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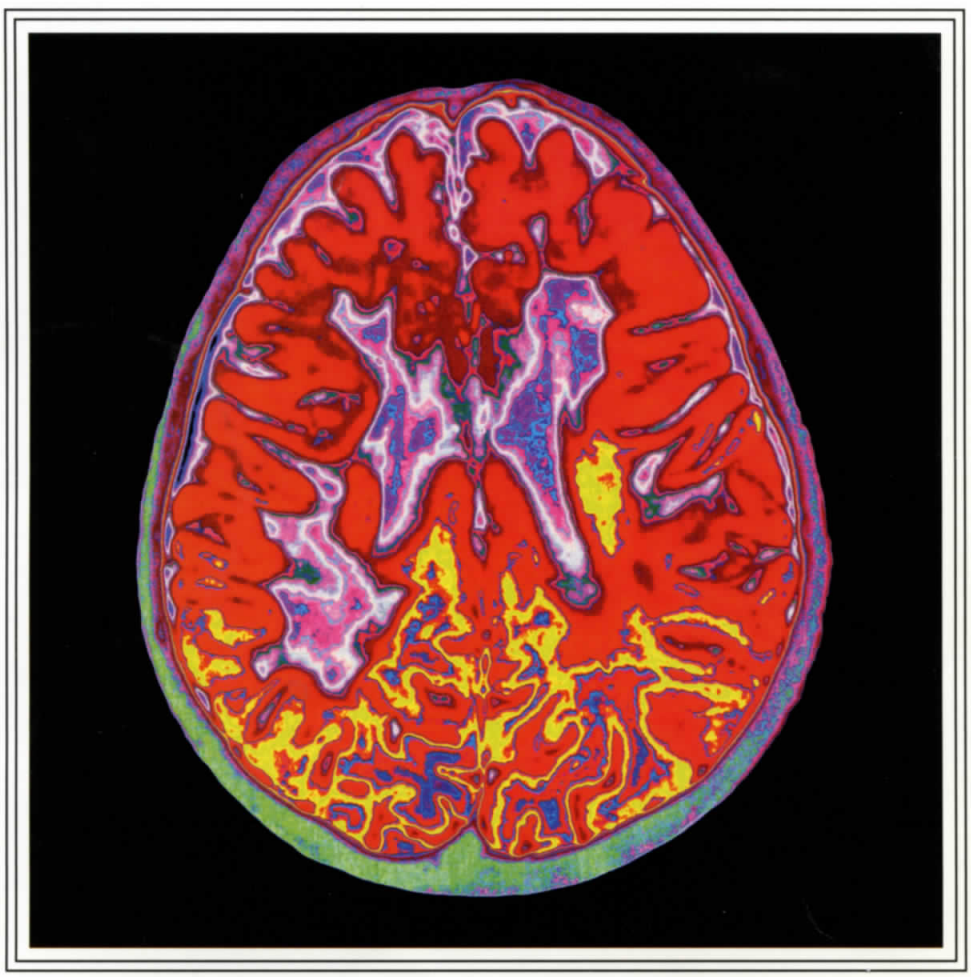

Multiple Sclerosis

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Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system that usually first affects people in their 20s or 30s. MS is one of the most common causes of nontraumatic disability among young and middle-aged individuals. Because symptoms of MS are extremely variable and often quite subtle, the use of magnetic resonance (MR) imaging plays a crucial role in diagnosis and management. Early diagnosis and treatment can slow the progression and limit the impact of this potentially devastating disease.

This article is a Directed Reading.

After completing this article, readers should be able to:

- *Understand the relationship between the demographics, epidemiology and immunopathology of multiple sclerosis (MS).*
- *Describe the 4 distinct immunopathologic subgroups of MS.*
- *Know the 4 categories of MS based on clinical characteristics.*
- *Know the types of imaging used in the diagnosis and ongoing monitoring of MS.*
- *Recognize the presentation of plaques or lesions on images.*

A simple 14th century woodcut of a fallen ice skater being helped to her feet[1] is likely the first image of multiple sclerosis (MS), an enigmatic disease that continues to bewilder physicians and scientists.[2] The woodcut depicts a Dutch teenager, Lidwina, who soon after a fall ice skating, developed a mysterious debilitating disease characterized by recurring and remitting pain, paralysis, headaches, drooping facial muscles, bladder and bowel and vision problems that continued until her death at age 53. A priest carefully documented Lidwina's condition and her unusual response to it: an unwavering belief that her pain and suffering were actually joy and a sign that she was called to be a victim for the sins of others. Ludwina's periodic remissions of symptoms were attributed to acts of God.[3]

Medaer[4] described the priest's documentation: "These could be the oldest known documents, describing a case of multiple sclerosis. A number of documents written before or shortly after the death of St. Lidwina of Schiedam (1380-1433) surprised us by their very accurate description of symptoms which for the most part correspond to the clinical criteria prevailing nowadays for the diagnosis of multiple sclerosis." Lidwina was canonized by Pope Leo XIII in 1890 and is regarded as the patron saint of ice skaters.[5]

The next known description of MS did not appear until the 19th century when Sir Augustus d'Esté, the illegitimate grandson of King George III of England, began a diary in 1822 that spanned 26 years. In his diary he described an increasingly debilitating illness that began soon after a bout of measles, characterized by visual impairment, fatigue and unpleasant sensations.[3]

During that same time period, pathologist Robert Carswell documented strange lesions in the spinal cord of an unidentified subject during a postmortem examination. He included a painted illustration of the then-unknown lesions in his *Atlas of Pathology*, published in 1838.[1] Unaware of Carswell's work, Parisian anatomist Jean Cruveilhier not only described and illustrated the pathology of MS-type lesions in 1842, but he also recorded the clinical history of a patient who, over several years, developed weakness in both legs and arms, spasms, difficulty in swallowing

and visual disturbances.[1] Later in the 19th century, other pathologists, including Friedrich von Frerichs, Carl Rokitansky and Eduard Rindfleisch, contributed additional observations to the growing body of knowledge of a mysterious illness that still had no name.[1]

In 1868, Jean-Martin Charcot, professor of neurology at the University of Paris, wrote the first complete description of MS and associated changes in the brain.[3] Charcot, often called "the father of neurology,"[6] developed the first clinical description of MS, making definite links between symptoms and the pathological changes seen in postmortem samples of the disease he named *sclérose en plaques*. Charcot developed the first complete histological account of MS lesions, describing the loss of myelin (a phospholipid that insulates neurons from one another) and proliferation of glial fibers and nuclei. Charcot's observations of his own housekeeper were the basis of a diagnostic criteria still used today called Charcot's triad, which includes diplopia (double vision), ataxia (disturbances of balance or co-ordination) and dysarthria (difficulties with, or slurred speech).[4]

By the turn of the 20th century, the prevailing theory for the etiology of MS was an inborn error in myelin metabolism.[4] In 1916, with new microscopy techniques and chemicals to enhance the visibility of nerve cells under the microscope, James Dawson of the University of Edinburgh performed detailed microscopic examinations of the brains of dead MS patients. Dawson's descriptions of the inflammation around blood vessels and the damage to the myelin were written with such clarity and thoroughness that they stand to this day. However, because so little was known about the brain's function in 1916, the actual meaning of these changes could only be speculated.[6]

In the 1920s, MS was thought to be more prevalent in men. Women with MS symptoms were diagnosed with "hysteria" because the transient symptoms of MS are frequently exacerbated by the menstrual cycle.[7]

One of the most significant MS discoveries occurred in 1935, but it would be decades before MS researchers realized its importance. An MS-like illness was created in laboratory animals by Thomas Rivers at the Rockefeller Institute in New York City. Rivers, who sought to demonstrate that nerve tissue, not viruses, produced the symptoms of MS, injected myelin he knew to be virus-free into animals. This induced their immune systems to attack their own myelin, producing an autoimmune reaction called experimental allergic encephalomyelitis (EAE), which is very similar to MS. EAE would become one of the most important models for studying the immunology and theories of autoimmunity of MS. Unfortunately, Rivers' work and the importance of EAE to MS research was virtually ignored because the favored theories of the time speculated that toxins or blood circulation problems were the cause of MS.[6]

Major advances in MS research did not occur again until the 1980s, due to the refinement of magnetic resonance (MR) imaging as a tool for both diagnosis and disease management.[1]

Demographics

MS symptoms usually manifest between the ages of 20 and 40. However, actual diagnosis often is delayed due the transitory nature of the disease and the lack of a specific diagnostic test. MS symptoms rarely appear before age 15 or after age 60. Whites are more than twice as likely to develop MS, and women are affected at almost twice the rate of men. Among those who develop symptoms at a later age, the gender ratio is more balanced.

Epidemiology

MS is 5 times more prevalent in the temperate climates of the northern United States, Canada and Europe than in tropical regions. In addition, the age of 15 seems to be significant in terms of risk for developing the disease. A person moving from a high-risk, temperate climate to a low-risk tropical area before the age of 15 adopts the risk factor of the tropical climate. Those moving from a tropical climate to a temperate climate before age 15 increase their risk of MS. Those who move after age 15 maintain the risk of the area where they grew up.[8]

The incidence of MS increases with latitude northward or southward from the equator with essentially no risk at the equator to more than 50 cases per 1 million at latitudes of at least 45° north or south latitude. One explanation posited for this latitudinal discrepancy is exposure to ultraviolet radiation and the positive effect of vitamin D on the immune system. In Australia, MS is 4 times more likely to occur between Brisbane at 28° south latitude and Hobart at 43° south latitude. This corresponds to a 4.9-fold decrease in daily ultraviolet radiation. At high latitudes, the risk of MS may be moderated by factors that improve the biosynthesis or dietary availability of vitamin D. In Switzerland, risk is reported to vary inversely with altitude (and presumably with ultraviolet radiation). In Norway, risk varies inversely with consumption of oil-rich fish high in vitamin D, since MS is rarest along the Norwegian coast.[9]

However, geographic or climatic risk may actually be a matter of genetic predilection and reflect racial and ethnic susceptibility factors. For instance, European gypsies, Eskimos and African Bantu do not develop MS, while indigenous people of North and South America, Japanese and other Asian groups have a low incidence.[10]

Further complicating latitudinal risk factors is a birth month risk factor in countries in the northern hemisphere. A pooled analysis of data sets from Canada, Great Britain, Denmark and Sweden showed that significantly fewer (8.5%) people with MS were born in November and significantly more (9.1%) were born in May. The effect of birth month was most evident in Scotland, the country with highest rate of MS. Researchers concluded that the month of birth, coupled with familial history, are risk factors for MS.[11]

The birth month risk may be a function of sunlight and vitamin D synthesis because biologically active vitamin D is generated in the skin with exposure to ultraviolet radiation. Vitamin D treatment reduces both the severity of symptoms and disease progression in EAE, the animal model of MS.[6] This suggests the increased risk of MS related to birth month may be a function of seasonal deficiency in maternal concentrations of vitamin D at the end of the second or the third trimester – a crucial time for the potentially protective effects of vitamin D.[11]

MS also occurs in geographic cluster outbreaks, an uneven geographic distribution of MS within ethnically homogeneous populations. More than 61 prevalence clusters of MS have been reported in the English language medical literature subsequent to 1966.[12] The most notable MS cluster was actually 4 separate clusters of outbreaks that occurred between 1943 and 1989 in the Faroe Islands, located between Iceland and Scandinavia. These cluster outbreaks began in the years following the arrival of British troops during World War II. Kurtzke performed an extensive retrospective epidemiologic study of this cluster and concluded, "clinical MS is the rare late outcome of a specific but unknown infectious disease of adolescence and young adulthood and that this infection could well be caused by a thus-far-unidentified (retro)virus."[13]

Several MS clusters in the United States have received extensive scrutiny:

- Galion, Ohio, where dirt removed from a cemetery and distributed to various residents was the only common element.
- DePue, Ilinois, where residents were exposed to trace metals in water and soil from an abandoned zinc smelter plant.
- Rochester, NY, where zinc was the suspected environmental factor.
- El Paso, Texas, where a metal smelter had contaminated air and soil with high levels of metals, such as lead, arsenic, zinc and cadmium.

Of these 4 MS clusters, researchers concluded that exposure to zinc or other trace metals may have been a factor in the DePue, Illinois cluster, although they had no direct evidence that zinc or any other metal is, in fact, related to MS.[14]

Pathogenesis and Etiology

The etiology, pathogenesis and epidemiology of MS are closely intertwined and are the subject of wide-ranging debate in MS research. Currently, the leading hypothesis in this debate is that MS occurs in genetically susceptible individuals who are exposed to an environmental assault, in the form of a virus[15] or toxin. The virus or toxin disrupts the blood-brain barrier, resulting in a convergence of immune factors in nerve cells that trigger inflammation and an autoimmune attack on myelin.

Because some viruses are strikingly similar to the myelin protein, an immune response may cause the T-cells to attack the body's own protein rather than the viral antigen. In addition, more than 1 antigen may be involved; some may trigger the disease and others may continue to stimulate the process.[16] Eventually, the immune system's attack on these proteins strips the protective coating of myelin and forms plaques or lesions throughout the central nervous system (CNS), including the white matter, optic nerve, brainstem, spinal cord and cerebellum.[15]

The theory that MS is related to a virus or viruses with a long dormancy period is supported by 3 factors: environment, viral presence and reproducibility in animal models.[17]

Environment

The relationship between a higher incidence of MS and the distance from the equator during the first 15 years of life[8] suggests childhood exposure to a virus followed by a long dormant period. In addition, ethnic or racial immunities occur in higher risk areas.[10] The wealthiest countries with the best hygiene have the highest incidence of MS, while poor countries with less sanitary conditions have the lowest percentage of cases. This paradox suggests that early exposure to a virus or bacteria not present in more sanitary environs may stimulate immunity to MS.[17]

Viral Presence

Abnormal levels of viral antibodies as well as viral particles and other signs of viral infection are consistently found in people with MS. A specific virus directly associated with MS has not been identified; however, studies conducted over the past 50 years have revealed more than 10 types of antibodies in the cerebrospinal fluid of MS patients. Most people with MS have at least 1 type of viral antibody.[17]

Herpes virus HHV-6 is a form of herpes virus that causes roseola, a mild viral illness usually affecting babies and young children; roseola causes several days of fever, followed by a rash.[18] Herpes virus HHV-6 is also known to cause encephalitis in patients with impaired immune systems. One study found cells infected with HHV-6 in CNS tissue of 73% of people with MS, and 90% of the tissue sections showed active demyelination. Compared to tissue sections without active disease, only 13% were infected with the virus. In CNS tissue from 28 individuals without MS, only 2 were HHV-6 infected.

Active HHV-6 infections also were found in blood samples from 54% of MS test subjects. None of the blood samples from the 61 healthy controls tested positive.

In comparing those with MS who had active HHV-6 infections in their blood to those who did not, no difference was found in terms of disease types. Those testing positive, however, were much younger and had MS for a shorter time vs those with MS who tested negative, possibly indicating a change in the pathology of MS over time. Despite these apparent associations, a causative link between MS and HHV-6 has yet to be established.[17]

Other herpes viruses also can infect brain cells including herpes simplex 1 and 2 (the causes of oral and genital herpes), varicella-zoster virus (the cause of chicken pox and shingles) and cytomegalovirus.[17]

Nearly all people with MS have some evidence of Epstein-Barr virus (an EBV infection), the cause of mononucleosis. EBV, however, is also very common in people who never develop mono. Indeed, EBV may infect up to 95% of U.S. adults by the age of 40. One study demonstrated that 99% of MS patients had evidence of EBV; however, so did 93% of people without MS. EBV is linked to other illnesses, including cancers and disorders affecting the nerves.[17]

Harvard University Nurses Health Studies found that women with high levels of EBV antibodies "offer evidence that Epstein-Barr virus infection may increase the risk of multiple sclerosis."[19] The authors did qualify that statement, noting that "because few individuals infected with EBV develop multiple sclerosis, other cofactors are required."[19] Still, other research has shown that people without EBV antibodies are rarely diagnosed with MS.[17]

Intriguing research on viruses as a causal effect of MS sometimes takes bizarre twists down a promising path that only leads to a dead end. Such was the interesting correlation between a dramatic rise in canine distemper virus (CDV) among dog populations in Iceland and on islands near Great Britain and a similar rise in MS cases 10 years later.

CDV was associated with the environmental and latitudinal risk factors linked to MS: CDV thrives in cold, damp weather and, in such conditions, people and dogs are more likely to be indoors and in close contact. CDV is rapidly inactivated in warm weather, indicating a possible correlation with the absence of MS near the equator. However, extensive studies failed to show a definitive association between CDV and MS.[17]

Reproducibility in Animal Models

Relapsing-remitting (a clinical MS classification) and demyelinating diseases can be induced in animals infected with EAE or Theiler's murine encephalomyelitis virus, both of which provide MS researchers insight into the cellular processes that occur in MS.[17]

Although the viral-trigger hypothesis predominates, other infectious agents and toxins are still being studied. For instance *Chlamydia pneumoniae*, an atypical bacterium, is associated with persistent inflammation in small vessels. Several studies have reported significantly higher rates of a previous *Chlamydia* infection in MS patients than in individuals without MS, while other studies reported no connection at all between *Chlamydia* and MS. It is still possible that the infection, which can cause widespread inflammation, plays a role early in the course of the disease in some individuals.[16]

The Genetic Factor

MS is not a hereditary disease. That is, 50% of the children of a person diagnosed with MS will not develop MS.[17] However, MS does cluster in some families, increasing the risk for people who have close family members with the disease. Those affected with MS have a 10% to 20% chance of having 1 or more affected relatives, a much higher risk for a disease that has no genetic component.[20] However, MS occurs in only 25% to 30% of monozygotic twin pairs.[21] In addition, MS is significantly more common in those of white northern European ancestry, even when controlling for geographic risk factors.[8,20]

Evidence of a genetic link is indicated in studies showing a common age of onset in families with more than 1 affected member, ruling out a common environmental event such as a virus epidemic causing all the MS in a family.[22]

Current research indicates that MS is not a disease that results solely from the inheritance of a single defective gene, but rather requires multiple causal factors as well as several different configurations of genes.[20] While future research may identify a Mendelian MS gene,[23] all the genes that have thus far been associated with MS are also common in the general population. One gene common in white populations, HLA-DR (DRB1*1501), has been repeatedly associated with MS, but not everyone with the disease has this gene.[20]

Further complicating the genetic aspect of MS are the genetic changes that can occur after conception, such as the postgenomic changes that can happen when retroviruses insert their DNA into the DNA of infected cells.[20]

Immunopathology

MS inflammation appears to be caused by an overactive proinflammatory T(H)1 profile in T cells.[24] However, T cells and the associated inflammatory molecules they secrete are not the sole cause of the inflammation process. T-cell activation apparently creates a cascade of immune system responses that also contribute to demyelination and axon loss. The precise order of events of this cascade, the antigens targeted by T-cells and the contributions of B lymphocytes and other cells of the immune system are unknown.[25]

Recent research suggests there are 4 distinct immunopathologic MS subgroups based on distinct patterns of plaques. The plaque patterns display specific features of myelin protein loss, geography, patterns of oligodendrocyte (myelin-producing glial cells that make up CNS tissue) destruction and deposition of antibody and complement.

- Pattern I. Macrophage and T-cell–mediated demyelinating process with marked activation of macrophages and microglia. Oligodendrocyte numbers relatively preserved. Spontaneous CNS repair and remyelination.
- Pattern II. Very similar to Pattern I, with a critical distinction: Antibody and complement deposition is prominent and plays a key amplifying role in the myelin and tissue damage.
- Pattern III. Less severe T-cell and macrophage inflammation with more pronounced oligodendrogliopathy perhaps due to an apoptosis mechanism. No evidence of remylination.
- Pattern IV. Significant loss of oligodendrocytes due to necrosis, consistent with a primary oligodendrocyte injury and secondary demyelination. No evidence of remyelination.

Patterns I and II are similar to EAE.[26] EAE studies demonstrated a pathogenetic role of autoreactive antibodies and B cells, disregulation of proinflammatory and anti-inflammatory cytokines, hyperactive Th1 (T helper 1)-mediated immune responses, disturbance in costimulatory pathway and apoptosis, and reduction in suppressor cell activity.[27] Patterns III and IV appear to involve a targeted attack against oligodendrocytes.[26]

Pathophysiology

In the earliest phases of MS, inflammatory lesions don't produce any symptoms and a person with MS is unaware of the disease. This phase is known as asymptomatic MS and it can only be detected by MR.[28] The real paradox of MS lesions is the wide range of physical impact from nonexistent in asymptomatic MS discovered at autopsy to a disease that is fatal in less than 12 months.[29]

The majority of MS patients are disabled by the disease. Sixty percent of MS patients are still walking unassisted 10 years after first relapse; 5% are wheelchair users or bed confined by year 5; 40% need ambulation assistance by year 10. When patients experience a relapse that leaves them nonambulatory, approximately 50% will not improve enough to become ambulatory again.

In terms of cognitive function, memory and cognitive dysfunction may occur even when physical disabilty is minor. Because MS strikes a younger population, patients may be significantly neurologically impaired by their fifth and sixth decades of life.[30]

There are 4 categories of MS based upon clinical characteristics that are empiric rather than defined by specific biologic pathophysiology. The types of MS provide a framework for diagnosis and long-term disease management.[31]

Relapsing Remitting

Relapsing-remitting MS (RRMS) is the most common form of the disease, occurring in 85% of MS patients; it is characterized by clearly defined flare-ups followed by periods of remission. The flare-ups typically appear suddenly, last a few weeks or months, and resolve spontaneously. Most people with MS have this form at the

time of diagnosis. Serial MR studies indicate that lesions develop up to 10 to 20 times more frequently than clinical relapses. That means inflammatory lesions develop and evolve almost continuously during the clinically active and quiescent periods of RRMS.

Primary Progressive

Primary progressive MS (PPMS) occurs in 15% of patients and is characterized by gradual decline from the onset of symptoms without clinical relapses. People with PPMS are usually older than 40 when symptoms begin and fewer abnormalities are visible on brain MR scans.

Secondary Progressive

As tissue damage accumulates over many years, patients usually enter the secondary progressive stage of MS (SPMS). Relapses may occur during the early stages of SPMS, but become uncommon as the disease progresses. The progression of disability in SPMS may occur when ongoing irreversible tissue injury exceeds a critical threshold beyond which the nervous system can no longer compensate. At this point, the disease becomes a degenerative process, with neurologic deterioration independent of ongoing inflammation.

Progressive Relapsing

Progressive relapsing MS (PRMS) manifests as gradual neurological decline from the onset with subsequent superimposed relapses. PRMS is suspected to represent SPMS where the initial relapses were not diagnosed or were clinically silent. This form is relatively rare.[30-32]

A pathophysiological hypothesis related to both the initial onset of MS symptoms and relapse episodes is the role of injury, stress or emotional trauma. Alterations of the blood-brain barrier secondary to trauma to the brain or spinal cord of MS patients may exacerbate a previously asymptomatic plaque, produce symptoms from a silent lesion or result in the formation of a new plaque in an area of vulnerability. Injury to the nervous system also may cause the development of new plaques in previously damaged areas associated with disease onset.[33] One study demonstrated that stressful events were associated with increased exacerbations in RRMS. This association was independent of the triggering effect of infection on multiple sclerosis exacerbation.[34]

Diagnosis

There is no single diagnostic test that confirms MS. The diagnostic process typically involves a patient history of symptoms, clinical examination for physical signs and testing. All 3 aspects of the diagnostic process are necessary to rule out other possible causes and to gather facts consistent with an MS diagnosis[35] because other diseases, such as Lyme disease, mimic MS.[36] MS symptoms vary dramatically and are usually experienced for unpredictable periods of time. Primary symptoms that are a direct result of demyelination include:

- Fatigue.
- Mobility problems.
- Bowel and bladder problems.
- Visual problems.
- Diminished cognitive function such as memory, attention and problem-solving difficulties.
- Unpleasant physical sensations like numbness or "pins and needles."
- Sexual dysfunction.
- Pain.
- Depression or mood swings.[35]

Misdiagnosis is common as all MS symptoms could be the result of diseases or conditions other than MS. Diagnostic criteria that guide clinicians in evaluating the wide disparity of presentation in MS patients are updated as technology and understanding of the disease advance. The most recent criteria, the MacDonald criteria, were adopted in 2001. This system emphasizes the importance of MR and early diagnosis and has replaced the Poser criteria, which became outdated with the development of new treatments and therapies that are most effective when started early in the course of the disease.[36]

The MacDonald criteria define the spread of lesions, or plaques, over time and space. The time component of the criteria is defined as the onset of a second attack at least 1 month after a first attack, or the appearance of new lesions on an MR scan at least 3 months after the first MR procedure. The dissemination in space is established on the basis of either 9 typical white matter lesions demonstrated on MR or 1 enhancing lesion. If cerebrospinal fluid (CSF) studies show increased immunoglobulin G (IgG) values or oligoclonal banding, the presence of only 2 typical MR lesions satisfy the dissemination-in-time criteria.[37]

Diagnostic Imaging of Multiple Sclerosis

MR revolutionized the research, diagnosis and treatment of MS.[37] With sensitivity in detecting MS at approximately 85%[38] and excellent tissue contrast, MR far surpasses computed tomography (CT) scanning in imaging the presence of plaques or scarring caused by MS. Brains that appear normal on CT images show MS

plaques on MR images. On T2 images, brain tissue is dark, cerebrospinal fluid is bright and MS plaques are bright areas or spots.

On MS images, the distribution of lesions are random in the CNS white matter of the supratentorium, infratentorium and spinal cord. The most common locations are periventricular white matter, corpus callosum, visual system from optic nerve to occipital lobe and spinal cord. Spinal cord involvement is often symptomatic, while brain lesions are more likely to be asymptomatic.[39]

Contrast Agents

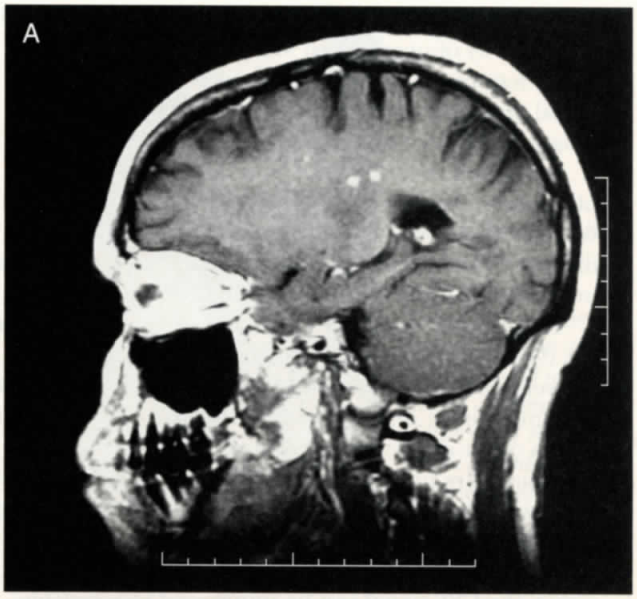
Gadolinium-diethylene-triaminepentaaceticacid (Gd-DTPA) enhancement is used to show inflammation-induced permeability changes to the blood-brain barrier and distinguish active from inactive lesions.[32] (See Fig. 1.) It also objectively monitors disease activity at the CNS level and assesses the effectiveness of treatment modalities.[1] Gd-DTPA enhancement is used in relapsing-remitting and secondary progressive MS during relapse stage. Enhancement is rare in primary progressive MS.

MR sensitivity for detecting active brain lesions can be increased by injecting larger doses of contrast material, up to a triple dose (0.3 mmol/kg). Sensitivity can be further improved by delaying scanning by as much as 40 to 60 minutes after injection.[32]

Brain Imaging

MS plaques in the brain are commonly ovoid or round in shape and can have a lesion-within-a-lesion, bull's-eye appearance.[38] The most common lesions in MS are Dawson fingers, which are ovoid lesions perpendicular to the ventricles that occur along the path of the deep medullary veins, and corpus callosum lesions occurring at the interface with the septum pellucidum.[38,39] Another paradox of MS is that the distribution and number of plaques seen on MR images may not be representative of the severity of the clinical disease state. A finding of 3 or more lesions of at least 5 mm in size in a periventricular location is considered suggestive of MS.[38]

Despite the sensitivity and superiority of MR as a diagnostic tool, a definitive diagnosis of MS cannot be made solely on the basis of MR imaging. Other neurologic diseases, such as glioma, cause lesions in the brain that appear similar to MS plaques on MR images.[39] Abnormalities not related to any disease process, called unidentified bright objects (UBOs), are sometimes found in healthy older individuals.[40]



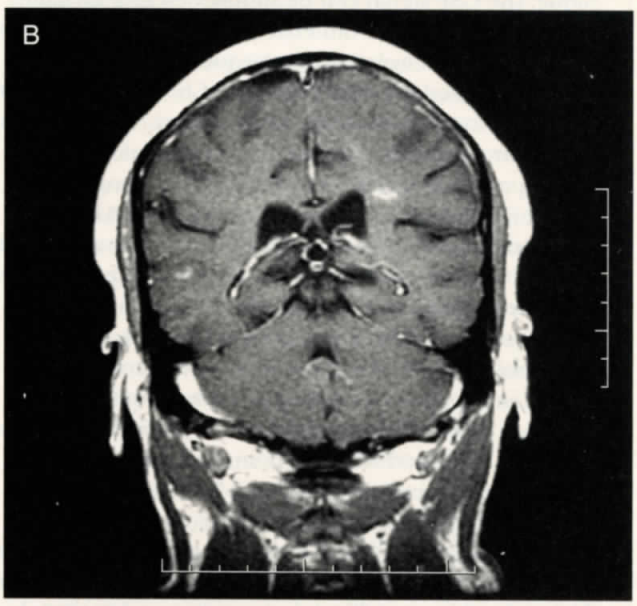


Fig. 1. *Postgadolinium contrast image demonstrating enhancing MS plaques. A. Sagittal T1 image. B. Coronal T1 image. (Image courtesy of University of Massachusetts Memorial Medical Center, Central Massachusetts Magnetic Imaging Center, Worcester, Mass.)*

Conversely, a normal MR does not rule out a diagnosis of MS. Approximately 5% of patients confirmed to have multiple sclerosis on the basis of other criteria do not show any plaques or lesions in the brain on MR images. Their lesions may be in the spinal cord or they may

have plaques that cannot be detected by MR[39] Eventually, the majority of people with MS will have brain and/or spinal lesions that will be visible on MR. However, an initial diagnosis of MS becomes more questionable the longer an MR examination remains negative.[40]

As a result of inflammation and breakdown of the blood-brain barrier in MS lesions, the presence of extravascular fluid induces hyperintensity on T2-weighted images. Typically, MR scans of MS patients demonstrate more than 1 hyperintense white matter lesion.[37]

T2-weighted images are used to assess edema and tissue destruction early in the inflammatory stage of MS. T2-weighted images have limited sensitivity and specificity in measuring disease burden when demyelination and gliosis occur in later stages of disease progression.[41]

Lesions are more easily identified with proton density (PD)-weighted MR as opposed to standard T2 imaging. In a PD series, MS lesions remain hyperintense, while the CSF signal is suppressed. Depending on the PD technique, the CSF signal can be suppressed to a variable degree, rendering it isointense to hypointense relative to the brain parenchyma. Such a sequence results in substantial suppression of perivascular CSF spaces that may penetrate to the subcortical white matter. These spaces, called Virchow-Robin spaces, may appear as hyperintense spots on standard T2-weighted MR images.[37]

A fluid-attenuated inversion recovery (FLAIR) sequence is a widely used variant of T2 imaging. (See Fig. 2.) Ventricles are starkly differentiated from periventricular white matter lesions on FLAIR imaging and FLAIR suppresses the T2 hyperintensity of fluid. Parenchymal hemisphere lesions stand out more prominently with FLAIR imaging, and the ability to detect juxtacortical lesions is improved as opposed to conventional T2 scans.[41]

On T1-weighted scans, hypointense lesions that do not persist may indicate a reversible change such as edema. Persistent lesions are indicative of axonal loss and demyelination.[41] Severe disease progression can be gauged by the presence of "black holes" on hypointense T1-weighted images. Black holes emit very low signals, and some evidence suggests they may represent iron deposits in the brain.[41,42]

Spinal Cord Imaging

Spinal cord imaging is technically challenging because of the thin, longitudinal anatomy of the spinal cord and the introduction of artifacts by voluntary and involuntary motions.[41] MS plaques, depending on their age, appear as areas of slightly low to low signal intensity on unenhanced T1-weighted images. The plaques are

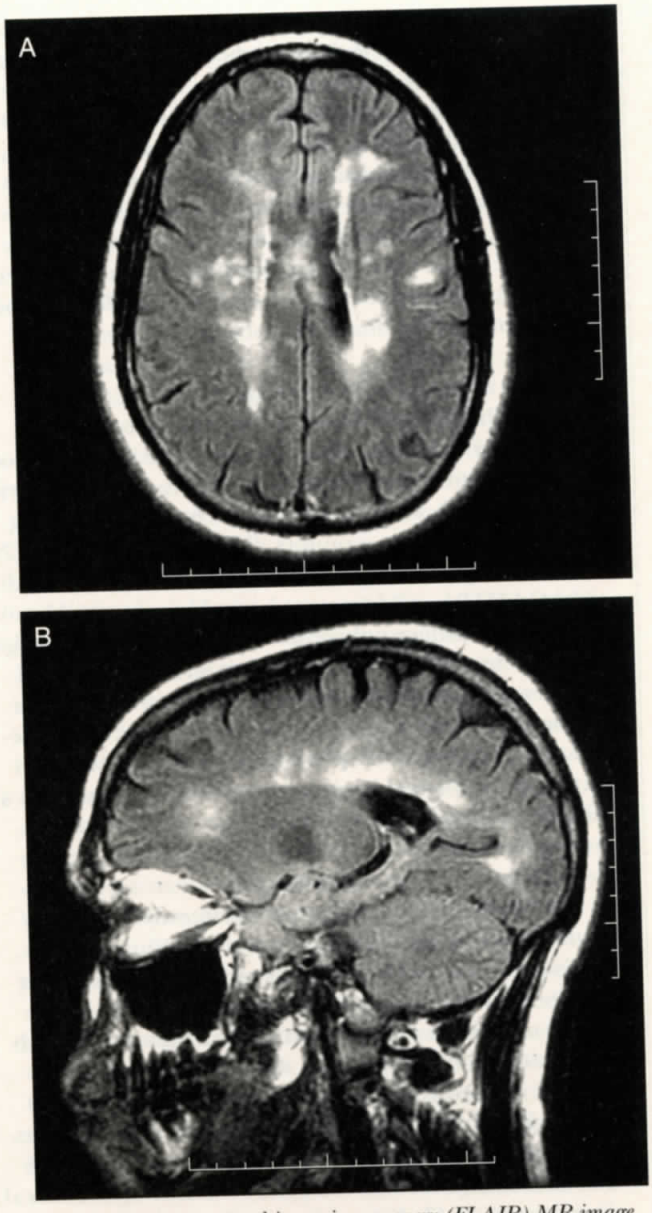


Fig. 2. *Fluid-attenuated inversion recovery (FLAIR) MR image showing abnormal areas. Hyperintense signal in periventricular white matter demonstrates characteristic pattern of a perivascular distribution (long axis perpendicular to body of lateral ventricle). A. Axial FLAIR image. B. Sagittal FLAIR image. (Image courtesy of University of Massachusetts Memorial Medical Center, Central Massachusetts Magnetic Imaging Center, Worcester, Mass.)*

shaped like nodules, rings or arcs, generally less than 2 vertebral bodies in length. Active disease responds rapidly to gadolinium enhancement. The enhancement

may last 2 to 8 weeks and steroids (used in treatment) typically do not suppress the enhancement of active plaques. Chronic lesions do not respond to contrast enhancement.

On T2-weighted images, MS plaques appear hyperintense and the spinal cord may or may not be focally enlarged. (See Fig. 3.) Cord enlargement is characteristic of active disease. Larger active lesions may have extensive edema with associated cord expansion. Chronic lesions often demonstrate focal cord atrophy. Spinal lesions usually coexist with more severe concomitant brain plaques. As many as 20% of spinal MS lesions are isolated. Spinal cord narrowing due to atrophic changes is present in 10% of patients with spinal cord involvement. A demyelinating process should always be considered if any mass-like lesions are present because tumefacient MS may mimic a neoplasm.[43]

Because artifacts are a concern in spinal imaging, FLAIR techniques are not as useful as conventional T2 to evaluate the spinal cord or posterior fossa. More effective imaging in these anatomic areas are PD or spin echo sequences.[41]

New Trends

Magnetization Transfer MRI

Although conventional MR is sensitive for detecting lesions and their changes over time, it cannot be used to characterize and quantify the tissue damage within and outside such lesions. Magnetization transfer MRI (MT-MRI) is a quantitative MR technique with the potential to overcome this limitation and to provide additional information about the nature and the extent of tissue damage.[44]

MT-MRI compares proton interactions in an unrestricted environment, such as water, with proton interactions in a restricted environment, such as tissue. An off-resonance pulse is applied to tissue, which saturates the magnetization of protons. The magnetization is then transferred from these protons to more mobile protons, reducing the tissue signal. The degree of signal loss depends on the density of macromolecules in the tissue. A low MT ratio shows the reduced ability of macromolecules in tissue to exchange magnetization with water molecules, indicating damage to myelin and axonal membranes.[41]

MT-MRI demonstrates a significantly lower signal in MS patients with cognitive dysfunction. A low MT-MRI signal is indicative of myelin loss and reduced axonal density in surrounding tissues. MT-MRI measurements are reproducible, sensitive to longitudinal disease changes and correlate with physical disability and cognitive impairment.[45]

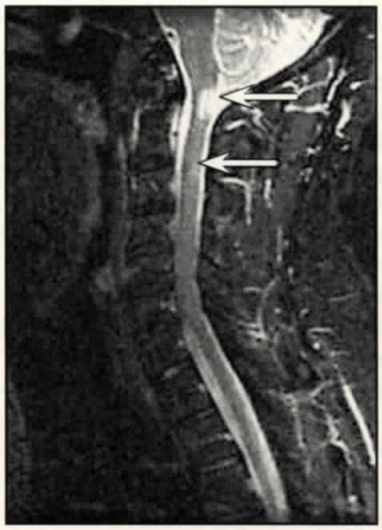


Fig. 3. *Sagittal MR image of the cervical spine showing MS lesions at the craniocervical junction and posterior to C3 (arrows). (Image courtesy of University of Rochester School of Medicine Department of Imaging Sciences, Rochester, NY.)*

Diffusion-weighted/Diffusion-tensor MRI

Diffusion-tensor MRI (DT-MRI) is based on variable water molecule movement through tissues and fluids and how pathological processes affect that movement and tissue permeability. MS alters the permeability and geometry of cellular structures, as well as in vivo diffusion of water. In some brain tissues, such as white matter, molecular mobility is not the same in all directions. DT-MRI can image regional distribution and unique patterns of white matter lesions characteristic of cognitive deficits and measure abnormalities in the corpus callosum that indicate impaired attention and concentration.[44,45]

DT-MRI images have identified diffusion abnormalities associated with the different MS disease phenotypes. Changes in normal-appearing gray matter are more obvious in patients who have secondary progressive MS than in patients who have relapsing-remitting MS or primary progressive MS.

DT-MRI may also prove valuable in understanding the underlying mechanisms of MS damage and repair, because edema, inflammation, demyelination, remyelination, gliosis and axonal loss are each likely to have different effects on the size, integrity and orientation of fluid-filled spaces.[44]

Proton Magnetic Resonance Spectroscopy

Proton magnetic resonance spectroscopy (MRS) provides a quantitative and continuous measure of the biochemical composition of brain tissues by suppress-

ing the signal from water and fat protons, and detecting and measuring the amounts of the hydrogen-rich compounds choline, creatine, N-acetylaspartate and lactate. Identifying these compounds is useful to evaluate disease progression.

- Choline. Phosphocholine and glycerolphosphocholine are components of membrane phospholipids that are released during active myelin breakdown.
- Creatine. Decreased creatine concentrations are associated with acute demyelinating lesions.
- N-acetylaspartate (NAA). NAA is associated with neurons and neuronal processes in the normal adult brain. Decreased concentrations are associated with axonal dysfunction.
- Lactate. Higher than normal lactate concentrations in tissue reflect the metabolism of inflammation, as well as tissue injury, mitochondrial dysfunction and ischemia.[44,45]

Functional MRI

Functional MRI (fMR) measures signal intensity related to blood oxygenation levels in the brain during motor, sensory and cognitive operations. It is used to study neuronal mechanisms that underlie CNS function and define abnormal patterns of brain activity caused by disease. Blood oxygenation level-dependent contrast material demonstrates a change in the signal strength of water protons in the brain produced by venous blood deoxyhemoglobin paramagnetic changes. These changes may reflect increased neuronal activity in the "working" areas compared to the "silent" areas of the brain. fMR can assess changes in the brain in response to a specific cognitive task, as well as the brain's ability to change in response to treatment.[44,45]

Treatment and Therapies

There is no cure for MS. MS is highly variable from individual to individual, so MS treatments and therapies address 4 major aspects of disease management with the goal of controlling symptoms and maintaining a normal quality of life.[47]

Modify Disease Course

To prevent or reduce the long-term risk of clinically significant disability, current therapies target the immune dysfunction that produces neural tissue damage. Immune-modulating therapy requires injections under the skin or in the muscle once or several times a week. First-line therapies currently available in the United States include interferon (IFN)ß-1a (Avonex), IFNß-1a (Rebif), IFNß-1b (Betaseron) and glatiramer acetate (Copaxone).

All of these first-line, disease-modifying medications have limitations and all are expensive, costing about $12 800 to $17 300 per year. The most important limitation of these agents is their partial effectiveness. A substantial proportion of patients treated with each of these medications continue to have evidence of clinical disease, as measured by clinical relapse, progression of disability or new lesions on T2 brain MR scans.[31]

Even with the limitations of these medications, the executive committee of the medical advisory board of the National Multiple Sclerosis Society has adopted the following recommendations:

- Treatment should be considered as soon as possible following a definite diagnosis of MS with active disease (ie, recent relapses and/or new lesions on MR images) and also may be considered for some patients with a first attack who are at high risk for developing MS (known as clinically isolated syndrome).
- Treatment should be continued unless the person is not benefiting from therapy, the side effects are intolerable or a better treatment becomes available.
- Changing from one immunomodulatory therapy to another should occur only for medically appropriate reasons.
- Immunosuppressant therapy with mitoxantrone (Novantrone) may be considered for some individuals with worsening relapsing MS or with secondary progressive MS.
- Most individuals with other medical conditions in addition to their MS can safely take these medications.
- None of these medications have been approved by the U. S. Food and Drug Administration (FDA) for use by women who are trying to become pregnant, are pregnant or are nursing mothers.[49]

Treat Exacerbations

No highly effective treatment is currently available to counteract MS attacks after their onset. The most widely used treatment is intravenous (IV) methylprednisolone (1 g administered daily for 3-5 days). This medication may help expedite the recovery process but will not affect the actual degree of recovery.[47]

Manage Symptoms

The following medications may be used to manage MS symptoms:

- Lioresal (Baclofen), tizanidine (Zanaflex) or a benzodiazepine to reduce muscle spasticity.
- Cholinergic medications to reduce urinary problems.
- Antidepressant or antianxiety drugs for mood or behavioral symptoms.
- Amantadine for fatigue.[47]

Improve Function and Safety

Physical therapy, speech therapy, occupational therapy and support groups can help improve outlook, reduce depression, maximize function and improve coping skills. A planned exercise program early in the course of the disorder can help maintain muscle tone.[47]

Research

The National MS Society is the largest private sponsor of MS research in the world. In 2004, the society spent more than $35 millon on more than 300 MS research projects, including the launch of 115 new studies. The following are some of the more promising research projects:

- A Harvard University-led study, supported in part by the National MS Society, involving 187 563 women enrolled in the Nurses' Health Study, suggested that those with higher intake of vitamin D (in multivitamin supplements) may have a reduced risk of developing MS. The study did not determine whether vitamin D affects the course of MS once it has begun.
- Researchers from Australia found evidence in brain samples suggesting that the primary pathology in some people with MS involves a "killing-off" of myelin-making cells with little or no evidence of immune attack. If confirmed, these findings raise intriguing questions about the MS disease process and how it begins, about how and when the immune attack becomes involved and about the potential for different forms of MS and different underlying brain damage categories for MS.
- Results from a study of the oral immune-modulating drug laquinimod (Teva Pharmaceutical Industries Ltd., Jerusalem, Israel, and Active Biotech AB, Lund, Sweden) indicated that in 209 persons with relapsing forms of MS, the drug was well tolerated. Those on a higher dose had significantly fewer new active MS brain lesions during 24 weeks of testing. Larger studies needed to explore the drug's potential for treating MS are beginning now.
- An international team of investigators from Australia and the United States successfully reduced the severity and duration of MS-like disease in mice by vaccinating them with Nogo, a protein normally found in the brain that is known to inhibit nerve regeneration. They determined that the vaccinations caused the mice's immune systems to produce antibodies that neutralized Nogo's inhibitory activity in the nervous system.
- Acorda Therapeutics (Hawthorne, NY) announced preliminary results of a phase II clinical trial of Fampridine-SR, an oral, sustained-release formula of 4-aminopyridine, to treat MS symptoms. According to the company, the drug may improve walking speed and significantly improved leg muscle strength. Fampridine-SR blocks tiny pores on the surface of nerve fibers to improve nerve impulse conduction.

Conclusion

MS is a complex degenerative neurological disease characterized by relapsing and remitting symptoms that usually manifest for the first time in adults between the ages of 20 and 40. Although it is generally regarded as an automimmune disorder, MS cannot be attributed to one specific cause. MR imaging with gadolinium contrast is key to diagnosing the disease (to exclude other diseases that can mimic multiple sclerosis) and monitoring progression. There is no cure for MS; however, new treatments are sometimes effective in reducing exacerbations and may slow the progression of disability. Other treatments include symptom-specific drugs to relieve spasticity, bladder dysfunction, depression and fatigue.

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Directed Reading Continuing Education Quiz

DRI0006006
Expiration Date:
April 30, 2008*
Approved for 2.0
Cat. A CE credits

Multiple Sclerosis

To receive Category A continuing education credit for this Directed Reading, read the preceding article and circle the correct response to each statement. Choose the answer that is most correct based on the text. **Transfer your responses to the answer sheet on Page 333** and then follow the directions for submitting the answer sheet to the American Society of Radiologic Technologists. You also may take Directed Reading quizzes online at www.asrt.org. **Effective October 1, 2002, new and reinstated members are ineligible to take DRs from journals published prior to their most recent join date unless they have purchased a back issue from ASRT.**

***Your answer sheet for this Directed Reading must be received in the ASRT office on or before this date.**

1. Diagnostic criteria that include diplopia, ataxia and dysarthia are known as _____ triad.
   a. Charcot's
   b. Carswell's
   c. Cruveiher's
   d. Dawson's

2. Which of the following groups is more than twice as likely to develop multiple sclerosis (MS)?
   a. indigenous people of Southeast Asia
   b. whites
   c. blacks
   d. native people of South America

3. MS is _____ times more prevalent in temperate climates that in tropical regions.
   a. 20
   b. 15
   c. 10
   d. 5

4. What is experimental allergic encephalomyelitis?
   a. an autoimmune reaction similar to MS
   b. a discarded theory of the cause of MS
   c. a proposed MS treatment
   d. a model of the Epstein-Barr virus

5. Nearly all people with MS have some evidence of an Epstein-Barr virus.
   a. true
   b. false

6. Relapsing-remitting and demylinating diseases can be induced in animals infected with:
   a. Epstein-Barr virus.
   b. canine distemper virus.
   c. Theiler's murine-encephalomyelitis virus.
   d. herpes virus HHV-6.

7. MS is ***not*** a hereditary disease.
   a. true
   b. false

8. What causes inflammation in MS?
   a. bacterial infection
   b. an overactive proinflammatory T(H)1 profile in T cells
   c. T-cell deactivation
   d. a single defective gene

Continued on next page

Directed Reading Continuing Education Quiz

9. Research suggests that there are 4 distinct immunopathologic MS subgroups based on distinct patterns of plaques. The plaque patterns display specific features of _____, geography, pattern of oligodendrocyte destruction and deposition of antibody and complement.
   a. marked activation of macrophages and microglia
   b. autoreactive antibodies
   c. myelin protein loss
   d. apoptosis

10. Ten years after first relapse, 60% of MS patients are:
   a. confined to bed.
   b. wheelchair bound.
   c. walking assisted.
   d. walking unassisted.

11. People who are older than 40 when symptoms begin but have few abnormalities seen on brain MR scans are considered to be in the _____ MS category.
   a. relapsing remitting
   b. primary progressive
   c. secondary progressive
   d. progressive relapsing

12. Which of the following conditions characterizes the secondary progressive stage of MS?
   a. increasing frequency of relapses
   b. neurologic deterioration independent of ongoing inflammation
   c. gradual decline from the onset of symptoms without clinical relapses
   d. clearly defined flare-ups followed by periods of remission

13. A study demonstrated that stressful events were associated with increased exacerbations in _____ MS.
   a. relapsing remitting
   b. primary progressive
   c. the secondary progressive stage of
   d. progressive relapsing

14. Demylination symptoms include:
   1. fatigue.
   2. visual problems.
   3. numbness

   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2 and 3

15. Which of the following is ***not*** a component of the MacDonald criteria?
   a. the onset of a second attack at least 1 month after a first attack
   b. 9 typical white matter lesions on an MR scan or 1 enhancing lesion
   c. the appearance of new lesions on the MR scan at least 3 months after the first MR procedure
   d. oligodendrocyte injury and secondary demyelination

16. MR surpasses computed tomography in imaging the presence of plaques or scarring caused by MS.
   a. true
   b. false

Continued on next page

Directed Reading Continuing Education Quiz

17. The most common locations for MS lesions are periventricular white matter, _____, visual system from optic nerve to occipital lobe and the spinal cord.
    a. corpus callosum
    b. pons
    c. reticular formation
    d. cingulate gyrus

18. Gadolinium-diethylene-triaminepentaaceticacid (Gd-DTPA) lesion enhancement is rare in:
    a. relapsing remitting MS.
    b. primary progressive MS.
    c. secondary progressive MS.
    d. progressive relapsing MS.

19. MR sensitivity for detecting active brain lesions can be increased by injecting a triple dose of contrast material and waiting _____ to _____ minutes.
    a. 20, 40
    b. 40, 60
    c. 60, 80
    d. 80, 100

20. Which of the following is ***not*** a common characteristic of MS plaques in the brain?
    a. ovoid or round in shape
    b. located perpendicular to the ventricles
    c. irregular, branching lesion
    d. bull's-eye appearance

21. A finding of _____ or more lesions of at least _____ mm in size in a periventricular location is considered suggestive of MS.
    a. 1, 3
    b. 3, 1
    c. 3, 5
    d. 5, 3

22. As a result of inflammation and breakdown of the blood-brain barrier in MS lesions, the presence of _____ induce(s) hyperintensity on T2-weighted images.
    a. ovoid lesions
    b. extravascular fluid
    c. Gd-DTPA
    d. cerebrospinal fluid (CSF)

23. Which of the following imaging techniques suppresses the CSF signal, making lesion identification easier than for standard T2 imaging?
    a. Gd-DTPA
    b. magnetization transfer magnetic resonance imaging (MT-MRI)
    c. proton density (PD)-weighted MRI
    d. functional MRI (fMR)

24. Fluid-attenuated inversion recovery (FLAIR) sequence is used to:
    a. study neuronal mechanisms that underlie central nervous system function.
    b. increase the T2 hyperintensity of fluid.
    c. reduce artifacts.
    d. better differentiate ventricles from periventricular white matter lesions.

25. On T1-weighted scans, hypointense lesions that do not persist may indicate:
    a. edema.
    b. demyelination.
    c. parenchymal hemisphere lesions.
    d. periventricular white matter lesions.

Continued on next page

Directed Reading Continuing Education Quiz

26. Which of the following statements is ***true*** concerning spinal cord imaging to diagnose MS?
    a. It is rarely performed because of the hypointense nature of plaques.
    b. Imaging is most effective using a FLAIR sequence.
    c. Imaging is difficult to perform due to the anatomy of the spinal cord and artifacts.
    d. It is the best way to detect axonal loss and demyelination.

27. What does a low MT-MRI signal indicate?
    a. myelin loss and reduced axonal density in surrounding tissues
    b. severe disease progression as gauged by the presence of "black holes"
    c. suppressed CSF signal
    d. Virchow-Robin spaces

28. Diffusion-tensor magnetic resonance imaging (DT-MRI) can image regional distribution and unique patterns of white matter lesions that are characteristic of:
    a. Dawson fingers.
    b. progressive relapsing MS.
    c. cognitive deficits.
    d. oligoclonal banding.

29. Proton magnetic resonance spectroscopy (MRS) suppresses the signal from water and fat protons to detect and measure the amounts of choline, creatine, _____ and lactate.
    a. lysine
    b. taurine
    c. citrate
    d. N-acetylaspartate

30. _____ measures signal intensity related to blood oxygenation levels in the brain during motor, sensory and cognitive operations.
    a. MR
    b. DT-MR
    c. MRS
    d. fMRI