INTRODUCTION

The diagnosis of multiple sclerosis (MS) is based on demonstrating evidence of inflammatory-demyelinating injury within the central nervous system (CNS) that is disseminated in both time and space. Diagnosis is made through a combination of the clinical history, neurologic examination, magnetic resonance imaging (MRI) and the exclusion of other diagnostic possibilities. Other so-called “paraclinical” tests, including the examination of the cerebrospinal fluid (CSF), the recording of evoked potentials, urodynamic studies of bladder function, and ocular coherence tomography (OCT), may be helpful in establishing the diagnosis for individual patients, but are often unnecessary (Poser et al., 1983; McDonald et al., 2001; Polman et al., 2005, 2011).

Dissemination in time means that there must have been at least two discrete episodes of inflammatory disease activity separated by at least 1 month (Polman et al., 2005, 2011). The purpose of this requirement is to ensure that monophasic illnesses do not get classified as MS, which, by definition, is a recurrent, inflammatory process. In the pre-MRI era, these episodes needed to be identified clinically, but the most recent international diagnostic criteria permit the use of purely imaging events to establish such time dissemination (Polman et al., 2011).

Dissemination in space requires demonstration that the disease process involves at least two discrete neuroanatomic areas within the CNS. In the pre-MRI era, this demonstration required the elicitation of neurologic signs, which could be attributed, unequivocally, to two or more locations within the CNS. By contrast, in the modern era, dissemination in space can be established using paraclinical evidence, primarily MRI, in addition to the clinical findings (Poser et al., 1983; McDonald et al., 2001; Polman et al., 2005, 2011).

Clinically, MS is characterized by discrete episodes (“attacks” or “relapses”) of neurologic dysfunction. The symptoms produced by these episodes vary considerably between patients and depend upon the site of neurologic involvement. Commonly patients may experience numbness, tingling, weakness, vision loss, gait impairment, incoordination, imbalance, and bladder dysfunction. In between these attacks, at least during the relapsing-remitting (RR) phase of the illness, patients are neurologically stable (Lublin and Reingold, 1996). Nevertheless, residual symptoms may persist and many patients experience fatigue or heat sensitivity in the interval between attacks. Over several years to decades, many patients who begin with RRMS evolve to the secondary progressive (SP) phase of the illness, in which they experience an insidious worsening of function and the accumulation of neurologic disability unrelated to any acute attacks that may or may not occur. For example, in a large cohort of MS patients in Ontario, Canada, with a median follow-up time of 20 years, 66% of MS patients who started in the relapsing phase of disease went on to develop SPMS at a median time of 15 years (Scalfari et al., 2013), whereas in a British Columbia cohort, 58% of patients with relapsing MS developed SPMS after a median time of 19.1 years (Tremlett et al., 2008). A small percentage of patients (~10–20%) experience a clinical course of primary progressive (PP) MS, in which they only experience insidious worsening and never have acute attacks. An even smaller
number (~5%) begin as PPMS but ultimately experience clinical episodes. These patients are said to have progressive relapsing (PR) MS (Lublin and Reingold, 1996).

### COMMON PRESENTATIONS

#### Optic neuritis

Acute demyelinating optic neuritis is the presenting symptom in about 20% of MS patients and affects about half of MS patients at some point in the disease course (Balcer, 2006).

Optic neuritis is diagnosed clinically based on a history of subacute visual blurring or loss, evolving over hours to days, typically associated with eye pain (Optic Neuritis Study Group, 1991). Color vision, especially red desaturation, and low-contrast vision are most prominently affected. Patients may complain of a “blind spot” or “blurry spot” within the visual field corresponding with a scotoma on formal visual field testing.

During the acute phase of optic neuritis, in two-thirds of the cases, the optic disc appears normal on funduscopic examination (retrobulbar optic neuritis); in the other third of cases, the optic nerve appears swollen (papillitis) (Optic Neuritis Study Group, 1991). A relative afferent papillary defect (a Marcus Gunn pupil) is usually present (Balcer, 2006).

In acute optic neuritis, MRI usually demonstrates a hyperintensity on T2-weighted images (i.e., a T2 lesion) of the affected optic nerve as well as contrast enhancement within the nerve, best appreciated on fat-saturated sequences of the orbit. Full-field pattern reversal visual evoked potentials (VEPs) typically exhibit a prolongation in the latency of a well-formed P100 potential following stimulation of the affected eye. This pattern of latency delay is suggestive of a demyelinating injury. After the acute optic neuritis subsides, most patients exhibit some degree of retinal nerve fiber layer (RNFL) loss detectable on funduscopic, with or without optic disc pallor (Frisen and Hoyt, 1974). The magnitude of RNFL loss can be quantified using retinal OCT (Costello et al., 2006).

The differential diagnosis for acute optic neuritis includes ischemic optic neuropathy, infections (e.g., syphilis, Lyme disease, bartonella, varicella-zoster virus, herpes simplex virus), inflammatory disorders (neuromyelitis optica (NMO), systemic lupus erythematosus (SLE)), infiltrative disorders (sarcoidosis, lymphoma), compressive lesions or those related to elevated intracranial pressure (tumors, pseudotumor cerebri), toxic/nutritional (deficiencies of vitamins B1 or B12, malnutrition), hereditary (mitochondrial, autosomal) as well as primary retinal disorders (e.g., central serous retinopathy).

Certain clinical features that are atypical for inflammatory optic neuritis should raise concern that the acute optic neuropathy may not be due to demyelinating disease. These include: a completely painless syndrome, complete visual loss, a hyperacute onset (which suggests an ischemic/vascular cause), bilateral involvement (which is common in NMO as well as Leber’s hereditary optic neuropathy), neuroretinitis (which is characterized by the presence of a macular “star” on retinal examination and often associated with bartonella infection), retinal hemorrhages, fever, or poor clinical recovery by one month or more following the onset of clinical symptoms (Miller et al., 2008).

#### Myelitis

Transverse myelitis is defined as impairment of motor, sensory, and bowel or bladder tracts in the spinal cord secondary to inflammatory-mediated injury.

Partial myelitis is defined as involvement of one or more, but not all, of these functional spinal tracts.

The occurrence of a band-like tightening sensation around the chest or abdomen (the so-called MS “hug”) is a typical symptom of myelitis and suggests involvement of the posterior columns of the spinal cord. It is often accompanied by a horizontal sensory level.

The myelitis that occurs in MS is typically partial and usually presents subacutely (Cordonnier et al., 2003; Bourre et al., 2012). This corresponds with the typical imaging and neuropathologic appearance of MS involvement in the spinal cord of patchy asymmetric inflammatory-demyelinating lesions.

By contrast, a complete transverse myelitis should prompt a detailed evaluation for other potential causes, especially if it is: hyperacute in onset, longitudinally extensive (involves three or more vertebral segments on T2-weighted MRI images), accompanied by prominent radicular pain, or associated with absent reflexes (Miller et al., 2008).

#### Brainstem syndromes

The brainstem is commonly affected in MS. The clinical syndromes produced by brainstem involvement in MS include: double vision (cranial nerves III, IV, VI), internuclear ophthalmoplegia (medial longitudinal fasciculus), facial weakness or myokymia (cranial nerve VII), vertigo (cranial nerve VIII), or bulbar (medullary) symptoms such as dysphagia, dysarthria, and tongue weakness (cranial nerves IX, X, XII). Facial sensory impairment (cranial nerve V) may arise from multiple localizations, including the brainstem, cervical cord (due to the fact that afferent trigeminal pathways descend from their entry at the pontomedullary junction to the level of the upper cervical spine), subcortical and cortical sensory pathways. Less common brainstem symptoms in MS include hearing loss and severe bulbar signs. Involvement of cerebellar networks that connect...
with the brainstem can lead to unilateral ataxia, dysmetria, or dysdiadochokinesia.

Acquired pendular nystagmus in MS is thought to be caused by a disruption of the cerebellopontine networks involved in neural integration and maintenance of gaze (Gresty et al., 1982; Lopez et al., 1996; Tilikete et al., 2011). This syndrome manifests as a “shimmering” or oscillation of vision and can be confirmed on funduscopic examination by detecting pendular movements of the optic disc, even when eye movements may otherwise appear grossly normal on standard pursuit testing.

**Motor symptoms**

Weakness affects up to 89% of MS patients at some point in the disease course (Swingler and Compston, 1992). Focal weakness in the limbs in MS is usually due to involvement of the corticospinal tract and, thus, it is often accompanied by other signs of the upper motor neuron syndrome, such as hyperreflexia, spasticity, and an extensor plantar response on Babinski or Chaddock testing.

Spasticity, a velocity-dependent increase in resistance to passive muscle stretch, is associated with stiffness, spasms, cramping, and gait impairment and can occur in the absence of weakness.

Paroxysmal tonic “seizures” are involuntary contractions of the limbs, which are sometimes rhythmic. Tonic seizures are often seen in association with spinal cord and brainstem lesions (Matthews, 1958). They consist of tonic spasms confined to one side of the body, lasting about 30 seconds to a minute; occur multiple (often >15) times a day; are frequently preceded by sensory symptoms on the opposite side of the body; and can be precipitated by movements or hyperventilation. They are presumably distinct from true cortical seizures because electroencephalogram recordings during ictal events are invariably normal (Watson and Chiu, 1979), and, moreover, several case histories are strongly suggestive of a spinal origin (Castaigne et al., 1968; Ekbom et al., 1968). Tonic spasms should be distinguished from muscle spasms, which are often associated with spasticity, as the treatments are different. Tonic spasms are probably related to other paroxysmal syndromes that occur in MS, such as paroxysmal dysarthria-ataxia (Andermann et al., 1959; Ostermann and Westerberg, 1975; Blanco et al., 2008). Treatment with low doses of carbamazepine or related agents often provides rapid and substantial relief (Espir and Millac, 1970).

**Sensory impairment**

Numbness and paresthesias are common symptoms experienced by MS patients. When these symptoms are transient, lasting only seconds to minutes, they are unlikely to be due to an acute relapse in MS. Conversely, when they last many hours to days they may well reflect an acute inflammatory-demyelinating injury. Sensory complaints affect 87% of MS patients at some point in the disease course and are part of the presenting syndrome in 34% (Swingler and Compston, 1992).

Pain and other unpleasant sensations were reported as troubling symptoms by 54% of MS patients in a large survey (Minden et al., 2006). Pain in MS usually has neuropathic features such as burning, electrical or sharp sensations.

Lhermitte’s symptom—an electrical-shock-like sensation running down the spine upon neck flexion—occurs in up to one-third of MS patients at some point in the disease (Kanchandani and Howe, 1982). The neuroanatomic localization of Lhermitte’s symptom is the posterior column in the cervical or upper thoracic spinal cord.

**Imbalance**

MS patients often describe the sensation of being off-balance, unsteady, or uncoordinated. In these circumstances, a careful neurologic examination is essential to localize the problem, because these symptoms can arise from cerebellar dysfunction (tremor, dysmetria, dysdiadochokinesia, gait ataxia, eye movement abnormalities), sensory impairment (sensory ataxia), vestibular dysfunction, spasticity, or weakness.

**Cognitive impairment**

Subtle cognitive deficits affect up to 40–70% of MS patients depending on the study population and testing approach (Chiaravalloti and DeLuca, 2008). MS can lead to frank dementia, but this is rare and usually occurs in the context of extensive disease (Staff et al., 2009). The most common domains affected in MS on formal neuropsychologic testing are slowed information processing, executive dysfunction, and impairment of long-term verbal and visual memory (Chiaravalloti and DeLuca, 2008). Cognitive impairment in MS is associated with white-matter involvement and brain atrophy as well as cortical demyelinating plaques that are not well visualized using conventional MRI sequences (Rao et al., 1989; Calabrese et al., 2009).

**Depression**

Major depression affects about 30–45% of MS patients depending on the screening methodology used (Patten et al., 2003; Beiske et al., 2008; Jones et al., 2012). The cause is unclear, but in some patients may relate to injury of frontotemporal networks from MS, whereas in others it may simply be a comorbid condition (Zorzon et al., 2002).
Fatigue

Fatigue is one of the most debilitating symptoms in MS and was reported as a current symptom in 83% of patients in a large survey (Minden et al., 2006). Patients often describe the fatigue of MS as a general sense of low energy. It is important to distinguish complaints of fatigue from complaints of motor weakness. Fatigue can persist between clinical relapses, but often worsens in association with disease activity. Fatigue is a distinct feature of MS and probably relates to chronic CNS inflammation (Krupp et al., 1988). However, it is always important in the evaluation of MS patients with fatigue to exclude alternate causes, particularly depression, hypothyroidism, adrenal insufficiency, anemia, sleep disorders, and sleep disruption (such as from nocturia or pain).

Bladder and bowel dysfunction

Neurogenic bladder and lower urinary tract impairment is an important cause of disability in MS (de Seze et al., 2007; Fowler et al., 2009; De Ridder et al., 2013). One of the most common manifestations of neurogenic bladder in MS is detrusor hyperreflexia – “overactive” bladder – which is present in about two-thirds of MS patients who undergo formal urodynamic testing (Litwiller et al., 1999; de Seze et al., 2007). This reflex involves the coordinated contraction of the detrusor muscle with a simultaneous relaxation of the urethral sphincter. The detrusor reflex is inhibited voluntarily through pathways originating in the cortex and traveling in the spinal cord and is controlled by muscarinic cholinergic innervation. Loss of this inhibition leads to overactivation of the reflex at small bladder volumes and automatic emptying, resulting in symptoms of urinary urgency, frequency, and incontinence. Treatment with antimuscarinic anticholinergic medications can provide symptomatic relief. However, anticholinergic therapies can aggravate symptoms of poor emptying and cause urinary retention, particularly in patients with elevated postvoid residual testing, so monitoring of postvoid residual and attention to the presence of more than one pathology is advisable (Fowler et al., 2009). Clean intermittent catheterization may be needed in severe cases of detrusor hyperactivity and in cases with mixed pathology. Local injection of botulinum toxin into the bladder can also provide symptomatic relief from detrusor overactivity when oral therapy is insufficient (Herschorn et al., 2011; Ginsberg et al., 2012; Nitti et al., 2013). About 20–25% of MS patients with bladder symptoms exhibit findings of bladder underactivity from low contractility on urodynamic testing, which leads to the symptoms of urinary frequency and incomplete emptying. The most difficult urinary condition to manage in MS is that of detrusor-sphincter dyssynergia, the prevalence of which varies widely in the literature, but was identified in about 25% of patients undergoing urodynamic studies in a large meta-analysis (Litwiller et al., 1999). Detrusor-sphincter dyssynergia arises from the loss of coordination between the detrusor and sphincter muscles, and leads to urinary hesitancy, interruptions of the urinary stream, and incomplete emptying. Detrusor-sphincter dyssynergia usually requires clean intermittent catheterization. In MS patients, mixed pathologies of neurogenic bladder dysfunction are remarkably common (Nakipoglu et al., 2009). Recurrent urinary tract infections in an MS patient are highly suggestive of neurogenic bladder dysfunction.

Stress incontinence (leakage associated with laughing, jumping, or other physical maneuvers) is a common urologic comorbidity, particularly in women, but is typically unrelated to the MS disease process and needs to be distinguished from neurogenic causes of urinary incontinence.

Acute urinary retention can be a presenting symptom of acute myelitis. A postvoid residual, or straight catheterization, is an important measure of neurogenic bladder function in this context.

Bowel dysfunction in MS is less common than bladder involvement, and constipation is the most frequent complaint. Bowel incontinence from MS usually occurs in the context of severe spinal cord injury (Chia et al., 1995; Hennessey et al., 1999).

Sexual dysfunction is reported to affect up to one-third of patients in some series and up to 80% of men and 50–70% of women in others. The most common pathologies identified are erectile dysfunction in men and loss of libido and/or fatigue in women (Hennessey et al., 1999; Litwiller et al., 1999; Demirkiran et al., 2006; Minden et al., 2006).

Heat sensitivity

Heat characteristically aggravates MS symptoms and can transiently bring out old symptoms that had previously remitted. This can occur in the context of a hot day, a hot shower, or with vigorous exercise. The physiologic basis for heat sensitivity in MS – Uthoff’s phenomenon – is less efficient conduction of demyelinated nerves at higher temperatures (Davis and Jacobson, 1971). Cooling down core body temperature helps to ameliorate this physiologic process (Watson, 1959). Symptoms transiently brought out by heat in MS can be uncomfortable and temporarily disabling, but they do not cause or indicate new inflammatory-mediated injury and are not considered relapses.

Headache

About two-thirds of MS patients complain of headaches, and most headaches in MS patients are attributable to migraine (Kister et al., 2010). In the Nurses’
Health Study II, migraine was slightly more common in women with MS; having migraine was associated with a small increased risk of MS; but having MS was not significantly associated with developing migraine (Kister et al., 2012). Accurate diagnosis of migraine is important in MS in order to distinguish between migraine and MS symptomatology, guide appropriate treatment, and not misclassify migraine symptoms as MS attacks (Gelfand et al., 2013). Migraineurs have altered sensory perception, which may also influence the patient experience of some MS-related symptoms, such as fatigue and neuropathic pain.

**Pseudorelapse**

Transient worsening or recrudescence of MS symptoms can occur in the context of infection or other stressors (Hufschmidt et al., 2010). A common culprit is a urinary tract infection, which may otherwise be asymptomatic, particularly in women (Rakusa et al., 2013).

**DIAGNOSIS AND CLINICAL PHENOTYPES**

**Preclinical MS – the radiologically isolated syndrome**

The increasing use (and overuse) of MRI has led to renewed interest in the concept of “preclinical” MS – the incidental identification of imaging abnormalities indicative of MS in patients who have never had a clinical attack. This clinical scenario has been called the “radiologically isolated syndrome” (Okuda et al., 2009). About one-third of patients with preclinical MS identified incidentally on MRI will experience a clinical attack within 5 years (Lebrun et al., 2009; Okuda et al., 2009). Identification of an asymptomatic spinal cord lesion in a patient with preclinical MS is strongly predictive of clinical progression (Okuda et al., 2011). In the pre-MRI era, the incidence of finding MS incidentally at autopsy was about 0.1% (Georgi, 1961; Vost et al., 1964; Gilbert and Sadler, 1983; Engell, 1989), which suggests that as many as a third of patients with pathologic MS were asymptomatic during life in that era or at least did not have symptoms that brought them to medical attention.

**The first clinical demyelinating attack – clinically isolated syndromes**

A first lifetime clinical demyelinating attack, such as an acute optic neuritis, partial myelitis, or a brainstem syndrome, is called a “clinically isolated syndrome” (CIS).

The risk of developing MS after a CIS is highest if there is at least one T2 lesion typical of demyelination on the baseline brain MRI. Identification of oligoclonal bands in the CSF at the time of a CIS doubles the risk of progression to MS independent of MRI findings (Tintore et al., 2008). In the Optic Neuritis Treatment Trial, 75% of patients with acute demyelinating optic neuritis and at least one subclinical T2 lesion on baseline brain MRI went on to develop MS at 15 years of follow-up compared to 25% of those with a normal baseline brain MRI (Halperin, 2008). A similar risk stratification was observed in a cohort at Queens Square Hospital in London of patients with any kind of CIS, in which 82% of CIS patients with an abnormal baseline brain MRI progressed to MS clinically at 20 years of follow-up compared to 21% of those with a normal baseline brain MRI (Fisniku et al., 2008). The absolute number of T2 lesions does not appear to increase the long-term risk of developing MS, just their presence or absence.

**Relapsing-remitting multiple sclerosis**

RRMS is the commonest form of MS, and about 80–90% of all MS patients will fall into this category at some point in their disease course. Relapses (“attacks” or “flares”) are discrete episodes of neurologic dysfunction that typically evolve over hours to days and then persist for days to weeks before remitting. In between attacks, patients tend to be stable but often experience fatigue and heat sensitivity.

**Secondary progressive MS**

Most, but not all, patients with RRMS will go on to develop insidious neurologic worsening and accumulation of disability – “secondary progression” – that is not directly related to discrete attacks. The median time to development of secondary progression has varied in different studies, from 10–15 years in Canadian series to about 19 years in Swedish, French, and Italian cohorts (Minderhoud et al., 1988; Weinschenker et al., 1989; Runmarker and Andersen, 1993; Confavreux and Vukusic, 2006; Rovaris et al., 2006; Tremlett et al., 2009). Time to development of secondary progression is shorter when the age at clinical onset is greater (Confavreux et al., 1980; Eriksson et al., 2003; Salfari et al., 2013).

Progression, and not relapse activity, accounts for most of the long-term disability burden in MS (Confavreux et al., 2000).

The transition from RRMS to SPMS is often a continuum, with insidious progression sometimes occurring in the background of clinical relapses and inflammatory disease activity on MRI.

Before attributing insidious neurologic progression to MS in a patient with established MS, it is important to exclude secondary causes, such as cervical spondylosis.
Evolving diagnostic criteria for the relapsing-remitting form of multiple sclerosis

Diagnostic criteria for MS have evolved over the past several decades, with each revision impacting the apparent prevalence and prognosis of the disorder. The result has been to encourage earlier diagnosis without compromising accuracy.

In the pre-MRI era, the diagnosis of MS was based solely on clinical history and examination and required demonstration of at least two clinical attacks disseminated in time and space. In 1983 a working group chaired by Poser allowed “paraclinical” evidence, specifically neuroimaging or electrophysiologic abnormalities, to substitute as evidence of dissemination in space for diagnosis of “clinically definite” MS (Poser et al., 1983). Under Poser criteria, an “attack” was defined as an occurrence of neurologic dysfunction lasting more than 24 hours.

In 2001, an international panel chaired by McDonald (McDonald criteria), allowed MRI evidence of disease activity to serve as evidence of dissemination in time and space (McDonald et al., 2001). The use of MRI was designed to encourage more accurate exclusion of diagnostic mimics (Miller et al., 2006). The “clinically definite” terminology was discarded and the diagnosis was simply said to be “MS.” MRI criteria for dissemination in space required satisfying three of the following four features: (1) ≥1 gadolinium-enhancing lesion or ≥9 T2 hyperintense lesions; (2) ≥1 infratentorial lesion (or spinal cord lesion, as modified by a 2005 revision: Polman et al., 2005); (3) ≥1 juxtacortical lesion; and (4) ≥3 periventricular lesions. These MRI criteria (commonly referred to as Barkhof criteria) were derived from studies that identified imaging features most predictive of conversion from CIS to clinically definite MS (Barkhof et al., 1997; Tintore et al., 2000). The panel also allowed for two T2 hyperintense lesions in a patient with oligoclonal bands on CSF examination to satisfy the criteria for dissemination in space (McDonald et al., 2001). A 2005 revision allowed for a new subclinical T2 hyperintense lesion occurring at least 1 month after a reference scan obtained >1 month after the onset of the first clinical episode to satisfy the requirement for dissemination in time (Polman et al., 2005; Swanton et al., 2006). This was simplified in 2011 criteria to allow for any new T2 lesion with reference to the baseline scan irrespective of the timing of the baseline MRI (Polman et al., 2011).

McDonald criteria were most recently updated in 2010 and published in 2011 (Table 12.1) (Polman et al., 2011). MRI criteria for dissemination in space were simplified to allow ≥1 T2 hyperintense lesion in two of four of the following regions: (1) periventricular white matter; (2) juxtacortical white matter; (3) infratentorial white matter; and (4) spinal cord (excluding symptomatic lesions from the cord or brainstem), which was found to have a similar specificity with preserved sensitivity and accuracy compared to earlier iterations for predicting conversion from CIS to MS (Swanton et al., 2006, 2007). The other major update was to allow the “simultaneous presence” of an asymptomatic (subclinical) enhancing lesion to count as dissemination in time (Rovira et al., 2009; Montalban et al., 2010).

As an example of how these approaches differ, a patient who experiences a single clinical attack and develops a new subclinical gadolinium-enhancing lesion on follow-up MRI would be said to have MS under McDonald, but not Poser, criteria. If the same patient had a single subclinical enhancing lesion on baseline MRI at the time of the first clinical attack, the diagnosis would be MS under 2011 criteria (but CIS under 2001 and 2005 McDonald criteria).

Use of McDonald compared to Poser criteria results in two to three times as many patients receiving a diagnosis of MS within 1 year after the first clinical attack (Dalton et al., 2002; Tintore et al., 2003; Sormani et al., 2008). However, the time it takes to reach early disability milestones is higher using Poser criteria, illustrating how simply changing diagnostic definitions can appear to influence prognosis (Sormani et al., 2008).

Primary progressive MS

About 10–20% of patients with MS never experience a discrete relapse, but instead present with insidious neurologic worsening and disability accumulation—“progression” (Weinshenker et al., 1989; Confavreux et al., 2000; Tremlett et al., 2009). This phenotype is called PPMS. The age at which clinical progression begins in patients with PPMS and SPMS is nearly identical in most (Tutuncu et al., 2013), but not all (Tremlett et al., 2009), large MS epidemiologic cohorts. Measures of axonal injury, such as RNFL thinning, are also nearly indistinguishable between patients with both progressive phenotypes (Gelfand et al., 2012), as is the cumulative burden of MS susceptibility genes (Gourgou et al., 2011). One compelling conceptualization is that “primary progressive” MS may simply be the manifestation of “secondary progression” in people with a subclinical course of “relapsing-remitting” disease (Confavreux and Vukusic, 2006).

Diagnostic criteria for primary progressive disease were most recently revised in 2011 (Table 12.2) (Polman et al., 2011). PPMS can be diagnosed when a patient has experienced at least 1 year of clinical progression plus two out of the following three criteria: (1) evidence for dissemination in space on MRI based on ≥1 T2
hyperintense lesion in at least one area characteristic for MS (periventricular, juxtacortical, or infratentorial); (2) ≥ 1 T2 lesion in the spinal cord; and (3) positive oligoclonal bands and/or elevated immunoglobulin G (IgG) index in the CSF as evidence of intrathecal inflammation (Polman et al., 2011).

**Progressive-relapsing MS (PRMS)**

About 5% of MS patients present with a hybrid course characterized by prominent progression at onset (what appears to be primary progressive disease initially), but then develop a few superimposed relapses (Confavreux and Vukusic, 2006).

### The cerebrospinal fluid examination in MS diagnosis

A CSF examination can be helpful for providing evidence of intrathecal inflammation and to exclude diagnostic mimics, but is not formally required for diagnosis (Polman et al., 2011).

Oligoclonal bands – IgGs unique to the CSF and that are not present in a corresponding serum sample – are the most specific of all CSF tests for MS. Over 95% of MS patients have oligoclonal bands (Andersson et al., 1994; Freedman et al., 2005), but the proportion is less in children with MS (63% of children who present at age 11 or older have oligoclonal...
bands and 43% of children who present with MS younger than age 11 have bands) (Chabas et al., 2010). Once present, oligoclonal bands tend to persist indefinitely and appear to have stable patterns of clonality (Walsh and Tourtellotte, 1986). Sometimes there are matching bands in serum and CSF without any that are unique to the CSF – this is a non-specific finding and not indicative of MS, but can sometimes be seen in association with paraproteinemias or systemic inflammatory disease.

An elevated IgG index is also a useful marker of intrathecal inflammation, but is less sensitive for MS than oligoclonal bands (Lefvert and Link, 1985; Ohman et al., 1992; Reiber et al., 1998; Freedman et al., 2005). It is rare in MS to see an elevated IgG index in the absence of oligoclonal bands (Freedman et al., 2005), although this can certainly occur in other CNS inflammatory syndromes.

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The CSF white blood cell count is usually normal or mildly elevated in MS; a white blood cell count of more than 50 ($\times 10^6$/L) is unusual in MS and should prompt a search for alternate explanations (Freedman et al., 2005). The white blood cell differential in MS is usually composed of lymphocytes and monocytes. The total CSF protein in MS is usually normal or mildly elevated. The glucose is usually normal in MS; a low CSF to serum ratio of glucose is suggestive of infection (bacterial, mycobacterial, fungal), malignancy (carcinoma), or another primary inflammatory process (sarcoidosis, gray-matter predominant myelitis in lupus).

### Evoked potentials in MS diagnosis

Evoked potentials can provide evidence of dysfunction in afferent and efferent pathways that may be unaffected clinically, and, thereby, provide additional corroboration of spatial dissemination to support the diagnosis of MS.

VEPs are the most common type of electrophysiologic testing utilized in MS diagnosis. Full-field pattern reversal VEPs are measured by having the patient focus on an alternating checkerboard pattern and measuring cortical responses from scalp electrodes placed over the mid-occiput. Given the prominent cortical representation of the macula, full-field VEP is primarily a measure of central vision. Multifocal VEPs can be helpful in identifying segmental latency delay when the full-field VEP is normal, which may be particularly relevant in cases in which the optic neuropathy or injury to the visual pathway spares central vision. Prolonged latency of the P100 response is typically interpreted as evidence of demyelinating injury. In clinical practice, VEPs are usually read in a binary fashion as either normal or abnormal based on the P100 latency exceeding 2.5 or 3 standard deviations from normal or based on having a similarly excessive difference in latency between eyes (interocular difference). However, demyelinating injury of the anterior visual pathway in MS occurs as a continuum (Fuhr et al., 2001), with median VEPs increasing by stage of disease, so many MS patients with milder degrees of anterior visual pathway demyelination will still have “normal” VEPs by conventional metrics (Songster et al., 2011). In the pre-MRI era, the latency

### Table 12.2

**Diagnosis of primary progressive multiple sclerosis (2011 revised McDonald criteria)**

<table>
<thead>
<tr>
<th>Clinical history</th>
<th>Additional evidence of dissemination in space and/or CSF inflammation</th>
<th>Additional factors</th>
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<tbody>
<tr>
<td>Insidiously progressive neurologic syndrome for more than 1 year (determined by history or prospective observation)</td>
<td>At least two of the following: 1. Dissemination in space with at least one T2 hyperintense lesion on brain MRI in an area characteristic for MS (periventricular, juxtacortical, infratentorial) 2. Dissemination in space with at least two T2 hypertense lesions in the spinal cord 3. Evidence of CNS inflammation with positive oligoclonal bands and/or elevated IgG index</td>
<td>Exclusion of other potential causes</td>
</tr>
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CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; MS, multiple sclerosis; CNS, central nervous system; IgG, immunoglobulin G. (Adapted from Polman et al., 2011).
on full-field pattern reversal VEP was abnormal in about 60–90% of patients with MS (Halliday et al., 1973; Asselman et al., 1975). The proportion of patients with relapsing MS with abnormal VEPs in the present era appears to be far lower, probably due to earlier detection of disease (Songster et al., 2011).

Somatosensory evoked potentials (SSEPs) are useful for measuring evidence of demyelination in central sensory pathways. SSEPs are probably most helpful in the assessment of suspected sensory myelopathy, especially when MRI is unremarkable or unattainable.

Motor evoked potentials, especially in combination with other evoked potential modalities, may be helpful prognostically in MS (Schlaeger et al., 2012), but are less useful diagnostically.

There is insufficient evidence to support the use of brainstem auditory evoked potentials for diagnosis of MS (Gronseth and Ashman, 2000).

**Retinal optical coherence tomography**

The RNFL is primarily made up of axons of retinal ganglion cells, which subsequently bundle together to form the optic nerve. Thinning of the RNFL is common in MS (Green et al., 2010), particularly in the region of the temporal peripapillary nerve fiber (Fisher et al., 2006; Pulicken et al., 2007; Henderson et al., 2008; Gelfand et al., 2012). RNFL loss in MS can be identified in clinic using direct funduscopy (Frisen and Hoyt, 1974), and can be quantified using retinal OCT. Retinal axonal loss is detectable from the earliest clinical stage of disease (CIS), but becomes more prominent in advanced stages (progressive MS > RRMS > CIS), with an additional component of thinning in eyes previously affected by acute optic neuritis (Gelfand et al., 2012). Retinal axonal loss can also occur insidiously in MS patients with an otherwise “benign” disease course and is associated with often-underappreciated visual disability (Miller et al., 2008). Macular volumes tend to be lower in MS than unaffected controls, and disproportionate thinning of inner and outer macular layers with relatively preserved RNFL in MS is associated with a more aggressive disease course (Saidha et al., 2011).

**Tissue biopsies in MS diagnosis**

Tissue biopsies are rarely performed for the purposes of MS diagnosis, except in fulminant/tumefactive presentations or very atypical cases.

The pathology of acute inflammatory lesions in MS is characterized by focal demyelination, macrophage, T-cell and B-cell-rich perivascular inflammation, and axonal loss (Filippi et al., 2012). Cortical demyelinating lesions, which are not well visualized using conventional clinical MR sequences, may also be apparent on biopsy depending on what is biopsied, but are commonly identified at autopsy (Filippi et al., 2012), and there may also be extensive microglial activation in otherwise “normal-appearing” white matter (Kutzelnigg et al., 2005; Frischer et al., 2009).

**First ever clinical attack in the elderly patient**

While insidious progression is common in elderly patients with MS, it is rare for an MS patient to present with a first clinical attack (relapse) after age 60 (Kis et al., 2008). Care should be taken to look for other potential causes, especially vascular disease. In the case of abnormally enhancing lesions on MRI in this age group, it is particularly important to exclude infection, metastases, lymphoma, and paraneoplasia.

**The patient with normal brain and spinal cord MRI**

With the notable exception of recurrent isolated optic neuritis (which does not technically fall under the MS rubric under McDonald criteria but did count as MS under Poser criteria), it would be extremely unusual in the 21st century to have MS with completely normal MRI of the neuroaxis, assuming the imaging is of adequate quality. Care should be taken to look for alternate diagnoses in such patients.

**DIFFERENTIAL DIAGNOSIS OF MS**

A critical component of MS diagnosis is the exclusion of alternate explanations (Miller et al., 2008). While the list of conditions that can mimic MS clinically or radiologically is long, in clinical practice there are very few conditions that truly mimic MS on both fronts (Rolak and Fleming, 2007). Differential diagnosis in MS must be guided by clinical presentation and neurologic localization. For example, evaluation of the patient with an insidiously progressive myelopathy will differ substantially from the patient with an isolated acute demyelinating optic neuritis.

What constitutes an adequate “rule out” panel of mimics for the patient with a typical presentation of MS will vary somewhat based on local epidemiology and practice patterns. The burden for excluding infection, for example, is necessarily higher in tropical settings where MS incidence is low and CNS infection is relatively high (Pandit, 2009). A “rule out” screening panel for a new diagnosis of MS typically includes: a vitamin B₁₂ level (for vitamin B₁₂ deficiency causing the syndrome of subacute combined degeneration), treponemal antibody testing (for syphilis), Borrelia serologies (for Lyme disease, depending on geography, local epidemiology, and season) and antiphospholipid
antibody syndrome screening. Aquaporin-4 antibody testing for NMO should be performed in any patient with a longitudinally extensive myelitis and, arguably, in all patients with a first-ever acute optic neuritis. An erythrocyte sedimentation rate may provide evidence of a systemic inflammatory process but is extremely non-specific. Antinuclear antibody testing is an important serologic marker of a number of systemic inflammatory (rheumatologic) syndromes, but is “falsely” positive in otherwise healthy individuals at rates of >30% at the 1:40 dilution and 5% at the 1:160 dilution (using HEp-2 cells as the antinuclear antibody test substrate) (Tan et al., 1997).

A positive test for a putative MS “mimic” does not unto itself exclude the diagnosis of MS. For example, a patient with MS can be vitamin B₁₂-deficient and still have MS.

**Acute disseminated encephalomyelitis (ADEM) and postinfectious encephalomyelitis**

ADEM is an inflammatory-demyelinating disorder that usually affects children and causes multifocal and polysymptomatic CNS inflammation (Menge et al., 2005; Krupp et al., 2007). ADEM is almost always monophasic. A preceding infection or febrile illness is identifiable in about 50–75% of children with ADEM (postinfectious encephalomyelitis) (Dale et al., 2000; Tenembaum et al., 2002; Menge et al., 2005). A preceding vaccination is identifiable in a small percentage of ADEM cases (Menge et al., 2005). Consensus guidelines have been proposed to distinguish between ADEM, CIS, MS, and NMO in children (Krupp et al., 2007).

ADEM is typically characterized by encephalopathy (behavioral change or alteration of consciousness) and fever and is associated with multifocal, extensive white-matter involvement on brain and spine MRI, as well as involvement of the basal ganglia and/or thalamus (Hynson et al., 2001; Tenembaum et al., 2002; Menge et al., 2005). The CSF is usually inflammatory, and the CSF pleocytosis may be greater than 50 cells/mm, a level atypical in MS (Krupp et al., 2007). ADEM may be recurrent or multiphasic in rare cases, but great care must be made to distinguish these cases from MS (Krupp et al., 2007). Histopathologically, monophasic ADEM is classically associated with perivascular demyelination (as opposed to confluent demyelination in MS), but there can be some overlap in practice (Young et al., 2010).

Adult-onset ADEM does occur, but is probably very rare, and usually involves patients in their late teens or early 20s. In our experience, many adult patients are loosely and often erroneously labeled as having a diagnosis of “ADEM” and are better categorized under the heading of a fulminant demyelinating syndrome, which can be a first presentation of MS.

**Neuromyelitis optica**

NMO (Devic’s disease) is an inflammatory disorder of the CNS characterized by injury to the spinal cord (longitudinally extensive myelitis), optic nerve (recurrent and often severe optic neuritis), and brainstem (especially the area postrema, causing nausea) (Jacob et al., 2007; Cree, 2008). Once thought to be an aggressive variant of MS, NMO is now known to have a distinct pathophysiology (Lennon et al., 2004; Roemer et al., 2007). Antibodies to aquaporin-4, a water channel expressed on the cell surface of astrocytes, are detectable in about 80% of patients with NMO and are highly specific for the diagnosis (>99%) (Lennon et al., 2004; Magana et al., 2009; McKeon et al., 2009).

The diagnosis of NMO was classically based on a combination of optic neuritis and acute myelitis and two out of three of the following: aquaporin-4 antibody seropositivity, a “longitudinally extensive” contiguous spinal cord lesion extending ≥3 vertebral segments on spine MRI and brain MRI abnormalities not meeting diagnostic criteria for MS (Wingerchuk et al., 2006). However, it was subsequently recognized that T2 hyperintense brain lesions on MRI occur frequently in NMO, and 10% of NMO patients have brain lesions that meet MS radiologic criteria, so such brain MRI findings should no longer be used to exclude the diagnosis of NMO (Pittock et al., 2006). NMO-spectrum disease is defined as an acute neurologic episode, such as an optic neuritis, brainstem syndrome, or longitudinally extensive myelitis, in a patient with aquaporin-4 antibodies who does not otherwise satisfy formal diagnostic criteria for NMO. In routine practice, NMO and NMO-spectrum disease are generally considered as the same disease process for the purposes of prognostication and therapy. The presence of NMO-IgG antibodies predicts a high risk of relapse in patients with recurrent optic neuritis without myelitis (Matiello et al., 2008) and a first episode of longitudinally extensive myelitis (Weinschenker et al., 2006).

By contrast to MS, neurologic disability in NMO results almost entirely from clinical relapses (Wingerchuk et al., 2007; Sellner et al., 2010), although secondary progression can occur as a late feature.

Animal models indicate that anti-aquaporin-4 antibodies are pathogenic within the context of an inflammatory response mediated by T cells, activated mononuclear cells, and involvement of the complement cascade (Bennett et al., 2009; Bradl et al., 2009).
Small-vessel ischemic white-matter disease and silent infarcts on brain MRI

Small-vessel ischemic white-matter disease and silent infarcts are observed on brain MRI in over 7% of middle-to-older-aged individuals in the general population (Vernooij et al., 2007). Both subclinical white-matter abnormalities and silent infarcts on MRI are predictive of an increased risk of stroke in the general population (Vermeer et al., 2003). In people with known atherosclerotic disease, both silent lacunar infarcts and greater white-matter lesion volume are associated with an increased risk of death and ischemic stroke (Conijn et al., 2011). Progression of periventricular white-matter disease in patients with known atherosclerotic disease is associated with brain atrophy (Kloppenborg et al., 2012). It is important to recognize that such white matter lesions and lacunar infarcts are not always truly “silent” clinically, as there may be underrecognition and underreporting of acute cognitive changes and focal neurologic dysfunction in a subset of patients, especially in the elderly (Saini et al., 2012).

Small-vessel ischemic white-matter abnormalities on brain MRI usually involve the subcortical and periventricular white matter. The lesions of small-vessel ischemic disease on MRI tend to be smaller, more punctate, and less ovoid than MS lesions, and when more severe often have the appearance of relative symmetry and confluence. Small-vessel ischemic disease can also involve the corpus callosum. Ultra-high-field MRI (7 T) may be able to distinguish MS lesions from subclinical white-matter ischemic abnormalities based on the presence of a central vein in a greater proportion of MS lesions (Tallantyre et al., 2011). The neuropathology of these incidental white-matter lesions on brain MRI reveals changes consistent with hypoperfusion, including upregulation of hypoxic inducible factors, endothelial activation, and associated microglial activation (Fernando et al., 2006).

Stroke

Cerebrovascular disease, especially multiple embolic infarcts, can certainly cause neurologic symptoms separated in space and time and is an important consideration in the differential diagnosis of MS, especially in older adults. Vascular syndromes usually present acutely, whereas MS symptoms tend to present subacutely. Both ischemia and acute demyelination can cause abnormalities on diffusion-weighted MRI.

Antiphospholipid antibody syndrome

The antiphospholipid antibody syndrome (APLAS) is a hypercoagulable disorder characterized by recurrent arterial and venous thrombosis in association with antiphospholipid autoantibodies (Levine et al., 2002). Transient ischemic attacks and stroke are the cardinal neurologic manifestations and can lead to evolving neurologic symptoms disseminated in time and space that mimic MS clinically. White-matter abnormalities on brain MRI are common in APLAS and can appear very similar to the pattern of white-matter disease in MS (Cuadrado et al., 2000). The CSF examination is not typically inflammatory in the context of isolated APLAS, and evidence of intrathecal inflammation on CSF examination in a patient with known APLAS should prompt evaluation for comorbid causes of CNS inflammation, including comorbid MS. Women with APLAS often have a history of recurrent embryonic loss (miscarriage), fetal loss, or pre-eclampsia. Thrombocytopenia is a common manifestation. Comprehensive screening should include not just anticardiolipin IgG and IgM antibodies, but also anti-β2-glycoprotein IgM and IgG antibodies as well as tests for lupus anticoagulant activity (i.e., dilute Russell viper venom time, hexagonal phospholipid neutralization test). Patients with positive results should have the test repeated at 12 weeks for diagnostic confirmation.

Systemic lupus erythematosus

SLE is a multisystem autoimmune inflammatory connective tissue disorder (D’Cruz et al., 2007). CNS involvement in SLE is common and select CNS manifestations, including seizures and psychosis, count towards one of the 11 American College of Rheumatology SLE diagnostic criteria, which include: a positive antinuclear antibody, malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal involvement, nervous system involvement, hematologic involvement (anemia, leukopenia, thrombocytopenia), and immunologic involvement (antiphospholipid antibodies, anti-double-stranded DNA-antibody or anti-smith antibodies) (Hochberg, 1997). The American College of Rheumatology defines 19 different “neuropsychiatric” syndromes that fall under the research case definition of neuropsychiatric lupus, 12 of which involve the CNS, ranging from stroke, seizure, and myelitis to depression, psychosis, and headache (American College of Rheumatology, 1999).

While certainly inclusive, this approach to “neuropsychiatric lupus” is problematic, as it lumps together CNS manifestations that probably stem from different pathophysiologic mechanisms, such as stroke, seizures, CNS inflammation, or chorea associated with the APLAS, or that may not relate directly to lupus, such as migraine (Bertsias et al., 2010).

The most likely potential CNS manifestation of SLE to cause diagnostic confusion with MS is APLAS, which can look similar to MS on MRI and cause relapsing and remitting symptoms (Cuadrado et al., 2000). The other
clinical scenario that may be confused diagnostically with MS is myelitis in a patient with SLE. Many cases of “lupus myelitis” are now known to be secondary to NMO or APLAS (Birnbaum et al., 2009). In SLE patients with myelitis who are negative for aquaporin-4 and anti-phospholipid antibodies, the myelitis can present as a “gray-matter” predominant syndrome with prominent bowel/bladder impairment and a CSF profile that can look concerning for infectious meningitis, including a low glucose (Birnbaum et al., 2009).

Anti-double-stranded DNA antibodies, which are specific in lupus and sometimes correlate with disease activity, cross-react with the NR2a and NR2b components of the N-methyl-D-aspartate receptor (DeGiorgio et al., 2001), but it is not clear whether such a mechanism, including any other lupus-related antibodies that may bind to neuronal cell surface antigens, ever accounts for neuropsychiatric symptoms in the human form of SLE (Laufsnes and Omdal, 2012).

It is important to exclude infection rigorously in immunosuppressed or immunocompromised SLE patients before settling on a diagnosis of neuropsychiatric lupus.

**Sjögren’s syndrome and the dubious entity of “CNS Sjögren’s”**

Sjögren’s syndrome is an inflammatory condition that causes salivary and lacrimal gland dysfunction and is characterized histopathologically by lymphocytic inflammation within affected glands. The diagnosis is based on various combinations of the presence of dry eyes and dry mouth (keratoconjunctivitis sicca), autoantibodies to SSA (anti-Ro) and SSB (anti-La), functional demonstration of decreased tear or salivary production, and lymphocytic foci on salivary gland biopsy (Vitali et al., 2002).

Sjögren’s patients who happen to have another known connective tissue disease, such as SLE, systemic sclerosis, rheumatoid arthritis, or autoimmune thyroid disease, are said to have “secondary” (Vitali et al., 2002), “overlapping,” or “associated” Sjögren’s (Theander and Jacobsson, 2008), whereas patients who do not have such a comorbidity are said to have “primary” Sjögren’s. Yet, when a patient with MS has Sjögren’s syndrome (or sometimes simply positive Sjögren’s autoantibodies), the dubious label of “CNS Sjögren’s” may sometimes be applied (Alexander et al., 1986; Delalande et al., 2004), although convincing neuropathologic evidence of a distinctive immunologic process in the CNS attributable to Sjögren’s has not been adequately demonstrated (Ioannidis and Moutsopoulos, 1999). About 15% of patients with longitudinally extensive myelitis have SSA antibody positivity, most of whom probably have NMO (Pittock et al., 2008). We suggest that a patient with RRMS who also happens to have Sjögren’s syndrome should be considered as having both RRMS and Sjögren’s, or perhaps MS with secondary Sjögren’s, but not labeled as having CNS Sjögren’s.

Sjögren’s syndrome is associated with certain peripheral neuropathy variants, including sensory neuronopathy (Mori et al., 2005), but the most common manifestation of neuropathy in biopsy-proven Sjögren’s syndrome is a painful, distal sensory axonal polyneuropathy (Gorson and Ropper, 2003).

**Behçet’s disease**

Behçet’s disease is a multisystem relapsing-remitting, inflammatory disorder characterized by recurrent oral ulcers, recurrent genital ulcers, uveitis, retinal vasculitis, skin lesions (papulopustular lesions or erythema nodosum), arthritis, gastrointestinal and nervous system involvement (Goodin, 1998; Al-Araji and Kidd, 2009). Many patients also have a positive skin pathergy test, although this is less common in Behçet’s patients of Northern European descent. The HLA-B51 allele appears to be a genetic risk factor for Behçet’s, but as a clinical test is not considered specific enough for diagnosis (Maldini et al., 2012). The major CNS manifestations of Behçet’s are meningoencephalitis, which can at least superficially mimic MS, and deep venous or arterial thrombosis. The neuropathology of the former is a meningoencephalitis with perivascular inflammation (Greer et al., 2009).

**Sarcoidosis**

Sarcoidosis is a multisystem disorder of unknown cause characterized histologically by non-caseating granulomatous inflammation. Direct involvement of the nervous system by the antigen-driven, granulomatous inflammatory process – neurosarcoidosis – occurs in about 5–15% of sarcoidosis patients (Stern et al., 1985; Chen and McLeod, 1989).

About two-thirds of patients with CNS sarcoidosis will have evidence of sarcoidosis outside of the nervous system at the time of neurologic presentation, most commonly in the lungs (which is usually subclinical and asymptomatic) and deep lymph nodes. However, one-third of patients with CNS-predominant sarcoidosis do not have obvious extraneurologic sarcoidosis at the time of neurologic presentation and would be considered to have “isolated” neurosarcoidosis (Joseph and Scolding, 2009; Pawate et al., 2009).

Sarcoidosis is often said to be protean in its clinical manifestations – to be able to “do anything.” However, most cases of CNS sarcoidosis involve active meningeal nodular enhancement, and, unlike MS, the disease tends
to extend and infiltrate locally along contiguous anatomic pathways. The location of this seeding of granulomatous inflammation determines the clinical syndrome, which typically involves some variation of chronic meningitis (with or without hydrocephalus), myelitis, optic neuropathy (usually from infiltration or compression), and pituitary/skull base involvement. Facial nerve palsy is frequently cited as the most common neurologic manifestation of sarcoidosis (Douglas and Maloney, 1973; James et al., 1976; Delaney, 1977; Stern et al., 1985; Oksanen, 1986; Chen and McLeod, 1989; Lower et al., 1997), but in cases of CNS-predominant sarcoidosis optic neuropathy is the most prevalent cranial nerve manifestation (Koczman et al., 2008; Joseph and Scolding, 2009; Pawate et al., 2009). Typical MRI features of CNS sarcoidosis include nodular and meningeal enhancement, but are non-specific (Christoforidis et al., 1999; Shah et al., 2009).

When the pretest probability for CNS sarcoidosis is high, a chest computed tomography (CT) scan with contrast is probably the most helpful screening test (to look for hilar and mediastinal lymphadenopathy and/or interstitial lung involvement). But, given the radiation exposure, cost, and potential for incidental findings (i.e., lung nodules of doubtful clinical significance), a chest CT is not recommended as part of the routine “rule out” for MS diagnosis. When the suspicion for neurosarcoidosis is high and the chest CT is normal, a whole-body 18-fluoro-deoxyglucose (FDG) positron emission tomography (PET) scan can be helpful in identifying sites of systemic active granulomatous inflammation, including lymph nodes that can be “hot” but normal in size, and that may, in turn, be safer and more accessible to biopsy than CNS tissue (Bolat et al., 2009).

Serum acetylcholinesterase (ACE) enzyme levels are elevated in up to 60% of patients with active pulmonary sarcoidosis (Bunting et al., 1987; De Smet et al., 2010), but are abnormal in less than a third of patients with active CNS sarcoidosis (Ferriby et al., 2001; Kellinghaus et al., 2004; Koczman et al., 2008; Joseph and Scolding, 2009). Elevation of serum ACE levels is also non-specific (Bunting et al., 1987) and can be influenced by polymorphisms in the ACE gene (Nesterovitch et al., 2009). For these reasons, serum ACE is a poor screening test for neurosarcoidosis. There is a small literature suggesting that CSF ACE may be helpful in neurosarcoidosis diagnosis, but the sensitivity is low (25–55%) and its specificity unclear, as the number of cases was relatively small and control groups did not have large numbers of true clinical mimics, such as mycobacterial and fungal meningitis or CNS lymphoma (Oksanen et al., 1985; Dale and O’Brien, 1999; Tahmoush et al., 2002). Serum lysozyme is elevated in a majority of patients with sarcoidosis (Pascual et al., 1973) and, while it is a popular screening lab in fields like ophthalmology, this test too suffers from a lack of necessary specificity. A CSF pleocytosis and elevated protein are common in neurosarcoidosis, but the pattern is non-specific (Zajicek et al., 1999). A low CSF glucose occurs in some patients with sarcoid meningitis (Pawate et al., 2009) and should raise suspicion for sarcoidosis when infectious and malignant causes are not found after rigorous exclusion. Oligoclonal bands are observed in 20–40% of patients with neurosarcoidosis (Zajicek et al., 1999; Kellinghaus et al., 2004; Joseph and Scolding, 2009; Pawate et al., 2009), and the IgG index is elevated in a similar proportion (Kellinghaus et al., 2004).

A definite (or highly probable) diagnosis of CNS sarcoidosis can be established by biopsy confirmation of non-caseating granulomatous inflammation from the CNS (Zajicek et al., 1999). A probable diagnosis of CNS sarcoidosis is made by demonstrating sarcoidosis elsewhere in the body in the context of a typical neurologic syndrome and exclusion of other causes. Published criteria suggest that an elevated ACE level and chest CT findings suggestive of sarcoidosis may be adequate for diagnosis of probable neurosarcoidosis in the absence of any biopsy (Zajicek et al., 1999), but caution is advised given the caveats about ACE testing and implications for informing the neurologic diagnosis. Possible neurosarcoidosis refers to cases where the diagnosis is suspected, but there is no pathologic confirmation. A “steroid-responsive” meningitis or meningoencephalitis may be a preferable term in some cases. While rarely reported in the literature, there is no intrinsic reason why some patients cannot have diagnoses of both MS and sarcoidosis, particularly sarcoidosis involving organ systems outside the CNS.

CNS lymphoma

Primary CNS lymphoma (PCNSL) is a rare form of non-Hodgkin’s lymphoma. In the context of immunosuppression or immunodeficiency (such as the acquired immunodeficiency syndrome: AIDS), PCNSL is associated with Epstein–Barr virus (EBV) infection. The pathogenesis of PCNSL is probably different in immunocompetent individuals, as no such EBV association has been established and the disease tends to occur later in life (Rubenstein et al., 2008). The pathology of PCNSL is typically of the diffuse large B-cell subtype. CNS lymphoma may also reflect neurologic organ system involvement of a systemic lymphoma. Imaging of CNS lymphoma typically reveals a single enhancing nodule or mass, multifocal enhancing nodules, or meningitis. Lymphoma is detectable in the CSF on cytology and flow cytometry in up to one-third of cases, but biopsy is usually necessary to secure the diagnosis (Scott et al.,
such as fever, night sweats, and weight loss. The clinical syndrome for MS, and/or prominent B-symptoms (e.g., paresthesias and numbness) are often present.

MS lesions usually tend to resolve within 1 or 2 months, though some lesions may persistently enhance on MRI over months (as in Susac syndrome). Clues to a diagnosis of CNS lymphoma include a persistently enhancing lesion on MRI over months (as many other non-inflammatory vasculopathies can have a similar appearance) (Kadkhodayan et al., 2004). CNS vasculitis can also occur in the context of a systemic inflammatory disease, malignancy, or infection.

Susac syndrome is an endotheliopathy that affects the microvasculature and is characterized by headache, encephalopathy (from microinfarcts, especially of the corpus callosum), vision impairment (from branch retinal artery occlusions), and hearing loss (from cochlear infarction) (Susac et al., 1979, 2007; Rennebohm et al., 2010). Leptomeningeal enhancement is observed in up to one-third of Susac syndrome cases (Rennebohm et al., 2010). The MRI appearance typically involves numerous microinfarcts of the corpus callosum with associated T1 hypointensity. Fluorescein angiography can be helpful in identifying subtle branch retinal artery occlusions. Women aged 20–40 are most typically affected.

CNS vasculitis and primary angiitis of the CNS

Vasculitis can affect the brain and spinal cord in isolation or as part of a systemic inflammatory process. While exceedingly rare relative to MS epidemiologically, the radiologic appearance of CNS vasculitis may superficially mimic MS, although the clinical syndrome is usually quite different. Patients with primary angiitis of the CNS are most commonly middle-aged, 2:1 male to female, and present with cognitive dysfunction, headaches, and seizures with multiple infarcts and sometimes hemorrhages on brain imaging and sometimes with mass lesions. CNS vasculitis can also present as a chronic meningitis. The CSF may or may not be inflammatory and is usually non-specific. A biopsy of the meninges and/or parenchyma demonstrating vasculitis is the gold standard for diagnosis, but has an imperfect sensitivity, probably due to sampling error. CT, MR, and conventional angiography may demonstrate a vasculopathy, but angiography is neither sensitive (because the vasculitis may only involve small and not medium-sized vessels) nor specific (as many other non-inflammatory vasculopathies can have a similar appearance) (Kadkhodayan et al., 2004). CNS vasculitis can also occur in the context of a systemic inflammatory disease, malignancy, or infection.

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal-dominant genetic disorder caused by a mutation in the NOTCH3 gene. CADASIL is characterized by migraine with aura, cerebrovascular disease, executive dysfunction, depression, apathy, and white-matter abnormalities on brain MRI (Markus et al., 2002). The imaging appearance may superficially mimic MS (Brex et al., 2002), but the clinical course is usually quite distinct. Involvement of the anterior temporal pole occurs early in CADASIL and is characteristic (Auer et al., 2001; Markus et al., 2002), but anterior temporal lobe lesions can certainly occur in MS as well, though usually not as striking as seen in CADASIL. Lacunar infarcts and microbleeds, rather than evolving white-matter abnormalities on brain MRI, correlate most with cognitive decline (Liem et al., 2009).

Lyme disease is a tick-borne infection caused by the *Borrelia* spirochete (Garcia-Monco and Benach, 1995; Halperin, 2008). The first symptom is usually a skin lesion, erythema migrans, which occurs within a few days to weeks after the tick bite. Neurologic involvement usually occurs in the second stage of disease, called early disseminated Lyme, and can consist of lymphocytic meningitis, cranial neuropathies (especially facial nerve palsy), and a painful myeloradiculoneuritis, which goes by the name Garin–Boujadoux–Bannwarth or Bannwarth syndrome in the European literature, where the radicular manifestations of disease are more common. Parenchymal involvement occurs rarely in neuroborreliosis, and may resemble MS on imaging (Halperin, 2008). There may also be segmental spinal cord involvement in the European form of lymphocytic myeloradiculoneuritis (Halperin, 2008).

To diagnose CNS Lyme disease, there must be direct evidence of antibodies to the *Borrelia* spirochete within the CSF (an important point in epidemic areas where MS patients can have positive serum IgG Lyme antibodies from prior infection) (Halperin et al., 1989). MS patients with positive serum Lyme serologies and negative CSF testing should still be considered as having a diagnosis of MS as well as evidence of prior Lyme disease (Coyle et al., 1993). Testing for Lyme disease consists of an initial enzyme-linked immunosorbent assay (ELISA) or immunofluorescent assay followed by a
confirmatory western blot. The Lyme CSF polymerase chain reaction is of questionable utility given its low sensitivity (Nocton et al., 1996).

**Neurosyphilis**

Syphilis is an infection caused by *Treponema pallidum*. Invasion of the CNS tends to occur early in untreated disease and used to be a frequent and feared manifestation of the disease in the pre-antibiotic era (Lukehart et al., 1988). In the current era, neurologic syphilis is most common early in disease and typically manifests as meningitis, cranial neuropathy (including optic neuropathy and papillitis), or stroke from blood vessel involvement (Golden et al., 2003). The late form of neurosyphilis, which classically manifested as a rapidly progressive dementia (general paresis of the insane) or progressive spinal cord syndrome (tabes dorsalis), is now exceedingly rare (Golden et al., 2003).

Nonetheless, given the ready availability of a cure, it is still prudent to exclude neurosyphilis as part of the differential diagnosis of MS. Initial screening is usually performed using “non-treponemal” tests of antibody response to a cross-reactive antigen, typically the rapid plasma reagin from serum and Venereal Disease Research Laboratory (VDRL) test from CSF, with confirmatory testing performed using treponemal-specific antibodies. The CSF VDRL has only moderate sensitivity, so specialized treponemal testing from the CSF should be obtained through specialized labs, such as the Centers for Disease Control and Prevention, in cases in which the suspicion for neurosyphilis is high (such as a patient with prior or partially treated syphilis and new neurologic symptoms). One advantage of non-treponemal testing is that it typically reverts to normal after successful treatment of the infection, whereas treponemal tests usually remain positive for good, which can be a problem for screening for reinfection in higher-prevalence areas (Centers for Disease Control and Prevention, 2012).

**Human T lymphotropic virus (HTLV)**

HTLV-1 is a retrovirus that is estimated to affect about 10–20 million people worldwide (de The and Bomford, 1993). HTLV-1 is endemic in parts of Asia, the Middle East, southern Africa, and the Caribbean, but is rare in the United States and Europe. HTLV is asymptomatic in the vast majority of those infected, but can cause a form of T-cell leukemia/lymphoma as well as a progressive meningomyelitis that preferentially affects the thoracic spinal cord (HTLV-associated spastic paraparesis or tropical spastic paraparesis) (Cooper et al., 2009). HTLV-2 is also associated with progressive myelopathy. The clinical syndrome of myelopathy-associated HTLV-1 and 2 infection is usually insidious, rather than acute or subacute. Spinal cord imaging may show cord atrophy, longitudinally extensive T2 hyperintensities, or may even be normal (Umehara et al., 2007). Brain MRI abnormalities in the subcortical and periventricular white matter are common in asymptomatic and symptomatic HTLV-1 patients alike, but the clinical relevance and specificity are unclear (Morgan et al., 2007).

HTLV proviral loads of infected white cells in the CSF are elevated in patients with HTLV-1 associated myelopathy (Lezin et al., 2005), and appear to be a useful discriminator between HTLV-1-associated spastic paraparesis and prior HTLV-1 exposure in patients with progressive MS in endemic areas (Fuccioni-Sohler et al., 2007).

**Vitamin B12 deficiency**

Vitamin B12 (cobalamin) deficiency causes combined degeneration of the spinal cord, a syndrome characterized by weakness, paresthesias, and impairment of dorsal column functioning (vibration and position sense loss) (Ropper and Samuels, 2009). There may also be associated cognitive dysfunction and optic neuropathy. The symptoms usually progress insidiously and progressively. While CSF total protein may be elevated, an otherwise inflammatory CSF is rare. Megaloblastic anemia is often absent. Vitamin B12 deficiency may mimic MS as a spinal cord syndrome, and rarely as a cortical syndrome (Ransohoff et al., 1990). However, a low B12 in a patient with otherwise classic MS usually means just that – an additional diagnosis of low B12 in a patient who also has MS. Low vitamin B12 levels are associated with latency delay on VEPs in MS patients (Kocer et al., 2009) and probably aggravate nerve conduction delay in patients who already have demyelination from MS, so repletion may also help symptomatically in MS patients with low or borderline levels.

Vitamin B12 deficiency is diagnosed by measuring B12 levels, but low-normal values should be followed up with methylenalonic acid and homocysteine levels, which rise when intracellular vitamin B12 is low. Holotranscobalamin may be a more sensitive screen for B12 deficiency (Heil et al., 2012).

In patients with vitamin B12 deficiency and neurologic symptomatology, it is important to evaluate for the cause of the deficiency and not simply replete, as the deficiency may recur when therapy ceases, depending on the cause. Pernicious anemia is assessed using intrinsic factor antibodies; the Schilling test is no longer practical in routine neurologic practice.

**Copper myelopathy**

Copper deficiency can cause a sensory-predominant myeloneuropathy as well as optic neuropathy (Kumar et al., 2004). Gastric bypass surgery is the
leading epidemiologic risk factor; zinc excess (from denture cream) is another identified cause.

**Paraneoplastic disorders**

Paraneoplastic disorders of the CNS are not typically confused with MS clinically or radiologically. One possible exception is paraneoplastic-associated myelopathy. Clues to diagnosis are an enhancing longitudinally extensive spinal cord lesion (which is atypical in MS) that typically involves the thoracic cord and prominent gray-matter involvement. Oligoclonal bands in the CSF are common in paraneoplastic myelopathy. The most common antibodies observed in association with paraneoplastic myelopathy are CRMP-5, amphiphysin and ri (ANNA-2) (Flanagan et al., 2011). Aquaporin-4 antibodies in NMO have been associated as a paraneoplastic phenomenon in a small number of cases (Pittock and Lennon, 2008).

**Demyelinating events in patients taking TNF-α inhibitors**

TNF-α inhibitors were studied as a potential therapy for MS in the 1990s but were found to be harmful, as they increased relapse activity. A randomized controlled trial of lenerecept, a recombinant TNF receptor p55 immunoglobulin fusion protein, had to be stopped early due to an increase in exacerbations relative to placebo (Flanagan et al., 2011). Another humanized-mouse monoclonal anti-TNF antibody caused a rapid increase in contrast-enhancing lesions and that study too had to be stopped early (van Oosten et al., 1996).

TNF-α inhibitors, which are commonly used for the treatment of arthritis and other rheumatologic conditions, have been associated with demyelination as an adverse effect (Solomon et al., 2011), but causality is difficult to prove. The Food and Drug Administration lists demyelination as a black box warning on this class of agents. While cessation of anti-TNF-α therapy leads to resolution of the syndrome in some patients, others go on to develop classic MS. It is not clear whether TNF-α inhibition “provokes” or brings out MS in genetically susceptible individuals or if such occurrences are coincidental.

**Transient neurologic symptoms of unclear cause with reassuring imaging and paraclinical evaluations**

Many patients referred for evaluation of MS are found to have an alternate etiology (Carmosino et al., 2005). Somatoform disorders or somatic symptoms in the context of primary psychiatric disease are one important diagnostic consideration (Carmosino et al., 2005), as are normal everyday neurologic sensations construed as pathologic (Rolak and Fleming, 2007). In a large series of outpatients in Scotland with neurologic symptoms “unexplained by organic disease,” only 4 of 1030 (0.4%) went on to develop an unexpected organic disease at 19 months of follow-up, which included 1 patient with MS in whom the diagnosis became readily apparent as part of recommended follow-up (Stone et al., 2009).

**REFERENCES**


