Here’s how to differentiate a number of pathologies that can resemble one of the trickiest diseases in neurology.
When a general practitioner refers a possible multiple sclerosis patient to a specialist, more often than not the neurologist confirms the diagnosis. GPs tend to have fairly good instincts for MS diagnosis and usually just need confirmation from someone more well-versed in the subject, especially given the implications of making such a diagnosis. However, there are just enough times when the patient does not present with a classic textbook presentation to give GPs and neurologists alike a reason to consider other underlying conditions that could look and act like MS but in reality stem from radically different pathologies.

At present there is no standard criteria or algorithm that will distinguish MS from its possible mimickers with 100 percent accuracy. The Schumacher and McDonald criteria, for instance, will not invariably sort out the symptoms of MS from other conditions such as Sjögren’s syndrome, migraine with white matter lesions or leukoaraiosis. Even when focused on the only true clinically distinguishing feature to MS—demyelination disseminated in time and space—there are some diseases that imitate this picture while running their course. Therefore, practitioners need to keep the possibility of a differential diagnosis in mind when examining a patient, especially since there are more than 100 conditions that have symptoms that seem to indicate a capricious case of MS.

In February, we reviewed many conditions of the central nervous system that can present in a similar fashion to MS (full text available online at www.practicalneurology.com/archive_PNFeb2005.htm). This month, we’ll look at conditions that originate from other parts of the body that could present with very similar signs. Some originate from the spinal cord, some from environmental factors, and others have an even more elusive pathology.

Similar Signs, Different Directions
Some systemic disorders may have cerebral involvement that mimics MS when the actual source of the problem lies elsewhere. Telling the difference may require asking about particular peripheral symptoms or taking a closer look at the MRI results and comparing them to “textbook” images. It’s often subtle differences in lesion shape and location that can prompt a rethinking of your diagnosis, and some of the more obvious symptoms can suggest when taking close look is necessary to confirm your opinion.

Collagen vascular disorders may mimic the outward symptoms of multiple sclerosis, particularly early in their presentation when there may be a paucity of other manifestations. As many as 50 percent of cases of systemic lupus erythematosus may occur with circulating antiphospholipid antibodies, resulting in a thrombotic microangiopathy with multifocal infarcts subcortically and in the deep white matter. This may need to be distinguished from multiple sclerosis by carefully reading the neuroimaging results.

For example, lesions perpendicular to the ventricular surface or in the corpus callosum would suggest MS, while subcortical or small lesions in the centrum semiovale would be more consistent with lupus. Additionally, the patient’s other symptoms will present a more obvious indicator. The most common central nervous system manifestations of systemic lupus erythematosus, including neuropsychiatric syndromes, dementia, seizures, meningitis and tremor, are not associated with multiple sclerosis and noting their presence can rule out this diagnosis.

Antiphospholipid syndrome can also occur independently of systemic lupus erythematosus. This condition, which presents with a wide range of symptoms, is typically associated with recurrent abortions and deep vein thromboses with IgG
and IgM anticardiolipid antibodies. It is also linked to migraine headaches and seizures, a correlation that help you differentiate it from MS. The MRI appearances are similar to those in systemic lupus erythematosus.

Most individuals with sarcoidosis will not have the symptoms that would make one think of MS, but about one out of 10 cases will have neurosarcoidosis, a severe variation of this autoimmune condition localized in the central nervous system. An MRI may show multiple lesions that appear very similar to MS, although large parenchymal lesions may indicate the need for a closer look. The most common presentation is one where meningeal enhancement is present and the base of the brain is prominently involved.

Brain parenchyma may be involved in isolation. There will be mostly mass lesions here, which either may be asymptomatic or manifest with focal signs or raised intracranial pressure. T2-weighted lesions often occur in the periventricular white matter. These demonstrate mass effect and linear contrast enhancement along blood vessels, unlike the solid or ring-enhancing lesions seen in multiple sclerosis. There may also be notable leptomeningeal enhancement. The spinal fluid could have a mononuclear pleocytosis with elevated protein and hypoglycorrhachia. About half of the cases will have elevated angiotensin converting enzyme levels. Oligoclonal bands may also be present.

A bite from a deer tick, an arachnid about the size of a sesame seed in its adult stage, can lead to one of the better known conditions that can be mistaken for MS. Lyme disease is a multi-system infection caused by the spirochete bacterium Borrelia burgdorferi, which the tick transmits to its host after feeding for hours. Since the bite is painless, most patients will not notice the parasite and may miss the rash that often forms around the bite as the first sign of infection. Clinical manifestations include a painful sensory radiculopathy, meningitis, focal neurologic signs, cranial neuropathy, encephalopathy and a progressive myelopathy.

This condition causes white matter symptoms, sometimes relapsing and remitting, occasionally with MRI changes mimicking MS. However, the classic MS picture is almost never present and most tests for Lyme disease will yield more true positives than false ones. Still, any diffuse cerebral demyelination or focal spinal cord infection needs to be differentiated from multiple sclerosis. Spinal fluid findings should include a significant pleocytosis, elevated protein levels and IgG index. Tests for Lyme antibodies and a positive Western blot analysis for antibodies binding multiple antigens are the standard diagnostic procedures. Multifocal T2-weighted hyperintensities may occur in cerebral white matter, brainstem, cerebellum and spinal cord on MRI. There may be meningeal contrast enhancement as well as focal or ring-enhancing parenchymal lesions.

The use of anti-TNF agents including a p75TNFR fusion protein (etanercept) or a chimeric anti-TNF monoclonal antibody (infliximab) can cause multifocal inflammatory leukoencephalopathy. This condition presents with parasthesias, optic neuritis, confusion, apraxia, facial palsy and weakness. MRI findings may include multifocal inflammatory white matter lesions in the brain and spinal cord. Diffuse confluent bilaterally symmetric white matter lesions also occasionally appear on the scans. The clinical and MRI features are atypical for multiple sclerosis and should help to differentiate this condition. Improvement usually occurs by having the patient withdraw from the agent, although some individuals may need a period of immunosuppression. Interestingly, both clinical and MRI measures of disease activity in multiple sclerosis have been aggravated by similar agents.

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**Across the Spine**

The syndrome of transverse myelitis (see Table 1) is defined as an acute or subacute presentation of motor, sensory or autonomic deficits arising from the spinal cord. The spinal cord may be involved either partially or completely in cross section. Common symptoms include numbness, parasthesias, band-like dysesthesias, interscapular pain, lower limb weakness and urinary retention. The onset of symptoms may be preceded by an acute infection or inoculation.

This syndrome may be idiopathic or secondary to an identifiable cause (see Table 2), and it is important to exclude spinal cord compression, infarction and infection when considering this diagnosis. Idiopathic transverse myelitis is distinguished from multiple sclerosis by the mostly thoracic presentation of the former, with the spinal cord being involved over multiple contiguous levels. There is often marked swelling and
the affected segments of the spinal cord could be enlarged. Multiple sclerosis, in contrast, usually involves the cervical cord. The affected cord is most commonly partially involved; particularly in the posterior and lateral columns. Brain MRI scans are unremarkable in idiopathic transverse myelitis.

The risk of developing multiple sclerosis following an initial presentation of transverse myelitis varies depending on the number of cerebral lesions. The risk is relatively low when none are present but rises increasingly with additional T2-weighted lesions in the brain. Spinal fluid abnormalities do not absolutely differentiate multiple sclerosis from other causes of transverse myelitis, so it is important to look for more specific symptoms.

Severe inflammatory myelitis can occur in the setting of acute disseminated encephalomyelitis, neuromyelitis optica and necrotizing myelitis. In acute disseminated encephalomyelitis, the cerebral manifestations and MRI appearances can differentiate the disorder from multiple sclerosis (see Table 3). Neuromyelitis optica is characterized by either a monophasic or a relapsing course involving the optic nerve and spinal cord.

Unlike multiple sclerosis, there is a necrotizing process associated with neuromyelitis optica or necrotizing myelitis, with a predominance of macrophages infiltrating the affected tissues in the spinal cord. This process may be the result of induction of interleukins 17 and 8, both of which promote macrophage and neutrophil infiltration and activation. Clinically and radiographically, the absence of cerebral involvement differentiates these conditions from multiple sclerosis. The MRI appearances in the spinal cord demonstrate extensive rostral-caudal T2 signal abnormalities as well as T1 hypointensi-
ties, with or without gadolinium enhancement. There will also be a greater pleocytosis in the spinal fluid than in multiple sclerosis. A putative autoantibody marker (NMO-IgG) may possibly help distinguish neuromyelitis optica from MS in the future.\textsuperscript{19}

**Myelopathy vs. MS**

Occasionally the clinician will need to distinguish other similar conditions from multiple sclerosis. In particular, vitamin B12 deficiency and adrenomyeloneuropathy are two conditions that need to be ruled out.

Vitamin B12 deficiency caused by an autoimmune disease or nitrous oxide exposure may involve the nervous system even in the absence of hematologic abnormalities.\textsuperscript{20-22} The clinical presentation of a myelopathy with dorsal column involvement and paraparesis may bear a very strong resemblance to the signs for multiple sclerosis. However, a low vitamin B12 level and elevated homocysteine and methylmalonic acid levels can differentiate this condition. When these conditions are present, the longitudinal T2 hyperintensities in the posterior and lateral columns will serve as distinctive indicators.\textsuperscript{23}

X-linked adult-onset adrenomyeloneuropathy (X-ALD)
Detecting MS Mimickers

occurs due to mutations in the ABCD1 ATP binding cassette transmembrane transporter gene.24 These mutations result in defective and very long chain fatty acid (VLCFA) oxidation in peroxisomes with VLCFA accumulation by unknown mechanisms. This, in turn, produces a distal axonopathy, in contrast to the cerebral inflammation with myelin breakdown and oligodendrocyte disruption in the childhood form of disease.

Either gender may present with a slowly progressive myelopathy. When viewed via MRI, the brain may be normal or there may be cerebral involvement similar to childhood disease with symmetric white matter lesions surrounding the atria with extension across the splenium of the corpus callosum. The lesion margins may be contrast enhancing.35 The thoracic cord may appear diffusely atrophic when viewed via MRI.

Miscellaneous Symptoms

The above conditions may be a challenge to diagnose, but at least they are recognized disorders with vast bodies of clinical data behind them. However, the typical neurologist will likely see a number of cases that defy all known description and diagnostic criteria that would force even neuroimmunology experts to rub their chins in contemplation.

Some patients can present with a bewildering array of neurologic complaints, with one appearing for almost for every nervous function reviewed. These individuals have usually gone through several other physicians and often insist that they have multiple sclerosis even if it has not been definitively diagnosed. Occasionally they are placed on therapy despite a lack of grounded, compelling reasons. The examination is often strikingly unremarkable unless signs of a conversion reaction, such as Hoover’s sign or split vibratory sense, are elicited. Significant MRI findings are usually absent. These complaints often reflect an underlying depression or unresolved psychological issues and require psychiatric intervention. Conversion reactions can, however, present in patients with multiple sclerosis. When this happens, it is important not to treat the new symptoms as reflective of disease activity.

Patients who report transient double vision, paresthesias, focal weakness and other neurologic symptoms may give the appearance of presenting with MS. When examined, however, none of the test results indicate any known conditions. The most likely diagnosis: It is a healthy person who is experiencing a transient symptom or two similar to MS that is likely to spontaneously resolve.

By using a systematic clinical and investigational approach to the primary presentations of multiple sclerosis, one can definitively differentiate this condition from those that mimic it. This approach should be helpful when handling cases that might otherwise be puzzling, and knowing some of the red flags that imply the presence of a condition other than MS can indicate the right choice. PN