The Differential Diagnosis of Multiple Sclerosis

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Objective: This article will discuss the diagnosis of multiple sclerosis (MS), with particular attention to differentiating it from other diseases that can mimic it.

Methods: We reviewed our own data, as well as the published experience on the differential diagnosis of MS and the most common errors leading to misdiagnosis.

Results: Psychiatric diseases are mistaken for multiple sclerosis more often than any other conditions. Other multifocal illnesses or white-matter diseases are seldom confused with multiple sclerosis.

Conclusion: Neurologists are most likely to misdiagnose multiple sclerosis in patients who have psychiatric problems or who have uncommon presentations of common diseases such as migraine, stroke, or neuropathies.

Key Words: multiple sclerosis, differential diagnosis, optic neuritis, Lyme disease, lupus, vitamin B12 deficiency, psychiatric disease

(*The Neurologist* 2007;13: 57–72)

Neurologists must often diagnose diseases for which there are no definitive tests: migraine headaches, Parkinson disease, and amyotrophic lateral sclerosis (ALS) are just some examples. For these patients, neurologists can nevertheless integrate features of the history, physical examination, and laboratory tests to achieve such accuracy that they rarely doubt their diagnosis. Yet with multiple sclerosis (MS), this same process seems more difficult, the diagnosis less certain, and the doubt much greater. The reputation of MS as a challenging disease to diagnose is well earned. Yet it is important to confirm MS, if possible, because the stakes can be high. When given a diagnosis of MS, a patient may lose his or her present job and his or her future employability. Peace of mind is also lost as the diagnosis of a chronic, relapsing, possibly disabling but unpredictable disease can crumble even the sturdiest psychologic defenses. The diagnosis may commit patients to medical treatments that could continue for years. In some settings, initiation of treatment early might result in later medical benefits. When faced with a patient who might have MS, neurologists thus feel many pressures to "get it right."

Ultimately, the diagnosis will depend upon the extent to which the patient's overall picture has the expected findings typical of multiple sclerosis.

THE DIAGNOSIS OF MULTIPLE SCLEROSIS

Diagnostic Principles

The goal of this article is to review the diseases often confused with MS, rather than to discuss the proper way to diagnose MS. Nevertheless, while analyzing the differential diagnoses, a few words are appropriate about recognizing the disease itself to distinguish it from its mimics.

Although "official" requirements have been proposed for diagnosing MS,[1] these are of limited value for clinicians. Confirming or refuting MS is not done by following any "cookbook" or algorithm of the same tests on each and every patient. Instead, the diagnosis must be reached by careful examination of all the evidence both for and against the disease, and through questioning, examining, and testing; the neurologist must assemble this evidence until it is sufficiently compelling to find the patient "guilty" or "not guilty" of having MS. Even when great care is used, the diagnosis may be made in error (innocent people found guilty) or inappropriately dismissed (guilty people found innocent), and expert neurologists may disagree among themselves (hung juries). The inability to sometimes prove the diagnosis "beyond a shadow of a doubt," combined with the many nuances and pitfalls in the history, physical examination, and testing for MS, create the challenges of diagnosing MS.[2] Ultimately, the diagnosis will depend upon the extent to which the patient's overall picture has the expected findings typical of MS.[3,4]

Red Flags and the Differential Diagnosis of MS

The diagnosis of MS should be questioned when clinical or laboratory findings are unexpected or atypical. These unusual features or "red flags" should raise suspicion that MS is not present.[5,6] Rare patients with these red flags do have MS. However, most patients with other diseases will be identified by the presence of one or more of these atypical

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The authors declare no conflicts of interest.

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ISSN: 1074-7931/07/1302-0057
DOI: 10.1097/01.nrl.0000254705.39956.34

TABLE 1. Red Flags for the Misdiagnosis of MS

I. Red flags in the history and examination
1. Normal neurologic examination
2. Abnormality in a single location; no dissemination in space
3. Progressive from onset; no dissemination in time
4. Onset in childhood or over age 50
5. Psychiatric disease present, ie, another explanation for findings
6. Systemic disease present, ie, another explanation for findings
7. Prominent family history; consider genetic disease
8. Gray matter symptoms: dementia, seizures, aphasia
9. Peripheral symptoms: peripheral neuropathy, fasciculations
10. Acute hemiparesis
11. Lack of typical symptoms: no optic neuritis, bladder problems, Lhermitte sign, sensory level, etc
12. Prolonged benign course, ie, diagnosis made years ago with few findings now

II. Red flags in the laboratory tests
1. Normal or atypical MRI
2. Normal CSF
3. Abnormal blood tests, though many are false positives

features. Table 1 is a summary of the findings which should alert the clinician to consider alternative diagnoses.

Prospective studies have shown that 2 factors most reliably identify patients who do not have MS.[6] The first is their lack of typical symptoms: no optic neuritis, Lhermitte sign, sensory level, neurogenic bladder, or other common deficits. The second is their lack of typical findings on magnetic resonance imaging (MRI) and CSF examination. Very few patients with MS have a normal MRI of the brain or normal CSF.

The "Abnormal" MRI

It has often been said that MS is a clinical diagnosis. This is not entirely true. It is unlikely a patient would be diagnosed with MS today (at least in Europe or North America) without undergoing MRI scanning. The introduction and refinement of MRI has changed the diagnostic process in MS, and most diagnostic criteria for MS rely heavily on interpretation of MRI.[1]

The most common reason for falsely attributing a patient's symptoms to multiple sclerosis is faulty interpretation of the magnetic resonance imaging.

This has also changed the misdiagnosis of MS. The most common reason for falsely attributing a patient's symptoms to MS is faulty interpretation of the MRI.[7] Signal abnormalities of one sort or another are so common on MRI as to be ubiquitous. Over-interpretation of such scans, falsely assuming the signal changes are MS, is the most common reason for misdiagnosing MS (Table 2). The MRI, like other clinical features or laboratory tests, is simply one piece of evidence that must be placed in context to arrive at a correct diagnosis.

TABLE 2. Partial Differential Diagnosis of MS on MRI

1. Age-related changes
2. Acute disseminated encephalomyelitis
3. CNS vasculitis
4. Behçet disease
5. Sjögren syndrome
6. Sarcoidosis
7. Metastatic neoplasm
8. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
9. Binswanger disease
10. Migrainous ischemia
11. Cerebrovascular disease
12. Progressive multifocal leukoencephalopathy
13. Inherited white matter diseases
14. Effects of radiation therapy or drugs
15. CNS lymphoma
16. Lyme disease
17. HTLV-1 infection
18. CNS lupus
19. Mitochondrial encephalopathies
20. Antiphospholipid antibody syndrome

THE DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS

Diagnostic Principles

MS is a disease disseminated in time and in space. Yet the differential of MS is almost never other diseases disseminated in time and in space. MS is a white-matter disease. Yet the differential of MS is almost never other white-matter diseases. Instead, the mimics of MS are the mundane conditions that most commonly affect the nervous system, such as migraine, stroke, and neuropathies. Of these, psychiatric illnesses dominate. Tables 3, 4, and 5 list many of the diseases disseminated in time and in space that most standard texts present as the differential diagnoses of MS.[4,8,9] In fact, most of these are rare conditions seldom, if ever, seen in clinical practice. They are presented here for the sake of completeness, but their occurrence is so unusual that a positive test for these diseases may be more often a false positive than a true one. The misinterpretation of false-positive tests in MS is such a hazard that it deserves special caution.

The Hazards of Routine Screening: Beware of False Positives

The majority of patients presenting with a clinical picture typical of MS do in fact have MS. Mindlessly screening these patients with an unvarying battery of tests seldom generates a different diagnosis and more often leads to confusing false-positive results.[10] This is especially true of many tests ordered for the evaluation of other white-matter

TABLE 3. Diseases Sometimes Disseminated in Space but Not in Time

1. Shower of cerebral emboli
2. Thrombocytopenic purpura
3. CNS vasculitis
4. Mitochondrial encephalopathies
5. Drugs and toxins
6. Acute disseminated encephalomyelitis
7. PML (progressive multifocal leukoencephalopathy)
8. Mycoplasma encephalopathy
9. Lyme disease
10. Vitamin B12 deficiency
11. Behçet disease
12. Sarcoidosis
13. Paraneoplastic syndromes
14. Periventricular leukomalacia
15. Psychiatric syndromes

TABLE 4. Diseases Sometimes Disseminated in Time but Not in Space

1. Tumor (brain or spinal cord)
2. Arteriovenous malformation (brain or spinal cord)
3. Familial cavernous hemangiomata
4. Cervical spondylosis
5. Chiari malformation
6. Foramen magnum lesions
7. Peripheral neuropathy
8. Leber optic atrophy
9. Familial spastic paraplegia
10. Adult-onset leukodystrophies
11. Migraine
12. Sjögren disease
13. HTLV-1
14. Cerebellar degeneration
15. Syringomyelia

TABLE 5. Diseases Often Disseminated in Both Time and Space

1. Cerebrovascular disease, including emboli
2. Familial cavernous hemangiomata
3. CNS lymphoma
4. SMON (Subacute myelo-opticoneuropathy)
5. CNS vasculitis
6. Migratory sensory neuritis
7. Myasthenia gravis
8. Mitochondrial disease
9. Sjögren disease
10. HIV
11. Eale disease
12. Systemic lupus erythematosus
13. Lyme disease
14. Porphyria
15. Sarcoidosis
16. Antiphospholipid antibody syndrome
17. Spinocerebellar degeneration
18. CADASIL
19. Psychiatric syndromes
20. Devic disease

diseases disseminated in time and in space (Tables 3–5). For many of these, the normal test ranges, sensitivities, and specificities are poorly established. (For example, when is a sedimentation rate abnormal? Or an ANA?)

The Optic Neuritis Treatment Trial

The Optic Neuritis Treatment Trial (ONTT) is an instructive example of the pitfalls of screening tests in demyelinating disease. This study enrolled 457 patients with optic neuritis to determine the effectiveness of treatment and natural history of the disease. Patients were diagnosed with optic neuritis on clinical grounds: acute monocular visual loss with a field defect and an APD in an otherwise healthy young person. All patients were screened for other diseases that could mimic optic neuritis by having an MRI scan of the brain, CBC, metabolic profile, chest x-ray (to exclude sarcoid), FTA, and ANA. Thirty-one percent had a spinal tap. Only 2 out of the 457 patients proved to have a disease other than optic neuritis (1 with a pituitary tumor and 1 with an aneurysm). There were no patients whose diagnosis was changed by CSF or chest x-ray. Six had a positive FTA and 15 had an elevated ANA, but all of these were false positive. These screening tests thus confused the management of a number of patients, but none ever led to a different diagnosis. This was true whether patients came from rural or urban settings, the North or the South, academic centers or elsewhere.[11,12]

Lyme Disease

Many authorities list Lyme disease high on the differential diagnosis of MS as a disease of young people capable of causing white-matter symptoms, sometimes relapsing and remitting, occasionally with MRI changes mimicking MS. In fact, the classic clinical and MRI picture of MS is almost never produced by Lyme disease, and routine screening in the absence of a specific indication will produce more false positives than true positives. In a study of MS patients in a Lyme-endemic area in New York, 283 consecutive patients with MS were screened for Lyme disease and 19 had positive Lyme serology. On further testing, including spinal tap with measurement of intrathecal antiborrelia antibodies, none of these 19 patients had Lyme disease.[13,14]

Vitamin B12 Deficiency

A deficiency in vitamin B12 can lead to myelin damage, including a myelopathy, which can mimic MS. So vitamin B12 deficiency is commonly listed in the differential diagnosis of MS. Clinicians can again be led astray by screening tests, with studies showing decreased levels in up to 19% of MS patients. The reason for low serum vitamin B12 levels in MS patients is not clear, but these are usually false-positive values. Most MS patients labeled instead as deficient in B12 actually do have MS.[15–17]

Screening for systemic, inflammatory, autoimmune, "collagen vascular" diseases is complicated by the presence of many immune-system changes in multiple sclerosis patients, including a high incidence of autoantibodies.

Lupus, Inflammatory Diseases, ANA, and Autoantibodies

The various causes of vasculitis figure prominently in most lists of MS mimics. For example, systemic lupus erythematosus affects the central nervous system in approximately 40% of patients and can cause optic neuritis, myelopathy, and even INOs. In the CSF, IgG and oligoclonal bands can occur in 50%-70% of patients with CNS lupus, and MRI changes may be indistinguishable from those of MS. However, CNS involvement almost always occurs in the setting of unmistakable systemic disease so that lupus should seldom be confused with MS. Patients with CNS lupus usually have joint disease, rashes, alopecia, fevers, renal failure, and other stigmata of systemic lupus. Their spinal fluid usually also shows much higher protein and polymorphonuclear cell counts, more closely mimicking meningitis than MS. What is true of lupus holds for most other "connective tissue" inflammatory diseases as well, such as Sjögren syndrome, Behçet syndrome, and sarcoid.[18]

Screening for these systemic, inflammatory, autoimmune, "collagen vascular" diseases is complicated by the presence of many immune-system changes in MS patients, including a high incidence of autoantibodies. But these are usually of no clinical significance. In one study, a positive ANA was found in 81% of MS patients.[19] Screening all suspected MS patients with an ANA will therefore yield too many false positives and too few cases of other inflammatory diseases.

Note that the same can be said for the lupus anticoagulant or antiphospholipid antibodies. These are also found in a high percentage of MS patients. Although their significance is still being debated, they are often of no clinical importance and merely confuse the diagnosis.[20]

An abnormal screening laboratory test is simply one piece of evidence, and it must be combined with additional data and seasoned with clinical judgment before arriving at a definite diagnosis. Beware of diagnosing rare diseases (Lyme, vitamin deficiency, vasculitis, etc) even when their tests are positive.

By far the most important disease confused with multiple sclerosis is psychiatric illness.

TABLE 6. Most Common Diagnoses for Patients Without MS

	Colorado (N = 139)	Dalhousie (N = 52)	Marshfield (N = 70)
Psychiatric disease	63 (45%)	14 (27%)	53 (76%)
Migraine headaches	29 (21%)	7 (14%)	2 (3%)
Stroke or TIA	7 (5%)	3 (6%)	2 (3%)
Peripheral neuropathy	6 (4%)	3 (6%)	1 (1%)
Cervical stenosis	4 (3%)	1 (2%)	1 (1%)
Benign sensory symptoms	0	11 (22%)	8 (11%)
Vertigo	0	3 (6%)	0

Psychiatric Disease and Normal People

By far the most important disease confused with MS is psychiatric illness.[21,22] Most patients referred to a neurologist for consideration of possible MS who do not have the disease instead suffer from some form of psychiatric disorder: somatization, hypochondriasis, malingering, depression, anxiety, or similar problems. In the few instances where the differential diagnosis of MS patients has been documented (as summarized in Table 6), psychiatric diseases emerged as the foremost problem. At the University of Colorado Multiple Sclerosis Center, 67% of patients referred for possible MS had some other condition, of which psychiatric disease was the most common.[22] Among patients referred to Dalhousie University's MS Unit from 1979–1983 (before the availability of MRI), 13% did not have MS; most had psychiatric problems.[21] Prospective data from the Marshfield Multiple Sclerosis Center, a private, nonuniversity referral clinic, shows that 49% of the 142 patients evaluated for possible MS since May 2004 had other diseases. Seventy-five percent of these had psychiatric diagnoses. As shown in Table 6, there are 7 conditions that accounted for almost all the alternative diagnoses at these 3 MS centers. None of these are other white-matter or inflammatory diseases disseminated in time or in space. Across diverse settings and referral patterns, over 3 decades, with or without MRI, the most common conditions mistaken for MS were psychiatric.

The second largest diagnostic category of "non-MS" patients is normal people describing everyday sensations that are misconstrued as abnormal. In one study, 32% of normal people between the ages of 20 and 45 reported transient neurologic symptoms, such as visual changes, loss of power, poor balance and coordination, and speech difficulty.[23] Care thus must be taken not to overemphasize the multitude of transient disturbances that plague all normal people: itches, twitches, "falling asleep" limbs, and fleeting visual obscurations.

Two useful features in distinguishing MS symptoms from normal or psychiatric problems are their anatomy and their time course. Psychiatric symptoms tend to be diffuse and difficult to explain anatomically, such as tingling in both hands and both feet simultaneously, numbness over the entire face, or generalized symptoms such as "feeling weak all over." In contrast, MS symptoms usually have a clear anatomic location. Even if an MS attack affects different foci in the nervous system, there will be distinct lesions (such as optic nerve plus spinal cord) rather than diffuse and general-

ized symptoms. True MS relapses also have a finite time course; they occur abruptly, evolve over minutes to days, and then slowly resolve within days to weeks. "Normal" transient symptoms in contrast tend to be quite brief, lasting seconds to minutes. Psychiatric symptoms may fluctuate, but usually without the pattern of sudden onset followed by gradual resolution. The persistence of symptoms can be another clue to their psychiatric origin. The "average" person with MS generally has 1 distinct neurologic episode per year—in many studies actually closer to every 24 months—and they are then free of symptoms until their next relapse. Patients with a psychiatric disease generally have multiple symptoms that come and go all the time. They are seldom free of symptoms. They seldom feel well.

The coexistence of known psychiatric problems is obviously another clue that a patient's neurologic symptoms might be psychiatric in origin. If a patient is known to be anxious or depressed or has a history of other psychosomatic problems, their current symptoms must be viewed with more suspicion. Studies have shown that when experienced clinicians conclude (after appropriate investigations) that a patient's symptoms are "nonorganic," they are seldom wrong.[24] Most of us correctly identify psychiatric findings. Nevertheless, people with psychiatric illness can also develop MS, and clinicians must guard against too superficial an evaluation of such patients.

HOW TO INFORM PATIENTS THAT THEY DO NOT HAVE MS

After a complete workup, often a diagnosis of MS, or any serious neurologic disorder, will not be established. The manner in which patients should be informed of this conclusion largely depends on their psychologic status. At one end of the spectrum are patients who, apart from understandable concern about the possibility of a disabling illness, are essentially normal psychologically. For these patients, the neurologist may explain the circumstances that led to the initial suspicion of MS (eg, over-reading of an MRI scan or misplaced concern about benign paresthesias) and the objective findings which have shown that MS is not present.

An intermediate class of patients consists of persons who have mild but persistent anxiety or mood disorder ("the worried well"), either constitutionally or because of the lingering suspicions on their part or the part of their neurologist that organic disease might be present. These patients will benefit from infrequent but regularly scheduled (eg, q. 3–6 months) return visits to the neurologist for reassurance and reevaluation. Eventually, these patients usually reach a point where they can be returned to the long-term supervision of their primary physician, always with the offer of a repeated neurologic assessment if needed.

At the other end of the psychologic spectrum are patients who have severe underlying mental disturbance and whose symptoms frequently evoke very negative emotions in physicians. For example, in an analysis of 300 new outpatient visits, Carson and colleagues[25] found that patients whose symptoms were not explained by organic disease were consistently rated as most difficult to help by neurologists. In this regard, O'Dowd[26] coined the term "heartsink patients" for persons who exasperate, defeat, and overwhelm their doctors by their behavior. Patients presenting with psychogenic symptoms often suffer from somatization disorder, anxiety disorder, hypochondriasis, depressive disorder, or an attachment to illness as a way of life.

Very few neurologists have the resources and skills to effectively manage patients with chronic psychogenic disorders. A major mistake for the neurologist in this circumstance is to attempt too much; for example, to try to cure the incurable by endeavoring to reverse an ingrained pattern of psychogenicity in one brief conversation. So if most patients with psychogenic symptoms reject immediate referral to a mental health professional and if the neurologist is usually not the best person to provide continued management, who is? The medical literature provides a consistent and positive answer to this question, namely, that the primary care physician, who deals with a high percentage of nonorganic or embellished complaints during each practice day,[27,28] is usually well qualified by experience and training to help these patients. Several authoritative guidelines endorse short, frequent visits to a primary care physician for a program based on reassurance and support; limiting of testing and subspecialty referrals to those that truly are necessary; first-line treatment of depression and anxiety; and a gradual, nonthreatening shift of focus to consideration of stress and other psychologic factors.[29,30] Eventually, psychogenic patients often reach the point that they will accept expert psychiatric referral. In summary, while the best hope for fundamental change over the long term lies with psychiatric treatment, in the short term, optimal management is usually based on supportive care with a primary care physician. Obvious exceptions to the recommendation for delayed psychiatric management are the rare patients who are psychotic or who are a danger to themselves or others.

CONCLUSION

The determination of MS is not made by following any set of diagnostic criteria. Rather, it depends upon the extent to which a patient's clinical and laboratory evidence is typical of MS. Other diseases usually have atypical features signaling they are not MS. Over-interpretation of the false-positive MRI is the most common mistake in misdiagnosing MS. The differential diagnosis of MS is not other white-matter diseases nor other diseases disseminated in time and space. Instead, the great mimicker of MS is psychiatric disease. On the rare occasions when another neurologic problem presents as MS, it will be a common condition such as migraine or stroke. Diagnoses of uncommon conditions are usually "false positives." Neurologists must learn to deal with psychiatric patients in a compassionate but firm manner and rely on primary care providers to help the well-being of those patients.

ADDENDUM

Table 7 is a comprehensive list of 100 conditions that might mimic MS. While we believe this can be a valuable resource, most of these are rare conditions that will seldom be encountered.

TABLE 7. One Hundred Conditions Sometimes Mistaken for Multiple Sclerosis

Disease	What It Is	How It Mimics MS	How to Tell It From MS
1. Clinically isolated syndrome or monosymptomatic demyelination	A single attack of optic neuritis, transverse myelitis, or other lesion confined to 1 anatomic localization at 1 point in time. This sometimes represents the first attack of MS.	Same symptoms. More than half have an abnormal MRI, with subclinical lesions elsewhere in the brain.	Time. Another attack disseminated in time and space will confirm MS. Another lesion on MRI done 1 mo later implies MS.
2. Balo concentric sclerosis	A demyelinating disease with lesions occurring in concentric bands of alternating demyelination and preserved normal white matter.	The symptoms may be identical to those of MS.	The MRI scan will show typical concentric white-matter lesions that are diagnostic. These may be mixed with MRI abnormalities very characteristic of typical MS as well.
3. Schilder disease (myelinoclastic diffuse sclerosis)	Bilateral hemispheric demyelination with onset usually in childhood. The classification and terminology are controversial. Onset of extensive demyelination at an early age.	The symptoms are very similar, with weakness, numbness, and focal neurologic deficits. The MRI will show large confluent areas of signal abnormality in the white matter.	The onset is often in childhood and usually includes symptoms seldom seen in MS, including aphasia, dementia, seizures, and increased intracranial pressure.
4. Tumefactive MS	A large focus of demyelination, often with mass effect and edema, resembling a brain tumor. In addition to focal signs, the patient may also have headaches and seizures.	The patient will have focal neurologic findings and abnormal MRI scan, though the lesion often appears distinctly different on MRI with mass effect and open-ring enhancement.	This form of MS may need to be confirmed with brain biopsy, but often the diagnosis can be suspected by finding oligoclonal bands and IgG abnormalities in the spinal fluid or abnormal evoked potentials in asymptomatic areas.
5. Marburg disease	A fulminant, acute, severe, demyelinating disease.	This is believed to be a variant of MS that shows unusual virulence and aggressiveness. The clinical features and MRI scan may be indistinguishable from MS.	This is felt to be a form of MS that is particularly destructive, with necrosis, axonal destruction, and progression to death in less than 12 mo.
6. Devic disease, or neuromyelitis optica (NMO)	Acute inflammatory demyelination predominantly affecting the optic nerves and spinal cord, associated with an NMO-IgG antibody against the aquaporin-4 channel.	Optic neuritis and transverse myelitis characterize NMO and are also common symptoms of MS. As many as 15% of NMO patients have lesions in areas other than the optic nerves and spinal cord, both clinically and on MRI.	Diagnostic criteria for NMO include lesions affecting the optic nerve and spinal cord, but with myelitis extending continuously over 3 or more contiguous segments of the cord. Patients should also be seropositive for the NMO-IgG antibody.
7. Acute disseminated encephalomyelitis (ADEM)	Monophasic demyelination occurring with or just after an infection, vaccination, or other immune-altering event.	The symptoms can be identical, including involvement of optic nerve, brain, and spinal cord, and the MRI may show identical scattered white-matter signal abnormalities.	There is no infallible method of distinguishing ADEM from MS. It occurs in the setting of infections, is more common in childhood, and may include altered consciousness and other unusual symptoms, and the MRI may show hemorrhagic lesions and/or gray matter lesions (or may even be normal).
8. Chronic inflammatory demyelinating polyneuropathy (CIDP)	A progressive, relapsing, demyelinating, peripheral neuropathy, sometimes associated with CNS demyelination.	May have MRI signal abnormalities in the brain associated with the neuropathy symptoms of weakness and numbness.	Brain MRI lesions are usually not as widespread as in classic MS, and IgG abnormalities are usually absent in CSF. Of course, patients have an associated peripheral neuropathy clinically, on EMG, and nerve biopsy.
9. Bickerstaff brainstem encephalitis	An inflammatory brainstem syndrome with CSF pleocytosis in a young adult, often accompanied by headache and malaise. It may be subacute in onset, is monophasic, and usually recovers fully. The etiology (? infectious versus immune) is unknown.	Symptoms may be identical, including brainstem symptoms of ophthalmoplegia, facial diplegia, dysarthria, and ataxia. The MRI may show white-matter signal abnormalities.	Some symptoms are unusual for MS, such as deafness, and CSF shows significant pleocytosis but no IgG abnormalities or oligoclonal bands.
10. Subacute myelo-optic neuritis (SMON)	A toxic demyelination primarily affecting optic nerves and spinal cord, caused by toxins (such as in contaminated cooking oil) and/or vitamin deficiencies, seen primarily in developing countries.	Similar symptoms of subacute optic nerve and spinal cord deficits. MRI may show white-matter abnormalities.	It affects all ages, usually in developing countries and in a clinical setting of poverty and nutritional deficiency. CSF does not have IgG abnormalities.

TABLE 7. Continued

Disease	What It Is	How It Mimics MS	How to Tell It From MS
11. Eale syndrome	A noninflammatory small-vessel occlusive disease predominantly affecting retinal vasculature and also causing vitreous hemorrhages, primarily affecting young males from India and the Middle East.	Similar symptoms including visual involvement, INO, vestibulopathy, focal weakness, and myelopathy. MRI may show white-matter lesions.	Very rare in North America. Ophthalmological examination, including fluorescein angiography, is definitive.
12. Behçet disease	An autoimmune syndrome of oral and genital ulcers, uveitis, and arthritis affecting predominantly Mediterranean and Middle East patients.	Rare reports of focal weakness and myelopathy, along with visual (uveitis/iritis) symptoms. MRI may show white-matter changes.	Rare in North America. CSF shows pleocytosis without characteristic IgG abnormalities. Biopsy of mucocutaneous ulcers is definitive.
13. Sarcoidosis	A granulomatous multisystem disease of unknown etiology.	May involve optic nerve or spinal cord. MRI may show white-matter lesions. Rare patients have oligoclonal bands in their CSF.	Often systemic symptoms, especially in the lungs. Serum and CSF ACE levels may be elevated. MRI often shows meningeal enhancement. Biopsy (of skin, lymph node or lung) is definitive.
14. Sjögren syndrome	An autoimmune disease of dry eyes and mouth with arthritis and vasculitis.	Occasional reports of neurologic symptoms, especially progressive myelopathy. MRI may show white-matter lesions and spinal fluid may show oligoclonal bands with increased IgG.	Positive serology for SS-A (Ro) and SS-B (La) autoantibodies. Prominent dry eyes and mouth. Salivary gland biopsy can be definitive.
15. Systemic lupus erythematous (SLE)	An autoimmune multisystem disease, including vasculitis that commonly affects the central nervous system.	Common in young women and may affect the nervous system, especially optic nerve and spinal cord. MRI white-matter changes are common, and up to 60% have oligoclonal bands and IgG abnormalities in CSF.	Positive serology with ANA and double-stranded DNA autoantibodies. Systemic involvement especially includes kidneys and skin and hematologic changes. Can be very difficult to distinguish from MS.
16. Eosinophilia-myalgia syndrome (EMS)	Syndrome of uncertain etiology producing eosinophilia and myalgia, often with other systemic symptoms.	Associated with a hypercoagulable state that can produce multiple infarctions and thus focal neurologic deficits. MRI may show white-matter lesions.	CBC shows marked eosinophilia. CSF does not show bands or IgG abnormalities. Patients usually have other systemic symptoms.
17. Systemic sclerosis (scleroderma)	Progressive deposition of connective tissue of uncertain etiology, sometimes producing neurologic deficits.	Neurologic problems are primarily peripheral but may produce numbness of face or hands (trigeminal or median neuropathies). MRI may show white-matter changes (possibly ischemic from accompanying vasculopathy).	CNS findings on examination are rare. CSF does not show IgG abnormalities.
18. Inflammatory ocular disease (uveitis, iritis, or retinitis)	Autoimmune inflammation of the eye, often as part of more systemic inflammation.	Patients have a variety of ocular signs and symptoms. Some conditions are also accompanied by typical MRI abnormalities.	Ophthalmologic examination, including fluorescein angiography, will confirm the ocular inflammation. (A uveitis can rarely be seen with MS but is seldom severe.)
19. Anterior ischemic optic neuropathy (AION)	Infarction of the optic nerve due to vascular disease, either atherosclerotic or vasculitic.	Sudden or subacute monocular visual loss with findings of optic nerve damage mimic the optic neuritis seen in MS.	Usually occurs in older patients (greater than age 50) with atherosclerotic risk factors. Patients would have no other signs or symptoms, normal CSF, and normal (or nonspecific aging changes) MRI scans.
20. Cogan syndrome	Syndrome of interstitial keratitis with vestibular dysfunction (sudden attacks of vertigo) and deafness.	Relapsing visual symptoms plus dizziness in young patients. Rare reports of abnormal MRI scans. Occasional reports also of ataxia.	Recognize the triad of inflammatory keratitis plus vertigo plus hearing loss; deafness is rare in MS. CSF will be normal.
21. Susac syndrome	A microangiopathy of unknown etiology affecting the brain, retina, and cochlea, occurring in women.	Relapsing symptoms of vertigo, vision loss, and encephalopathy, with white-matter changes on MRI scan in young women.	Ophthalmologic evaluation with fluorescein angiography and audiograms will be abnormal. CSF may have pleocytosis but no IgG abnormalities. Brain biopsy (showing multifocal microinfarcts) may be necessary.

TABLE 7. Continued

Disease	What It Is	How It Mimics MS	How to Tell It From MS
22. Sneddon syndrome	Antiendothelial cell antibodies causing livedo reticularis and strokes in young people.	Young patients have multiple strokes (recurrent focal CNS deficits), with accompanying signal changes on MRI scan.	Presence of livedo reticularis (clinically and on skin biopsy) is diagnostic. Antiphospholipid antibodies often present and gray matter (vascular) symptoms may be prominent.
23. Dego disease (malignant atrophic papulosis)	Multisystem occlusive vasculopathy (including ischemic and hemorrhagic strokes) with cutaneous and GI manifestations.	Neurologic symptoms can include paresthesias, visual symptoms, weakness, and myelopathy. The MRI has multifocal (ischemic) signal abnormalities. Rare reports of oligoclonal bands.	Skin lesions (porcelain white center surrounded by pink ring) are diagnostic and skin biopsy will show vasculopathy.
24. Central nervous system vasculitis (primary CNS angiitis)	Autoimmune vasculitis primarily or entirely restricted to the central nervous system, often in young patients.	Relapsing, multifocal CNS deficits in a young patient with multifocal MRI signal changes and inflammatory CSF.	May have abnormal serologies and autoantibodies on screening blood work. If not, angiography and brain biopsy may be necessary.
25. Antiphospholipid antibody syndrome	Recurrent venous and/or arterial occlusions with clotting abnormalities associated with IgG and IgM anticardiolipid antibodies. May be idiopathic or associated with other systemic inflammatory diseases.	Recurrent focal (ischemic) CNS deficits with accompanying MRI signal changes. Up to 20% have bands in their CSF.	High titers of autoantibodies. May have headaches, seizures, and systemic involvement (thrombosis, arthritis, skin changes) not seen in MS.
26. Central serous chorioretinopathy (CSC)	Recurrent monocular visual loss in young adults due to serous detachment of the retina.	It mimics recurrent optic neuritis. MS may be misdiagnosed if other "soft" symptoms are also present.	Ophthalmologic evaluation will detect the retinal detachment. MRI of the brain should be normal.
27. Stroke in the young	Arterial (or rarely venous) occlusion with ischemic strokes, often recurrent, in young patients, many of whom have no obvious stroke risk factors.	Recurrent focal strokes may mimic MS symptoms. MRI often shows multifocal (ischemic) signal abnormalities.	Signs and symptoms are usually typical of ischemic stroke rather than demyelination, and MRI often shows gray matter involvement. Tests may show a specific stroke etiology (hypercoagulable state, congenital heart disease, etc).
28. Migraine	Recurring complicated headache syndrome that can produce neurologic symptoms in a young person.	Young person with transient and recurring focal neurologic deficits, often without significant headache, and often with signal changes on MRI scan.	Typical symptoms of migraine are often present (hemicranial headache with nausea). CSF and evoked potentials should be normal.
29. Binswanger disease or leukoaraiosis	An ischemic leukoencephalopathy leading to primarily periventricular white-matter refraction; may be patchy and asymptomatic (leukoaraiosis) or accompanied by dementia and gait disorder.	MRI scan may resemble MS because of extensive white-matter signal abnormalities.	Patients are usually older and may have cerebrovascular risk factors. Dementia may be prominent. CSF should be normal.
30. Neuroretinitis (stellate retinitis)	Usually unilateral visual loss (predominantly idiopathic) caused by optic nerve capillary leak, often with macular star formation.	Monocular (or rarely binocular) sometimes recurrent visual loss mimics optic neuritis and can be confused with MS if other "soft" signs are found.	MRI and CSF should be normal and ophthalmologic evaluation with fluorescein angiography should be diagnostic.
31. Familial cavernous hemangiomata	Inherited multifocal CNS vascular malformations.	Multifocal hemorrhages produce recurrent CNS symptoms that can mimic MS.	MRI scanning will show characteristic appearance of hemangiomas.
32. Thrombotic thrombocytopenic purpura	Coagulopathy with low platelet counts and recurring thrombosis, especially in young women.	Recurrent focal thromboses may produce symptoms resembling MS, with accompanying MRI abnormalities.	Symptoms (and MRI changes) often involve gray matter. Clotting studies will be abnormal and CBC will show thrombocytopenia.
33. Progressive multifocal leukoencephalopathy (PML)	CNS infection by JC virus in an immunosuppressed patient, causing progressive (and sometimes relapsing) deficits leading to death within weeks or months.	Can have multifocal CNS deficits, which sometimes relapse. The MRI is abnormal, showing white-matter lesions.	It occurs in immune-compromised patients, the deficits are usually progressive rather than relapsing, the time course is short, and MRI lesions are generally larger and more confluent. CSF PCR may be positive for JC virus, but brain biopsy may be necessary for the diagnosis.

TABLE 7. Continued

Disease	What It Is	How It Mimics MS	How to Tell It From MS
34. Whipple disease	Chronic CNS (and systemic) bacillary infection causing primarily neurologic, GI, and joint symptoms. Steatorrhea, abdominal pain, and arthralgias may be present.	May cause eye movement abnormalities, myelopathy, and sometimes dementia and myoclonus. Usually progressive but may have fluctuations or relapses.	Systemic manifestations (especially GI) are present. The MRI shows more gray-matter involvement and rarely white matter, and the CSF PCR for the bacillus is often specific. Occasionally, small-bowel biopsy may be necessary to confirm the infection.
35. HTLV-1 myelopathy	Chronic retroviral infection of the nervous system indigenous to the Caribbean, causing progressive myelopathy.	Myelopathic symptoms, rarely with brain lesions as well, with white-matter abnormalities on MRI scan and sometimes with oligoclonal bands in CSF.	Clinical picture is usually confirmed to a progressive myelopathy and usually in people of Caribbean or Asian background. Positive HTLV-1 serology will make the diagnosis.
36. Lyme disease (neuroborreliosis)	Infection by tick-borne spirochete *Borrelia burgdorferi*.	It can cause persistent focal neurologic findings and signal abnormalities on MRI scan of the brain.	History of erythema migrans rash. Western blot is the most definitive serology, and CSF will show positive PCR.
37. Syphilis	Chronic CNS infection by the spirochete *Treponema pallidum*.	Can cause optic neuritis, myelopathy, and other focal neurologic findings.	MRI is usually normal. Negative serology (FTA-ABS) rules out syphilis. Infection now rare except in HIV-positive or immune-compromised patients.
38. HIV/AIDS	Retroviral infection with HIV-1 that can involve the nervous system, most commonly in gay males or intravenous drug users.	May cause optic neuritis, myelopathy, mental status changes, and focal deficits with white-matter changes on MRI scan and abnormal CSF.	Occurs in high-risk populations who may have diminished CD4 cell counts and positive HIV serology.
39. Variant Creutzfeldt-Jacob disease	Infection with the prion agent. The variant disease form, linked to "mad cow disease," occurs in younger populations than classic CJD.	May cause ataxia, diplopia, and sensory symptoms, along with dementia in a young person.	MRI and spinal fluid are usually normal. The course is rapidly progressive over months. Brain biopsy is seldom recommended. May have abnormal EEG or 14-3-3 protein in CSF.
40. Brucellosis	Systemic infection that can involve both central and peripheral nervous system, rare in developed countries and usually associated with agricultural or animal exposure.	Can cause optic neuritis, myelopathy, and focal neurologic findings, along with periventricular MRI signal abnormalities.	Usually a systemic infection including fever. Specific antibodies can be found in serum and in CSF.
41. Subacute sclerosing panencephalitis (SSPE)	Chronic CNS infection by measles virus, most common in childhood but rarely in young adults.	Progressing or relapsing neurologic deficits in a young patient, occasionally with MRI signal abnormalities and with oligoclonal bands in the CSF (which are directed against measles antigens).	Dementia and behavioral changes are usually prominent. The course is rapidly progressive over weeks or months. CSF PCR is available. Brain biopsy is definitive but rarely needed. EEG also shows characteristic paroxysmal pattern.
42. Human herpes virus-6 (HHV-6)	Reactivation of ubiquitous herpes infection, which is latent in the CNS.	May cause myelopathy or other focal neurologic findings in a young person. MRI can show signal abnormalities.	Positive serologic testing is available for HHV-6. The etiologic relationship of HHV-6 to MS is currently the subject of intensive research.
43. Hepatitis C	The hepatitis C virus has occasionally been reported to cause peripheral and rarely central nervous system damage.	Optic neuropathy and other CNS findings may occur in a young person. MRI may show signal abnormalities.	Usually occurs in the setting of active liver disease (often after IV drug abuse or blood transfusions) and serum antibodies and PCR are available.
44. Mycoplasma	An atypical pneumonia infection occasionally complicated by CNS deficits.	Can cause transverse myelitis, cranial neuropathies, and other neurologic abnormalities accompanied by signal changes on MRI.	Usually occurs in the setting of systemic infections, including pneumonia, fever, and malaise. CSF may have pleocytosis but no IgG abnormalities. Specific antibody testing can be done in the serum.
45. Central pontine myelinolysis (CPM)	Demyelination of the pons (and sometimes other areas), usually occurring in the setting of alcoholism or other severe illness, and especially after rapid correction of hyponatremia.	Can cause brainstem symptoms and/or quadriceps, with demyelination seen on MRI scan.	Usually occurs in the setting of severe illness, including hyponatremia. It has a monophasic course. CSF will be normal.

TABLE 7. Continued

Disease	What It Is	How It Mimics MS	How to Tell It From MS
46. Hashimoto encephalopathy	Subacute sometimes-relapsing encephalopathy associated with autoimmune thyroid disease.	May cause strokelike episodes and focal neurologic problems in a young person. Rare white-matter changes have been seen on MRI and rare reports of oligoclonal bands in the CSF.	Encephalopathy with confusion and myoclonus is usually prominent. EEG is diffusely abnormal. Serology will show antithyroglobulin and antimicrosomal antibodies.
47. Vitamin B12 deficiency	CNS damage due to deficiency of vitamin B12, commonly caused by pernicious anemia.	May cause CNS deficits, especially a progressive myelopathy, rarely with MRI signal abnormalities.	CBC is often abnormal and serum B12 levels are low. Methylmalonic acid and homocysteine are often abnormal.
48. Folate deficiency	Deficiency of folate, which may cause CNS abnormalities.	Can cause diplopia, myelopathy, and other CNS deficits, occasionally with signal changes on MRI.	Low blood folate levels, as well as abnormal methylmalonic acid homocysteine.
49. Celiac disease (gluten sensitivity or sprue)	An immune disease with many autoantibodies, including an immune response to ingested gluten, as well as antigliadin, antiendomysial, and antitransglutaminase antibodies, often causing small-bowel malabsorption, as well as occasional relapsing neurologic deficits.	Ataxia and brainstem signs are common, as are periventricular white-matter lesions on MRI.	Antibody testing is now available for antigliadin antibodies. More than 90% or patients are HLA-DQ2. Spinal fluid is normal.
50. Amyotrophic lateral sclerosis (ALS)	Acquired upper and lower motor neuron disease causing progressive motor deficits.	Can especially resemble primary progressive MS, with a progressive myelopathy.	MRI and CSF will be normal. EMG will show peripheral nervous system abnormalities of denervation.
51. Primary lateral sclerosis	Progressive upper motor neuron degenerative disease causing upper motor neuron (bulbar and spinal) deficits.	Especially resembles primary progressive MS, with a chronic progressive myelopathy.	VER, MRI, and CSF should be normal.
52. Adrenoleukodystrophy and adrenomyeloneuropathy	An X-linked genetic defect of a transporter protein, causing peroxisome dysfunction and an excess of very-long-chain fatty acids.	Adult forms commonly cause progressive paraparesis and ataxia, usually with confluent posterior white-matter changes on MRI. Female carriers may present with mild disease also.	Serum testing will show high levels of very-long-chain fatty acids. The ACTH stimulation test usually shows impaired adrenal function.
53. Metachromatic leukodystrophy	An autosomal recessive deficiency of arylsulfatase A.	May cause myelopathy and ataxia, with symmetric diffuse signal abnormalities on MRI.	Blood arylsulfatase A levels are low. Abnormal metabolism can be confirmed by study of cultured fibroblasts obtained by biopsy. DNA testing is now available.
54. Krabbe globoid cell leukodystrophy	Autosomal recessive deficiency of galactocerebroside β-galactosidase generally seen in infancy but rarely in young adults.	May cause paraparesis and visual symptoms in young patients, with confluent periventricular MRI signal abnormalities.	Patients have accompanying neuropathy, easily detected on nerve conduction testing. DNA testing is now available.
55. Fabry disease	An X-linked deficiency of the lysosomal enzyme α-galactosidase causing accumulation of ceramide trihexosidase in endothelium and smooth muscle cells. It is often of adult onset and can cause renal disease and angiokeratomas on the skin.	It causes recurrent strokes and thus focal neurologic findings in a young person with MRI signal abnormalities.	Patients may have skin lesions, corneal opacities, and renal disease. CSF will be normal. DNA testing and blood α-galactosidase levels are available.
56. Adult-onset autosomal dominant leukodystrophy	An autosomal-dominant leukodystrophy presenting in adulthood, causing motor and cerebellar deficits, usually with prominent autonomic dysfunction. The genetic defect is unknown.	Especially resembles primary progressive MS, with chronic upper motor neuron and cerebellar deficits accompanied by confluent white-matter lesions on MRI and occasionally IgG abnormalities in the CSF.	Family history with autosomal-dominant inheritance. Automatic involvement is also prominent early.
57. Organic acidemias	Autosomal-recessive diseases usually seen in childhood but occasionally in adults.	May cause spasticity, ataxia, and optic atrophy in young adults.	MRI is usually normal, as is CSF. May have a positive family history. Urinary organic acid screening will be abnormal.
58. Spinocerebellar ataxias	Nearly 2 dozen diseases have been described with autosomal dominant progressive ataxia and gait disturbances, some due to triplet repeats.	Progressive myelopathy and cerebellar deficits in a young person. Rarely, T2 lesions have been described on MRI.	Strong family history. CSF will be normal. DNA testing is commercially available for many of these syndromes.

TABLE 7. Continued

Disease	What It Is	How It Mimics MS	How to Tell It From MS
59. Friedreich ataxia	Autosomal recessive GAA triplet expansion of the gene coding for frataxin, with onset usually in the early teens, causing progressive ataxia and dorsal column sensory loss.	Progressive ataxia and sensory loss in a young person.	MRI and CSF usually normal. Peripheral neuropathy also present in Friedreich ataxia. DNA testing is now available.
60. Olivopontocerebellar atrophy (OPCA)	Autosomal-dominant mutation in the SCA-1 gene causing adult-onset progressive cerebellar and brainstem deficits.	Ophthalmoplegia, pyramidal deficits, optic atrophy, and ataxia may all appear in a young person. Rare reports of abnormal MRI scans.	Positive family history. CSF will be normal. Sometimes peripheral neuropathy is also present. DNA testing for SCA-1 is now available.
61. Mitochondrial cytopathies (MELAS, MERFF)	Maternally transmitted mitochondrial DNA abnormalities seen in children and young adults, which can cause optic atrophy, paraplegia, ataxia, seizures, and dementia.	Multiple and recurrent focal neurologic deficits, with signal abnormalities on MRI in a young person.	Lactic acidosis usually present. Muscle biopsy shows ragged red fibers. Specific genetic testing now available.
62. Neuropathy, ataxia, retinitis pigmentosa (NARP)	Mutations in the mitochondrial gene for ATPase-6 causing retinitis pigmentosa with other neurologic features, including sensory neuropathy, ataxia, and pyramidal signs.	Prominent visual and motor symptoms in a young person, with MRI signal abnormalities.	Patients have retinitis pigmentosa as a prominent feature. A sensory peripheral neuropathy is also present. Genetic testing for the abnormal mitochondrial gene is now commercially available.
63. Mitochondrial neurogastrointestinal encephalopathy (MNGIE)	Mitochondrial genetic abnormality causing GI malabsorption, as well as multiple neurologic symptoms.	May cause ophthalmoplegia and leukoencephalopathy, with white-matter abnormalities on MRI.	Prominent GI involvement. Patients often have ptosis and peripheral neuropathy, and muscle biopsy will show abnormal mitochondria.
64. Leber hereditary optic neuropathy	Mitochondrial mutation (many of which have been described) causing subacute bilateral optic neuropathy, often with other neurologic features.	Bilateral optic neuropathy, occasionally with myelopathy, ataxia, and other neurologic features, sometimes accompanied by abnormal MRI signal changes.	CSF will be normal. Mitochondrial genetic testing now commercially available.
65. Leigh syndrome	Genetically heterogeneous but usually autosomal recessive disease leading to interference with the pyruvate dehydrogenase system, causing elevated lactate and pyruvate, usually in childhood.	Can occur later in life and cause an acute necrotizing encephalomyelopathy. MRI scan usually shows brainstem and basal ganglion necrosis.	Usually a childhood disease. Plasma lactate and pyruvate will be elevated. Genetic testing not yet reliable.
66. Usher syndrome	Congenital syndrome of retinitis pigmentosa, with hearing loss, sometimes with cognitive deficits, and/or ataxia.	Neurologic symptoms with an MRI scan that can have white-matter abnormalities and CSF that can show oligoclonal bands.	Retinitis pigmentosa and deafness are prominent features.
67. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	Autosomal-dominant mutation in the notch-3 gene, causing a microangiography especially prominent in subcortical white matter, often associated with migraines and progressive dementia.	Multifocal neurologic symptoms in a young person with abnormal MRI scan.	Genetic testing is commercially available. Family history of neurologic problems usually present. Often associated with migraines. CSF usually normal.
68. Cerebroretinal vasculopathy	Autosomal dominant microangiopathy of brain and retina. A rare condition usually presenting in the 20s.	Can have gait disturbance, dysarthria, and visual abnormalities, with periventricular lesions on MRI scan.	Retinal changes are prominent, including abnormal fluorescein angiography. Rare condition with a strong family history.
69. Hereditary endotheliopathy, retinopathy, nephropathy, and stroke (HERNS)	An autosomal-dominant condition seen primarily in Chinese patients, causing leukoencephalopathy with renal dysfunction.	Dysarthria, hemiparesis, and other neurologic signs in young patients, with periventricular and white-matter lesions on MRI.	Very rare condition, described so far only in the Chinese. Strong family history. Dementia is usually prominent.
70. Wilson disease	Autosomal-recessive mutation in the ATP-7B gene, causing copper deposition in tissues, including brain and liver, usually presenting in young people.	Neurologic deficits, including ataxia and tremor in a young person. Rare reports of abnormal MRI scans.	Movement disorder and dementia are prominent. Liver functions may be abnormal, slit lamp shows Kayser-Fleischer rings, and serum copper is elevated. Liver biopsy is rarely required.
71. Adult polyglucosan body disease	Autosomal recessive mutations in glycogen branching enzyme genes, causing gait disturbance, sensory symptoms, and dementia.	Progressive neurologic symptoms in a young person, with extensive leukoencephalopathy on MRI scan.	Peripheral nerves also involved and are prominent. Biopsy will show accumulation of polyglucosan bodies.

TABLE 7. Continued

Disease	What It Is	How It Mimics MS	How to Tell It From MS
72. Hereditary spastic paraparesis	Genetic (usually autosomal dominant) syndrome of progressive spastic paraparesis, occasionally with other neurologic findings as well. Over 10 different genetic variants have been identified but most common in the spastin gene.	Easily confused with primary progressive MS because of its steady progressive spastic paraparesis, sometimes with optic nerve or peripheral nerve involvement.	MRI and CSF are usually normal. Genetic testing not yet reliable.
73. Porphyria	Usually autosomal-dominant disorder of heme biosynthesis, which can cause neurologic symptoms, including numbness and cranial neuropathies.	Can cause focal neurologic symptoms which relapse and remit, and the MRI scan is sometimes abnormal.	Psychiatric and behavioral symptoms are usually prominent. Abdominal symptoms also often present; 24-h urine will show elevations in ALA and PBG.
74. Vitamin E deficiency	Deficiency of vitamin E often caused by an autosomal-recessive defect in the TTPA gene, leading to spinocerebellar degeneration, often with retinitis pigmentosa and other changes as well.	Progressive neurologic symptoms, especially ataxia, in a young person, rarely with abnormal MRI scans reported as well.	Retinal pigmentation often present. Serum vitamin E levels will be decreased.
75. Abetalipoproteinemia	Autosomal-recessive defect causing absence of β lipoproteins, leading to multiple systemic symptoms, including neurologic deficits.	Progressive ataxia and ophthalmoplegia are prominent.	Often has systemic symptoms, including GI malabsorption and retinitis pigmentosa. Cholesterol and triglycerides are very low and acanthocytes are present on blood smear. MRI and CSF are normal.
76. CNS lymphoma	Lymphoma of the central nervous system, usually in immunocompromised patients.	Focal neurologic deficits with multifocal enhancing MRI lesions.	CSF does not have IgG abnormalities but will often show positive cytology. Lesions are highly steroid responsive. Brain biopsy may be necessary.
77. Intravascular lymphoma (malignant angioendotheliomatosis)	A rare intravascular lymphoma that can prominently involve the nervous system.	The vasculopathy causes multiple infarcts and focal lesions with white-matter changes on MRI scan.	Usually seen in elderly individuals, with a progressive course. Dementia is prominent. Sed rate is usually high. CSF does not have IgG abnormalities. Biopsy of skin or brain may be necessary.
78. Paraneoplastic syndromes	Indirect involvement of the central nervous system by antibodies produced in systemic cancers.	Symptoms of ophthalmoplegia and ataxia may occur abruptly, and oligoclonal bands are often present.	MRI is usually normal. Symptoms may be abrupt but are generally progressive. Antibodies can be measured in the serum (such as anti-Yo or anti-Hu).
79. Leukoencephalopathy after chemotherapy or radiation therapy	Leukoencephalopathy caused by toxic effects of chemotherapy or radiation therapy for systemic cancers.	Focal neurologic signs may be present, and the MRI shows extensive white-matter changes.	History of cancer and exposure to radiation or chemotherapy.
80. Glioblastoma	Primary malignancy of the central nervous system, often multifocal and often occurring in young people.	Focal neurologic deficits in a young person, with an abnormal MRI scan.	MRI usually shows surrounding edema and mass effect unusual for MS. CSF would be normal. Brain biopsy may be necessary.
81. Spinal tumor	Usually astrocytoma or ependymoma in the intramedullary spinal cord.	Progressive myelopathy in a young person, with abnormal signal in the spinal cord that can resemble demyelination.	Absence of lesions outside the spinal cord. VERs and CSF will be normal.
82. Somatization disorder	Psychiatric disorder characterized by a chronic pattern of physical expression of psychological distress.	Patients, who are often young, have multiple recurring and relapsing neurologic symptoms, which can include weakness, numbness, dizziness, and similar complaints.	MRI, CSF, evoked potentials, and neurologic examination will be normal. Difficulties arise when testing shows "nonspecific" changes. Many nonneurologic symptoms usually present.
83. Conversion disorder	Acute onset of motor or sensory loss unexplained by physical findings, not intentionally produced.	Patients may present with neurologic symptoms very similar to those seen in MS.	MRI, CSF, evoked potentials, and neurologic examination will be normal. Difficulties arise when testing shows "nonspecific" changes. Many nonneurologic symptoms usually present.
84. Hypochondriasis	Preoccupation with fears of having a serious disease.	Patients may present with neurologic symptoms very similar to those seen in MS.	MRI, CSF, evoked potentials, and neurologic examination will be normal. Difficulties arise when testing shows "nonspecific" changes. Many nonneurologic symptoms usually present.

TABLE 7. Continued

Disease	What It Is	How It Mimics MS	How to Tell It From MS
85. Other: psychiatric syndromes	Psychiatric disorders that often produce somatic symptoms.	Fatigue and other neurologic symptoms that can persist or relapse in a young person.	Other evidence of depression, anxiety, or psychiatric issues is often evident. MRI, CSF and other tests will be normal.
86. Spondylosis	Spinal cord compression due to cervical spondylosis and disc disease, resulting in a progressive myelopathy.	Easily mistaken for primary progressive MS, with a progressive cervical myelopathy. In an elderly patient, there are often nonspecific brain MRI signal changes.	MRI of the cervical spine will usually show cord compression. CSF and VERs should be normal.
87. Chiari malformation	Descent of the cerebellar tonsils below the foramen magnum, causing brainstem and spinal cord compression.	May cause cranial neuropathies, including ophthalmoplegia, nystagmus, and ataxia.	MRI scanning, especially on sagittal images, will detect the malformation. MRI of the brain is otherwise normal, as is CSF.
88. Syringomyelia	Malformation of the spinal cord, with enlarged central cavity producing progressive myelopathic symptoms.	Causes a progressive myelopathy in young patients, occasionally involving lower cranial nerves as well.	MRI scan will detect the syrinx. MRI of the brain is usually otherwise normal, as is CSF and VERs.
89. Spinal vascular malformation	Dural arteriovenous fistulas or intramedullary AVMs that often cause a progressive (and sometimes episodic) myelopathy.	Relapsing or progressive spinal cord symptoms, often in a young person. MRI of the spinal cord can show intrinsic signal abnormalities easily mistaken for MS.	MRI of the brain will be normal, as will CSF and VERs. No lesions outside of the spinal cord.
90. Arachnoiditis	Chronic inflammation of the arachnoid surrounding the spinal cord and roots, often seen following spinal surgery or use of intrathecal contrast or medications.	May cause a myelopathy or focal (radicular) neurologic deficits.	MRI scan usually shows enhancement from the inflammation. MRI of the brain will be normal. CSF may show inflammation but no IgG abnormalities, and VERs will be normal.
91. Foramen magnum and clivus lesions	Some tumors such as dermoid, teratoma, or meningioma can occur at the base of the skull in this central location and cause primarily cranial nerve and upper brainstem symptoms.	Progressive cranial nerve and brainstem symptoms, often in a young person.	MRI scanning will show the mass at the base of the skull.
92. Cranial nerve palsies: Bell palsy, abducens palsy, etc.	Isolated cranial neuropathy, often idiopathic, which can occur in young people.	Occasionally, MS can present as an isolated facial weakness, numbness, or diplopia.	No other neurologic signs or symptoms are present, and MRI and CSF should otherwise be normal.
93. Drugs	Multiple drugs are capable of affecting the nervous system, either as drugs of abuse (toluene, alcohol, cocaine) or as therapeutic agents (cyclosporine, phenytoin, etc).	A variety of neurologic signs and symptoms may appear as manifestations of drug toxicity. Many drugs also produce white-matter changes on the MRI scan.	Unfortunately, a history of drug exposure is often difficult to obtain. Symptoms are usually not relapsing and remitting unless the drug exposure continues. CSF should be normal.
94. Environmental toxins	Many toxins can cause neurologic damage, including carbon monoxide, heavy metals, and organic solvents.	Neurologic abnormalities often are accompanied by white-matter changes on the MRI scan.	Exposure to toxins is usually apparent. Symptoms will not be progressive or relapsing if exposure has ceased. CSF should be normal.
95. Periventricular leukomalacia	Periventricular white-matter necrosis occurring in neonates, but often not symptomatic until adulthood.	May be associated with a variety of neurologic symptoms, and the MRI will show periventricular white matter lesions.	Symptoms are usually not relapsing or remitting. CSF should be normal.
96. Migratory sensory neuritis	Controversial entity of "sensory neuritis" causing patchy relapsing areas of numbness and paresthesias, presumably due to peripheral nerve dysfunction.	Multifocal relapsing sensory symptoms, often in a young person.	Deficits are purely subjective (sensory) with no motor or other findings. MRI and CSF will be normal.
97. Chronic fatigue syndrome and fibromyalgia	Syndrome of chronic diffuse muscular pain and chronic fatigue, often with other somatic symptoms as well.	May report many neurologic symptoms that can mimic MS in a similar population (young women).	Neurological examination is objectively normal. Difficulties arise when the MRI shows "nonspecific" abnormalities, but MRI, CSF and VERs should be normal.
98. Myasthenia gravis	Autoimmune disorder producing antibodies against the acetylcholine receptor post synaptically on the muscle.	Can cause fluctuating weakness and diplopia, especially in young women.	Deficits are confined to weakness and fatigability in the motor system. MRI, CSF and VER will be normal.

TABLE 7. Continued

Disease	What It Is	How It Mimics MS	How to Tell It From MS
99. Progressive necrotic myelopathy	A stepwise myelopathy of unknown etiology, often causing hemorrhage and necrosis of the spinal cord.	Relapsing and progressive myelopathic symptoms, with MRI showing signal abnormalities in the spinal cord that can be mistaken for MS.	Lesions confined to the spinal cord; MRI of the brain will be normal. CSF does not show IgG abnormalities.
100. Normal	Studies have shown that normal people commonly report transient double vision, paresthesias, focal weakness, and other neurologic symptoms.	Perfectly normal people occasionally report that they experience focal, sometimes relapsing, neurologic symptoms identical to those that can be seen in MS.	Physical examination and laboratory tests will all be within normal limits.

This table is modified and derived in large part from similar information contained in: Flemming JO. *Diagnosis and Management of Multiple Sclerosis*. New York: Professional Communications Incorporated; 2002.

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