1) and its prevalence is between 2 and 150 per 100,000 in the white population.[6] The risk of significant morbidity combined with a comparatively early onset makes MS a devastating disease, both socially and economically.[7]

In 85%-90% of patients, MS initially presents with a first clinical symptom such as optic neuritis (ON) (21%), isolated brainstem syndrome (10%), or long-tract syndrome (46%), and it is referred to as clinically isolated syndrome (CIS) suggestive of MS. Approximately, 60%-80% of adult patients presenting with a CIS who have MRI-visible brain lesions develop clinically definite MS within 2 years (range 0.5-12).[8]

In terms of clinical course, most patients (80%-90%) present with relapsing-remitting MS (RR-MS) characterized by unpredictable relapses followed by periods of remission. Deficits suffered during attacks may either resolve completely or leave behind clinical sequelae. Approximately 65% of the patients with RR-MS develop secondary progressive MS (SP-MS) characterized by progressive neurologic decline between acute attacks without any definite period of remission. Approximately 10% of patients with MS present with a primary progressive course (PP-MS) characterized by constant progression of disability from onset with no improvement.[9] Currently, 9 Food and Drug Administration–approved disease-modifying pharmaceutical agents are available for the treatment of RR-MS: interferon β-1b (Betaseron and Extavia),

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interferon β-1a (Avonex and Rebif), glatiramer acetate (Copaxone), natalizumab (Tysabri), fingolimod (Gilenya), teriflunomide (Aubagio), and dimethyl fumarate (Tecfidera); and one for treatment of SP-MS: mitoxantrone (Novantrone).

MS is a clinical diagnosis, dependent on a detailed history, careful neurologic examination, and supportive paraclinical investigations including MRI scans, cerebrospinal fluid (CSF), evoked potentials, and blood tests to exclude confounding diagnoses.

## Diagnostic Conventional MRI

Owing to its exquisite sensitivity in detecting MS lesions, MRI is the most used paraclinical tool for supporting a diagnosis of MS. Lesions visible as hyperintensities on T2-weighted (T2-W) or fluid-attenuated inversion recovery (FLAIR) images or on both represent the MRI correlate of a focal inflammatory event. Although there are no pathognomonic MRI findings, some aspects of lesion morphology and localization are typical of MS, such as the predominant perivenous distribution of intracerebral foci. The ovoid shape is typical of perivascular lesions directly adjacent to the corpus callosum as well as perpendicular to the major axis of the lateral ventricles ("Dawson fingers"). Other typical sites of predilection of white matter (WM) MS lesions are the infratentorial, callosal, juxtacortical, and temporal brain areas (Fig. 1). Gadolinium (Gd)-enhancing lesions visible on postcontrast T1-weighted (T1-W) images reflect blood-brain barrier inflammatory disruption and may precede the development of both T2-visible lesions and clinical symptoms. The enhancement pattern is variable and may appear homogeneous, curvilinear, or nodular. The initial lesion usually appears as a nodule, which can evolve to a ring or arc shape. If lesions recrudesce, they usually have an arc or ring appearance.[1] Treatment with steroids during the acute phase may also be associated with a marked reduction in lesion enhancement and FLAIR-T2 hyperintensity. Contrast enhancement may be used to add specificity to the findings of multiple hyperintensities on T2-W images because the coexistence of enhancing and nonenhancing lesions is quite common in MS but makes many other diagnoses unlikely.[1]

Approximately 65%-80% of Gd-enhancing lesions appear acutely hypointense on corresponding precontrast T1-W images and evolve into lesions that are isointense with normal-appearing WM (NAWM) once the enhancement ceases. Almost 14%-41% of acute T1-hypointense lesions persist after Gd-enhancement resolution and evolve into chronic hypointense lesions or "black holes." As active lesions can appear hypointense on precontrast T1-W scans because of the presence of edema, only those persisting for a minimum of 6 months are defined as "black holes." Black holes are the result of demyelination, thinned matrix, and loss of axons.[10]

The spinal cord (SC) is another site of predilection of MS lesions and plays a major role in the development of clinical disability. At postmortem examination, 86% of patients with MS have SC lesions, and cord abnormalities are detected on MRI scans in up to 89% of patients with established disease.[11] MS lesions in SC are more frequent in the cervical portion, are located more peripherally and in less than half the cross-sectional area of the cord, are limited to 2 vertebral segments in length, and are not visible as T1 hypointensities (Fig. 2). Acute lesions can cause swelling of the cord and enhance after Gd administration.[1]

A classic MS diagnostic criterion is the evidence of lesions in the CNS disseminated in space (DIS) and disseminated in time (DIT) that is, more than 1 clinical episode involving more than 1 area of the CNS (brain, SC, and optic nerves). About two-thirds of patients experiencing a single episode of suspected demyelination or CIS have cerebral WM lesions indistinguishable from those seen in definite MS. As the presence of such lesions increases the likelihood of developing clinically definite MS, it is not surprising that formal MR imaging features for dissemination in space and time were incorporated within the diagnostic criteria for MS by an international

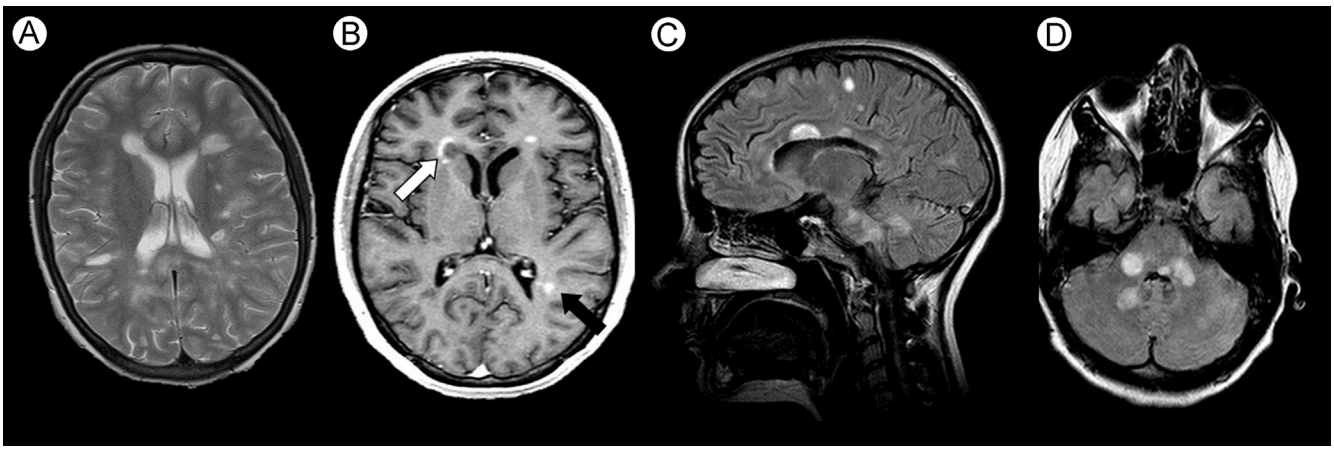


**Figure 1** MS lesions. Typical periventricular (A) distribution of MS lesions on a T2-weighted image. Corresponding contrast-enhanced T1 image (B) shows solid enhancement (black arrow) and typical "open-ring" enhancement (white arrow). Sagittal (C) and axial (D) FLAIR with typical lesion distribution in the body of the corpus callosum and the cerebellar peduncle.