The Importance of Early Diagnosis of Multiple Sclerosis

JAMES R. MILLER, MD

ABSTRACT

OBJECTIVE: To describe the current understanding of the diagnosis and treatment of multiple sclerosis (MS) and to explore the use of magnetic resonance imaging (MRI) assessment as a prognostic tool and an indicator in the diagnosis of MS.

SUMMARY: MS is a chronic, progressive, demyelinating disease of the central nervous system that is associated with a significant economic burden. At this time, immunomodulatory agents (interferon beta-1a (IFNβ-1a) [Avonex], IFNβ-1a [Rebif], IFNβ-1b [Betaseron], and glatiramer acetate [Copaxone]) are first-line agents, which are reported to reduce relapse rates.

The diagnostic criteria for MS have evolved over time to include MRI findings as an integral part of the diagnosis. However, the most recent criteria (McDonald) are focused on the diagnosis of definite MS and do not address the status of patients with a first demyelinating event (clinically isolated syndrome [CIS]). This is an important issue because a CIS is highly predictive of developing further inflammation and definite MS when the episode occurs in conjunction with lesions on the initial MRI. Many times, MRI findings do not correlate with clinical symptoms, and clinically silent lesions are identified. Therefore, the use of MRI is salient to the early diagnosis of high-risk patients.

The evolution of thought concerning early treatment in MS is based on an increased understanding of the pathology of the disease. Axonal loss occurs early in the disease process, and both white matter and gray matter are affected. Studies that have analyzed early treatment in patients highly likely to have MS (clinically isolated events with evidence of lesions on MRI) report significant benefits in delaying further changes on MRI and further attacks. Patients who begin treatment later do not reap the same benefits as those who begin treatment earlier during the disease course.

CONCLUSION: Patients with clinically isolated events should be referred promptly to a neurologist for assessment, including MRI scans. An early recognition of the inflammatory process enables patients to begin treatment with an immunomodulatory agent even before the technical diagnosis of definite MS so that the degenerative progression of MS can be retarded.

KEYWORDS: Magnetic resonance imaging, Interferon beta, Glatiramer acetate, Multiple sclerosis, Diagnosis

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Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system (CNS). This treatable but uncurable degenerative disease affects approximately 400,000 people in the United States.[1] Common symptoms of MS include spasticity, fatigue, sexual dysfunction, bladder dysfunction, pain, cognitive dysfunction, depression, bowel dysfunction, and weakness. The average age of onset of MS is 30 years.[2] Because this is the age when individuals may be beginning a family and workers have not typically reached their full earning potential, it has a particularly devastating impact on family, social, and professional relationships.

MS is associated with a considerable economic burden. National costs of MS are estimated to range from $6.8 to $11.9 billion annually (approximately $34,000 per patient).[3] The major components of these costs include earnings loss (incurred by the patient with MS) and costs of informal care (unpaid personal assistance).[3] According to a survey of MS patients, the annual loss in earnings was $17,900; this amount was even greater ($41,000) for men younger than 65 years.[3] In that same study, the annual expenditures for informal care were $6,452, which translated to about one fifth of the annual per-patient costs of MS.[3] Other large expenditures included costs for hospitalization and physician visits.[3]

In 90% of patients, MS's natural progression traditionally has been categorized in sequential stages, which include subclinical disease, monosymptomatic disease, relapsing-remitting disease (RRMS), and then secondary progressive MS (SPMS). Clinicians diagnose definite MS after a second attack occurs or evidence of new MS lesions are visualized on magnetic resonance imaging (MRI).[4] The clinical course of RRMS is described as clearly defined relapses with at least partial recovery of deficits. Periods between relapses are characterized by a lack of disease progression.[5] In contrast, SPMS occurs when some deficits begin to progress even between obvious relapses. Relapses occur less frequently than during the RRMS phase or do not occur at all.[5]

The progression of MS is discernible when the recovery between relapses is incomplete, with a sustained worsening on the Expanded Disability Status Scale (EDSS) or other rating scales; lesion burden assessed by MRI is increased; cognitive dysfunction accumulates; and brain atrophy advances.[6-8] In some patients, the cognitive effects of MS may be more severe than the physical effects during the early stages of the disease. If MS is left untreated, patients with RRMS develop SPMS (50% by 10 years; 90% by 30 years).[2,9]

Treatment of Multiple Sclerosis

Only a small subset of the medical community makes treatment decisions in patients with MS. Because MS is a chronic degenerative disease, treatment must be continuous, not intermittent. At this time, immunomodulatory agents (IMAs) are considered first-

line treatments for patients with RRMS, including the following: intramuscular (IM) interferon beta-1a (IM IFNβ-1a) [Avonex, Biogen Idec Inc., Cambridge, MA]), subcutaneous (SC) IFNβ-1a (SC IFNβ-1a [Rebif, Serono, Rockland, MA]), SC IFNβ-1b (Betaseron, Berlex Laboratories, Montville, NJ), and SC glatiramer acetate (Copaxone, Teva Pharmaceutical Industries, Kansas City, MO). Another agent, mitoxantrone (Novantrone, Immunex Corp., Seattle, WA), is indicated for reducing the progression of neurologic disability and the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or significantly worsening RRMS. IMA treatment goals include reducing inflammation, reducing the relapse rate, slowing disability, slowing the accumulation of cognitive dysfunction, reducing the progression of brain atrophy, and improving quality of life.

Several large randomized trials demonstrate that IMAs reduce attack rates.[10-13] Direct comparisons among the trials are impossible, but these data suggest that all agents reduce relapse rates similarly. For example, the phase III trial of IM IFNβ-1a reported a 32% reduction in relapses among patients who were treated for 2 years.[11] Similarly, the mean percentage reduction in relapse rates over 2 years was 33% in patients who received SC IFNβ-1a.[12] Two-year data from the SC IFNβ-1a trial revealed a 34% reduction in patients who received treatment.[10] Finally, in the glatiramer acetate study, the 2-year reduction in relapse rate was 29%.[13] Although trial outcomes were similar, there may be important differences among these agents with regard to their demonstrated ability to slow disability progression. For example, both IM IFNβ-1a and SC IFNβ-1a (44 mcg) have been associated with a significant reduction in sustained disability progression.[11,14]

Of note, sustained progression of disability must have occurred for ≥3 months during the SC IFNβ-1a trial and ≥6 months during the IM IFNβ-1a trial; the 6-month requirement provided a more stringent measurement of efficacy.[11] Sustained disability progression was not significantly affected during the IFNβ-1b study.[10] Reduction in sustained disability with glatiramer acetate was not statistically significant.[13] Sustained disability progression is the most important clinical measure in MS because the major proportion of clinical deficit is caused by clinically silent events not manifested by relapses.

TABLE 1 Summary of Studies Reporting Development of Clinically Definite Multiple Sclerosis (CDMS) in Patients Who Have Clinically Isolated Demyelinating Events With Lesions Assessed by Magnetic Resonance Imaging at Baseline

Reference	Follow-up (Years)	Baseline Findings Predictive of CDMS	Criteria for CDMS	Patients Who Developed CDMS
Paty et al.[18]	1	4 lesions, or 3 lesions with 1 periventricular lesion	Schumacher criteria[15]	95% (18/19)
Barkhof et al.[19]	≥2	9 lesions	Poser et al.[16]	80% PPV*
Optic Neuritis Study Group[20]	5	≥3 lesions ≥3 mm in size	Second attack confirmed by examination, with new neurologic disability	51% cumulative probability
O'Riordan et al.[21]	5–10	≥1 asymptomatic lesion compatible with demyelination	Poser et al.[16]	83% (45/54)
Sailer et al.[22]	10	≥1 asymptomatic lesion compatible with demyelination	Poser et al.[16]	82% (37/45)
Brex et al.[23]	1	≥1 gadolinium-enhancing lesion at baseline and at 3 months	Poser et al.[16]	70% PPV
Brex et al.[17]	14.1	≥1 asymptomatic lesion compatible with demyelination	Poser et al.[16]	88% (44/50)

**PPV = positive predictive value.*

Diagnosis of Multiple Sclerosis

Over the last 40 years, an important evolution has occurred in the diagnostic rubric of MS: the diagnostic criteria progressed from being solely clinical symptom-based (Schumacher[15] and Poser[16]) to integrating MRI assessments (McDonald[4]). This salient advance in MS management allows for a more timely diagnosis and earlier treatment in patients with MS.

In 1965, Schumacher et al. published the first criteria for diagnosing MS.[15] These early guidelines required the presence of CNS lesions disseminated in time and space and the exclusion of alternative diagnoses. The 1983 Poser criteria updated the Schumacher criteria.[16] The latter guidelines reflected detection technique advances, such as MRIs and spinal taps, which identify lesions and other paraclinical evidence.

Most recently, an international panel in association with the National Multiple Sclerosis Society of America recommended revised criteria, and the McDonald criteria were published.[4] These new criteria make use of advances in MRI imaging techniques and include criteria for dissemination of MS lesions in time and space. Prior to the McDonald criteria, a diagnosis of clinically definite MS (CDMS) might have taken several years. Still, these criteria focus on the diagnosis of CDMS and analyze inflammatory processes conservatively. They do not address the importance of MRI changes for the patient with a clinically isolated syndrome (CIS). For example, patients with an initial demyelinating event (such as optic neuritis, cerebellar syndrome, or spinal cord syndrome) must display changes over time in order to be diagnosed with definite MS. Despite the cautionary approach of the McDonald criteria, nearly 90% of patients with CISs who have MRI lesions will develop definite MS over time.[17]

In patients with CISs as well as with definite MS, MRI results usually reveal subclinical lesions. Data from a number of studies demonstrate that the presence of MRI-assessed lesions is strongly

FIGURE 1 Final Diagnosis of Multiple Sclerosis as Year 14 Compared With Lesion Load at Disease Onset

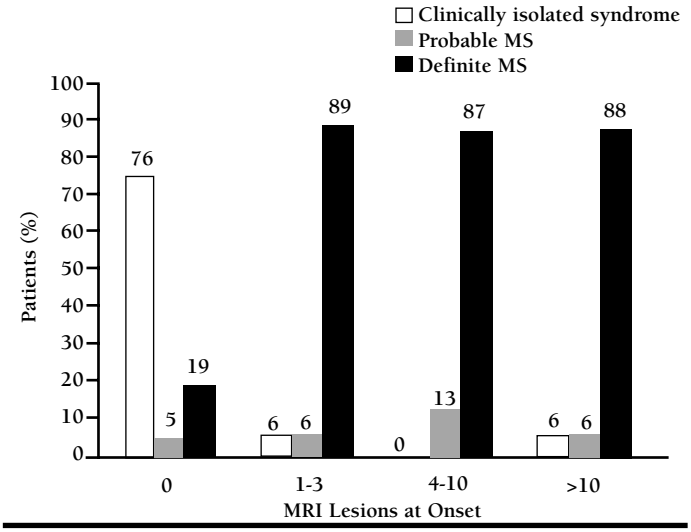
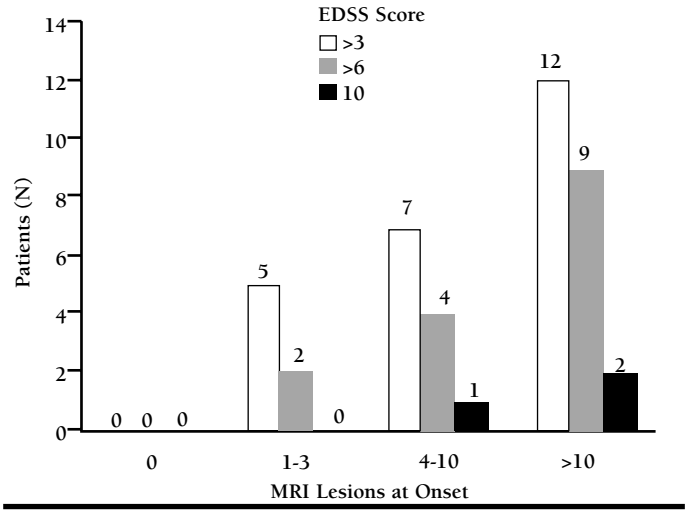


FIGURE 2 Expanded Disability Status Scale Score at Year 14 Compared with Lesion Load at Disease Onset



predictive of developing CDMS in patients who experience a clinically isolated event (Table 1).[17-23] The results of a prospective longitudinal study of patients with CISs demonstrated that 88% of patients with abnormal MRI findings at baseline had developed CDMS at 14 years (Figure 1).[17] Furthermore, at 14 years, the EDSS score was correlated with the number of lesions on MRI at baseline, with higher EDSS scores in patients who had more lesions at baseline (Figure 2).[17]

Our understanding of the pathophysiology of MS has caused our thinking about early treatment of MS to evolve. Current dogma states that MS is an episodic autoimmune disease. MS is largely T-cell–mediated and involves environmental factors. Immune cells, activated in the periphery, enter the CNS by migrating across the blood–brain barrier, where they attack myelin and oligodendroglia. Traditionally, researchers postulated that axonal loss occurs late in the disease, secondary to this process, and that MS is a disease of the white matter. However, the current dogma is being questioned.

For example, evidence exists that the pathology of MS may differ among patients, suggesting that several different diseases culminate in a final pathway: MS.[24,25] Studies of brain biopsy specimens and autopsies of patients with MS reveal that about 20% of patients have a major anti-CNS antibody component during acute flare-ups. Other lesions are associated with inflammatory macrophages. It is unknown whether various subtypes of MS exist or if these processes are part of a disease continuum in which different processes are active at various time points.

Evidence now suggests that axonal loss occurs early during the disease course and that it is prominent from the onset of MS.[26,27] Trapp et al. used autopsy findings from patients with MS to define changes in axons.[26] Their findings demonstrated that irreversible axonal transection occurred in both active and chronic lesions of patients, some of whom had MS for as few as 2 weeks.[26] Transected axons were commonly found in lesions, and their frequency was related to the degree of inflammation within the lesion.[26] These findings are critical; historically, axonal loss was not considered important in MS's pathology.[27] Moreover, axonal loss appears in normal-appearing white matter.[28-30] A study of a patient who had MS for 9 months reported that myelin was relatively preserved despite a 22% axonal loss in the ventral column.[28]

Reliable imaging of normal-appearing white matter and normal-appearing gray matter is challenging.[30] Results from magnetic transfer imaging and spectroscopy have demonstrated abnormalities in areas that appear normal on conventional scans.[31] Studies in which gadolinium is administered to patients before MRI to enhance MS lesions suggest that these gadolinium-enhanced (Gd+) lesions are preceded by abnormal findings on spectroscopy or magnetic transfer imaging.[32-37]

Extensive evidence reveals that lesions occur in MS patients' gray matter.[38-40] In fact, cortical lesions occur early and frequently.[29,41] One recent study reported that metabolic changes could be detected in the cortical gray matter of patients early in the disease course (mean duration of disease, 1.7 years).[29] Furthermore, metabolic changes in the cortical gray matter were related to disability as measured by the EDSS, Multiple Sclerosis Functional Composite, 9-Hole Peg Test, and Paced Auditory Serial Addition Task.[29] Abnormalities in normal-appearing gray matter are reported to correlate with cognitive deficits.[42] Detection of gray matter lesions by conventional MRI is difficult because the relaxation characteristics of these lesions result in a poor contrast between them and the surrounding normal gray matter because of partial volume effects with cerebrospinal fluid (CSF).[30]

Role of Magnetic Resonance Imaging

MRI-based assessments briefly discussed in this section are important tools in the diagnosis and management of patients with MS. In fact, MRI-based assessments are the most important ancillary tests performed in patients with MS. Gd+ T1-weighted scans display areas of blood–brain barrier disruption and are indicative of active inflammation and, therefore, reflect active disease.[43] Gd+ lesions display a spectrum of appearances (e.g., ringlike, homogeneous) and may be clinically silent (i.e., without symptoms). The sensitivity of these images may be increased with various techniques that are becoming more readily available.[44-46]

The most commonly used measure of disease burden is the presence and number (and, for research, volume) of hyperintense lesions on T2-weighted images.[31] However, these images are relatively insensitive to the underlying pathology and show both active and inactive lesions.[37] Modifications of T2-weighted scans can provide additional information. Fluid-attenuated inversion recovery (FLAIR) sequences, for example, can visualize 2 to 3 times the number of lesions seen on conventional T2-weighted imaging.[47]

Hypointense lesions on T1-weighted images are also called "black holes." Persistent T1 lesions indicate axonal loss, gliosis, loss of intracellular matrix, and demyelination; these lesions are thought to be markers for areas of more destructive focal CNS damage in MS patients.[48-50] T1 hypointense lesions are thought to have a greater correlation with the clinical features of MS than T2 lesions[48]; however, more studies are needed to explore this relationship.

Brain atrophy is the best MRI predictor of clinical status. In fact, the degree and rate of brain atrophy correlate with physical disability, quality of life, depression, and cognitive dysfunction.[47,51-61] Therefore, the measurement of brain atrophy has become increasingly important. Several measures can be used to quantify brain atrophy, including whole-brain and regional measures.[61-63] These techniques are still not ready for general clinical use and remain research tools. However, visual inspection of MRI images alone can provide a reasonable sense of the degree of atrophy and comparisons can be roughly made between scans at different times.

A correlation has been observed between clinical status of patients with MS and spinal cord lesions and atrophy.[64,65] These findings have increased the role of spinal cord MRI in the management of MS.[66-70] Spinal cord MRI scans reveal T2 lesions in approximately 50% to 90% of patients with MS.[31] Spinal cord scans can provide additional information when brain scans and clinical status are equivocal and can correlate spinal symptoms (cervical and thoracic). The frequency at which spinal cord MRI should be performed has not been fully determined but is advisable for tracking lesion load or atrophy.

Interestingly, 5 to 10 times more lesions occur on MRI than are manifested clinically.[71-75] Possible explanations for this discrepancy include inattention to cognitive aspects of the disease, lesions located in noneloquent areas of the brain, lack of histopathologic specificity, absence of spinal cord involvement, underestimation of the damage to normal-appearing white and gray matter, and masking effects of brain adaptation.[76] Recent improvements in MRI measures and techniques have increased their predictive value and improved their correlation with clinical status.[31]

MRI findings are needed to support the diagnosis of MS and are useful in evaluating patients with MS for other pathology. The appearance of Gd+ lesions in the appropriate clinical circumstances is particularly helpful in supporting the diagnosis of an inflammatory process. Furthermore, baseline MRI findings are helpful in determining patient prognosis. Therefore, Gd+ scans are recommended at diagnosis because Gd+ lesions are an indicator of active disease and have predictive value regarding the short-term course of MS[77-79] In patients with a CIS, MRI will support a diagnosis of MS if there are a significant number of lesions.[4] In addition, the longitudinal management of MS is increasingly utilizing MRI-based assessments.

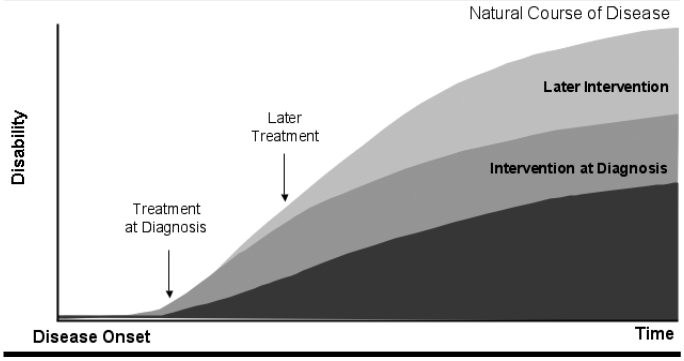
Effect of Early Treatment on Multiple Sclerosis

The presence of MS lesions in the brain or spinal cord as detected by MRI indicates that the disease is active in the nervous system. If treatment is delayed until MS manifests clinically, irreversible damage may occur. Subclinical disease activity and axonal loss occur early in the disease process; hence, MS should be treated as early as possible. The earliest stage that patients can be diagnosed and treated is after a first clinical demyelinating event. A number of trials have studied the effects of early treatment in patients with suspected MS.[80-82] Data from these trials reveal important clinical and MRI benefits in patients with syndromes that are suggestive of early disease who are treated promptly.

During the earliest randomized, placebo-controlled trial (the Controlled High Risk Subjects Avonex Multiple Sclerosis Prevention Study [CHAMPS]), patients with CISs were treated with IM IFNβ-1a to determine whether the time to the development of CDMS could be prolonged.[80] CISs were defined as those that involved the optic nerve (unilateral optic neuritis), spinal cord (incomplete transverse myelitis), or brainstem or cerebellum (brainstem or cerebellar syndrome).[80] Patients also must have had evidence of demyelination confirmed by MRI.[80] Results from this study showed that early treatment delayed or prevented CDMS and reduced the frequency of new lesions that would have allowed the diagnosis of definite MS by McDonald criteria.[80] The probability of developing CDMS was 44% lower in patients who received IM IFNβ-1a than in those who received placebo.[80] Furthermore, changes in lesion volume were significantly different between groups, and, at 18 months, there were 58% fewer new or enlarging lesions and 71% fewer Gd+ lesions in patients who received treatment than in those who received placebo.[80]

Results from a subsequent study (Early Treatment of Multiple Sclerosis [ETOMS]) were consistent with the findings of the CHAMPS trial.[81] During ETOMS, the effects of SC IFNβ-1a were studied in patients who had unifocal or multifocal neurologic syndromes and ≥4 T2 lesions (or 3 white-matter lesions if 1 lesion was infratentorial or Gd+).[81] Over 2 years, 24% fewer patients who

FIGURE 3 Current Understanding of Multiple Sclerosis Treatment Effects



received treatment developed CDMS than those who received placebo. Annual relapse rates were also lessened in the active treatment compared with the placebo group.[81] Moreover, MRI end points, including number and volume of T2 lesions, were significantly better in the treatment group than in the placebo group.[81]

The use of IM IFNβ-1a may be even more beneficial in patients at highest risk for MS.[82] A subgroup of patients from the CHAMPS trial was analyzed to study the effects of IM IFNβ-1a in patients with ≥9 T2 lesions and ≥1 Gd+ lesion on baseline MRI scans, findings that are highly predictive of the development of CDMS.[80,82] Of the total CHAMPS population, nearly one quarter met the criteria for the subanalysis (IFNβ-1b group, n = 51; placebo group, n = 40).[82] CDMS was identified in half of patients in the placebo group and in approximately one fifth of patients in the treatment group at 2 years.[82] This effect was maintained at 3 years because nearly one quarter of patients in the treatment group developed CDMS as compared with more than half in the placebo group.[82] The risk of developing CDMS was reduced by 66% at year 3 and by 63% at year 2.[82] IM IFNβ-1a is approved in the United States and Europe for use in patients who have a CIS associated with MRI scan changes consistent with an inflammatory-demyelinating process.

It is essential to initiate treatment as early as possible in patients who are eligible to receive IMAs. Study findings reveal that compared with patients who begin treatment early, patients who begin treatment later do not reap the same benefits (i.e., what was lost cannot be regained). Comparing parallel groups from the PRISMS-4 study demonstrates the benefits of early treatment. Crossover groups in PRISMS-4 received placebo for 2 years followed by treatment with 22-mcg or 44-mcg doses of SC IFNβ-1a for an additional 2 years. Other groups received 22-mcg or 44-mcg doses of SC IFNβ-1a continuously for 4 years. After 4 years, the crossover groups had greater increases in EDSS, and disease burden was progressively higher than that in groups who received continuous treatment.[14]

PRISMS-4's results are further supported by those of the CHAMPIONS study, an extension of the CHAMPS trial.[83] In CHAMPS, patients who experienced a first clinical demyelinating event immediately began treatment with IM IFNβ-1a or had treatment delayed for a median of 29.9 months (placebo group). In CHAMPIONS, all patients were offered IM IFNβ-1a and followed for up to 5 years. The rate ratio for the development of CDMS over 5 years was reduced by 35% in the group of patients who received immediate treatment. Relapse rates and MRI results also significantly favored immediate treatment. Based on these findings, it is apparent that early treatment initiation can reduce disease activity and can slow the progression of disability (Figure 3).

Identifying Patients at High Risk for Multiple Sclerosis

One of the most important questions is how to identify patients at risk for MS who should be referred to a neurologist to reap the benefits of IMA treatment. A key reason to refer patients to a neurologist is the sudden appearance of a focal neurologic event such as paresthesias, numbness, visual changes, or aphasia. The most important determinant of high risk for the development of CDMS is the confirmation of a first, well-defined neurologic event that is consistent with demyelination associated with MRI scan abnormalities. These types of events involve the optic nerve (unilateral optic neuritis), spinal cord (incomplete transverse myelitis), or brainstem or cerebellum (brainstem or cerebellum syndrome).[80] MRI findings should reveal lesions in the brain that are ≥3 mm in diameter, at least one of which is ovoid or periventricular.

Patients with a CIS who have ≥1 lesion on MRI are at a significantly higher risk for the development of CDMS.[84] In the Optic Neuritis Treatment Trial, the 10-year risk of developing MS after an initial episode of optic neuritis was 38%.[84] However, in the subgroup of patients with ≥1 lesion, the risk increased to 56%, while the risk in those with no lesions at baseline was 22%. Over 2 years, 86% of untreated patients with ≥1 new or enlarging lesion went on to develop MS compared with 38% of untreated patients without lesions.[84]

MS lesions typically are >5 mm in diameter and ovoid or oval. These lesions are usually in the periventricular, perivenular (Dawson's fingers), juxtacortical, and infratentorial regions. MS lesions are visualized in the corpus callosum and spinal cord. The morphology of Gd+ lesions may be ringlike or homogeneous. The duration of ringlike lesions is longer than that of homogeneously enhancing lesions, and ringlike lesions are thought to be related to aggressive disease activity and a higher level of tissue damage.[85-90] T1 black holes, a marker for considerable matrix destruction and axonal loss, are found most often in patients who have SPMS and higher EDSS scores.[76]

A number of diseases can cause MRI-signal hyperintensities of the white matter.[91] However, the signal abnormality patterns associated with these disorders usually differ from those associated with MS such that the potential for misdiagnosis is low. In the diagnosis of MS, the physician should evaluate MRI scans to rule

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