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Imaging of Multiple Sclerosis: Role in Neurotherapeutics

Rohit Bakshi,* Alireza Minagar,† Zeenat Jaisani,* and Jerry S. Wolinsky‡

**Departments of Neurology and Radiology, Partners MS Center, Center for Neurological Imaging, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115; †Department of Neurology, Louisiana State University Health Sciences Center, Shreveport, Louisiana 71130; and ‡Department of Neurology, University of Texas Health Science Center at Houston, Houston, Texas 77030*

Summary: Magnetic resonance imaging (MRI) plays an ever-expanding role in the evaluation of multiple sclerosis (MS). This includes its sensitivity for the diagnosis of the disease and its role in identifying patients at high risk for conversion to MS after a first presentation with selected clinically isolated syndromes. In addition, MRI is a key tool in providing primary therapeutic outcome measures for phase I/II trials and secondary outcome measures in phase III trials. The utility of MRI stems from its sensitivity to longitudinal changes including those in overt lesions and, with advanced MRI techniques, in areas affected by diffuse occult disease (the so-called normal-appearing brain tissue). However, all current MRI methodology suffers from limited specificity for the underlying histopathology. Conventional MRI techniques, including lesion detection and measurement of atrophy from T1- or T2-weighted images, have been the mainstay for monitoring disease activity in clinical trials, in which the use of gadolinium with T1-weighted images adds additional sensitivity and specificity for areas of acute inflammation. Advanced imaging methods including magnetization transfer, fluid attenuated inversion recovery, diffusion, magnetic resonance spectroscopy, functional MRI, and nuclear imaging techniques have added to our understanding of the pathogenesis of MS and may provide methods to monitor therapies more sensitively in the future. However, these advanced methods are limited by their cost, availability, complexity, and lack of validation. In this article, we review the role of conventional and advanced imaging techniques with an emphasis on neurotherapeutics. **Key Words:** Multiple sclerosis, magnetic resonance imaging, brain atrophy, diffusion imaging, magnetization transfer, spectroscopy, functional imaging.

INTRODUCTION

Since introduced into clinical medicine, magnetic resonance imaging (MRI) has played expanding roles in the evaluation of multiple sclerosis (MS). These include its essential place in the initial evaluation of patients suspected of having the disease to secure and sometimes reject the diagnosis of MS,[1,2] as a prognostic tool at first presentation of symptoms highly suspicious of acute inflammatory CNS demyelination,[3] in providing primary outcome measures in phase I/II trials, and as a source of critical supportive outcome measures in phase III trials of MS therapeutics. The utility of MRI in MS in large measure stems from its extreme sensitivity to changes in regional proton relaxation times that occur with processes that alter tissue water content and constraints on hydrogen molecule motion, particularly those associated with tissue bound and free water molecules. However, all current MRI methodology remains insensitive to the underlying disease processes that give rise to these alterations. Consequently, the specificity of altered MRI signals is limited, and overinterpretation of MRI to imply specific histopathologic tissue alterations abounds. Most patterns and distributions of lesions found on conventional and even advanced MRI are neither disease-specific nor reflect a specific histopathology. As a result, a broad differential diagnosis usually remains when MRI is viewed in isolation from the clinical history, physical and neurologic findings and laboratory investigations. Nevertheless, understanding the sequence of events that correlate with conventional MRI-visible lesion formation, and the most characteristic topography of lesions in the cerebrum, brainstem, and spinal cord help to determine the likelihood that a patient has MS and provide reasonable markers by which to infer therapeutic effects on the evolving underlying disease process.

Current conventional MRI consists of several series of image acquisitions based on generally available pulse sequences developed to provide optimal tissue contrast

Address correspondence and reprint requests to Rohit Bakshi, M.D., FAAN Brigham & Women's Hospital Harvard Medical School, 77 Avenue Louis Pasteur, HIM 730, Boston, MA 02115. E-mail: rbakshi@bwh.harvard.edu

for routine clinical diagnostic work. In general, these have also been the mainstay for addressing disease activity in clinical trials. A standardized approach to imaging MS patients developed by the Consortium of MS Centers (http://www.mscare.org/pdf/MRIProtocol2003.pdf) includes sagittal fluid attenuated inversion recovery (FLAIR), axial dual echo proton density and T2 weighted (TE1 usually <30 ms and TE2 $>$ 80 ms), axial FLAIR and an axial gadolinium chelate (Gd) enhanced T1-weighted image series. The post Gd T1 series is especially important in suspected MS if suspicious lesions are seen on T2-weighted or FLAIR images. Advanced MRI including quantification of magnetization transfer ratio (MTR), dual inversion recovery imaging, diffusion tensor imaging, single voxel, two-dimensional (2D) and three-dimensional (3D) chemical shift imaging, and unlocalized spectroscopy signal from whole brain magnetic resonance spectroscopy (MRS), among other methods have enriched our understanding of conventional MRI and have added insight into our understanding of the pathogenesis of MS.[4] However, these more advanced methods are not generally available, nor necessary for diagnosis and follow-up evaluations, although they may provide additional outcomes through which to determine drug efficacy.

In this article, we will review individual MRI-defined changes detected by a broad variety of conventional and advanced imaging approaches. We will emphasize their specific utility in understanding the pathogenesis of the disease and serving as biomarkers for evaluating treatment effects, including therapeutic effects on tissue preservation or repair within the otherwise relatively inaccessible CNS. To lay the groundwork for this review, it is important to first understand individual lesion development and maturation as currently viewed using conventional and advanced imaging.

LESION EVOLUTION

On conventional MRI, new lesions arising in previously normal appearing white matter (NAWM) are nearly always announced by a nodular area of Gd-enhancement on T1-weighted images (FIG. 1)[5] This is nearly invariably associated with a hyperintense lesion in the same location on T2-weighted images (FIG. 1).[6] Nearly 65% of the larger enhancements correspond to hypointense lesions visualized on noncontrast T1-weighted images[7] (FIG. 2). Most enhancements fade and disappear over 4-6 weeks, and 50% of the hypointensities spontaneously resolve within 4 weeks. A similar proportion of those found at 1 month disappear over the next 4–5 months[8] Return to the T1-isointense state or mild T1 hypointensity may indicate extensive or partial remyelination.[9] The extent of the new T2-hyperintense lesion usually contracts and its intensity is reduced as edema resolves and some tissue repair occurs. However, most lesions, once evident on T2-weighted images rarely disappear unless they are located in the brainstem or spinal cord. Potentially more aggressive lesions show ring-like propagation of the enhancement over a few weeks or longer before the enhancement begins to fade, are associated with more complex appearances on T2-weighted images, a central spherical hypointensity on T1-weighted images, and persistence over time (FIG. 3). An incomplete ring of enhancement ("open ring sign"), open where the lesion abuts gray matter, is characteristic of MS (FIG. 2).[10] A complete ring may also be seen, particularly when the lesions are confined to the white matter (FIG. 3). Careful inspection of the areas surrounding some of the larger T1-hypointense lesion that contract over time shows this apparent repair to be at the expense of surrounding tissue loss. As the center of such lesions likely undergoes gliosis and contraction there is regional ventricular enlargement and cortical volume loss directed toward the lesion. Although the evolution of T1-hypointense lesions is intimately associated with enhancements, the relationship must be more complex. Enhancement frequency is age dependent, being less frequent among older (rather than younger) MS patients of all disease subtypes.[11,12] Yet, hypointense lesions are more common with longer disease duration and among the progressive disease subtypes. The divergent behavior of these seemingly inter-related MRI metrics might suggest that whereas some hypointense lesions result directly from new inflammatory events that are readily monitored by enhancements on MRI, other hypointense lesions may evolve differently.

Lesion evolution is more complex when monitored with advanced imaging. Newly enhanced lesions that form within previously conventional MRI-defined NAWM provide informative regions for retrospective scrutiny for change that antedates lesion evolution on conventional MRI. Retrospective analyses suggest that regional abnormalities in MTR develop in NAWM months before the enhancement is seen by conventional MRI.[13,14] Unfortunately, these changes have not been robust enough to use prospectively. Focal increases in choline and the appearance of signals on MR spectroscopic imaging (MRSI) consistent with alterations in lipids or other myelin associated macromolecules also precede lesion formation by several months,[15,16] to suggest that focal disruptions of tissue integrity anticipate enhancements. It remains unclear whether these changes reflect some primary intrinsic tissue process that eventually signals a secondary influx of inflammatory cells, or whether they reflect microscopic inflammatory change beyond the resolution of conventional imaging that must first build before a cascading inflammatory response is evident. In either case, with enhancement there is a dramatic fall in regional MTR, drop in N-acetylaspartate (NAA), increase in choline, the appearance of signals

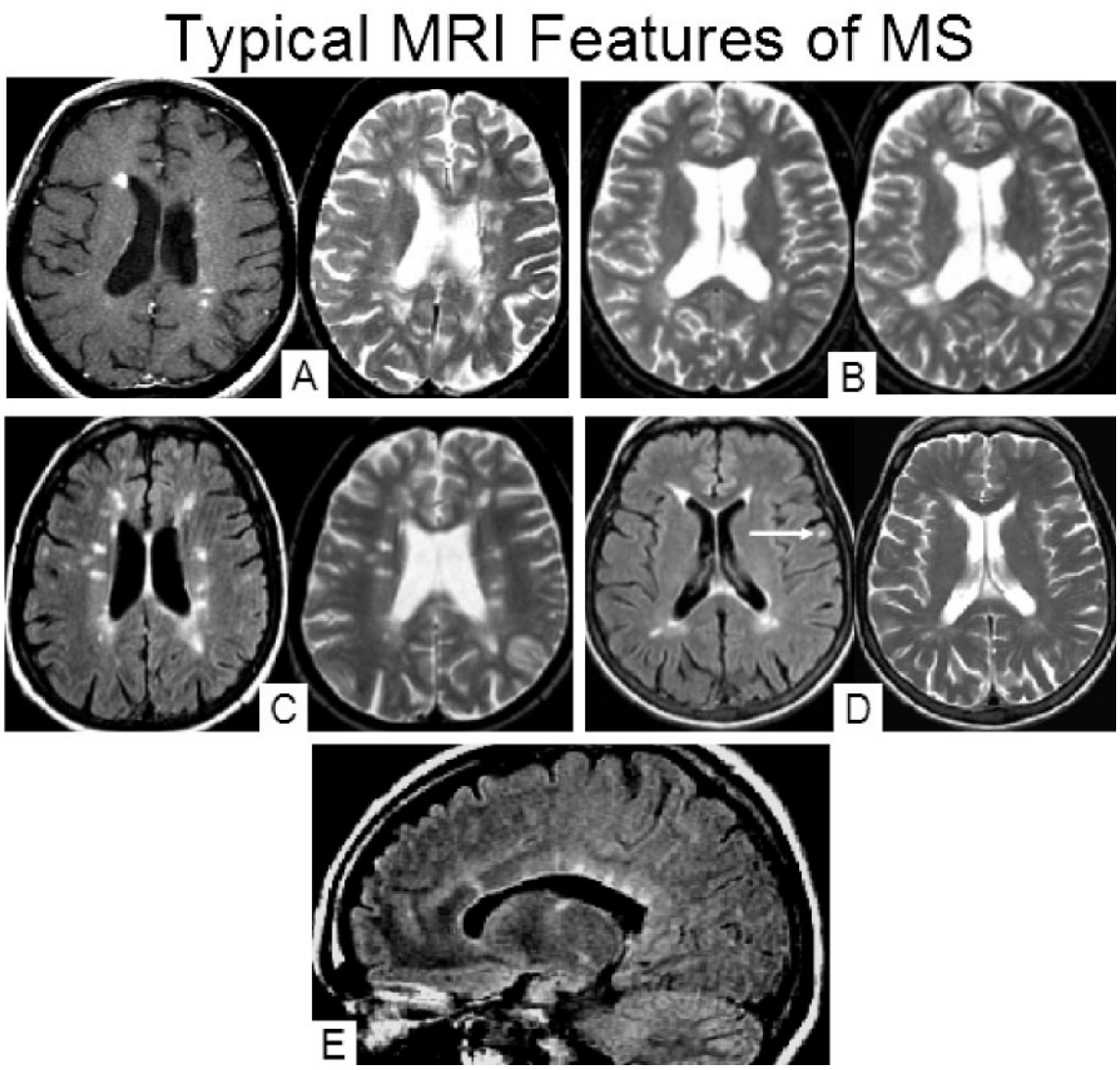

FIG. 1. Montage of five patients showing typical MRI features of MS. A: Post-contrast (left) and CSE T2-weighted (right) images are shown of a 51-year-old woman with RR MS. Note several enhancing foci in the periventricular region bilaterally. Lesions have a homogeneous appearance and show corresponding hyperintensity on the T2-weighted image. B: Baseline (left) and 5-year follow-up (right) CSE T2-weighted images of a 46-year-old woman with RR MS. EDSS score increased from 2.0 to 3.5 during this time. Note progressive number and total volume of T2-hyperintense lesions. C: FLAIR (left) and FSE T2-weighted (right) images of a 41-year-old woman with RR MS and EDSS score of 3 illustrates the superiority of FLAIR for the detection of periventricular lesions. Note the characteristic appearance of the lesions including an oval/ovoid morphology, size 5 mm or greater in diameter, and tendency to directly abut the ventricular margin. D: FLAIR (left) and FSE T2-weighted (right) images of a 51-year-old woman with RR MS and EDSS score of 4 shows the superiority of FLAIR for the detection of cortical/juxta-cortical lesions. Note the lesion in the left temporal lobe (arrow) seen by FLAIR but not on the T2-weighted image. E: Sagittal FLAIR of a 27-year-old woman with RR MS shows typical perivenular orientation of lesions. Note the lesions are perpendicular to the long axis of the lateral ventricles giving an appearance known as "Dawson's fingers."

from myelin breakdown products, and increases of myo-inositol, glutamate + glutamine (Glx) and lactate.[17] The biochemical changes are highly dynamic and the concentrations of various metabolites and MTR tend to recover toward their normal values with time. Some of the observed acute changes are in part explained by dilutional effects of acute vasogenic edema.[18] MTR values do not fully normalize, but a return toward normal is accompanied by partial or complete resolution of associated T1-hypointense lesions. Mildly T1-hypointense lesions that remain with intermediate MTR values correlate with histopathologic evidence of at least partial remyelination.[9] Persistent T1-hypointense lesions show diminished NAA indicative of irreversible axonal loss[19]; they may also show increased myo-inositol, possibly indicative of gliosis. Enhanced lesions generally have increased diffusion, decreased FA, and altered diffusion tensor values, and these alterations persist to a variable extent in those lesions that have the most severely altered tissue matrix.[20] The specialized anatomy of the brain results in

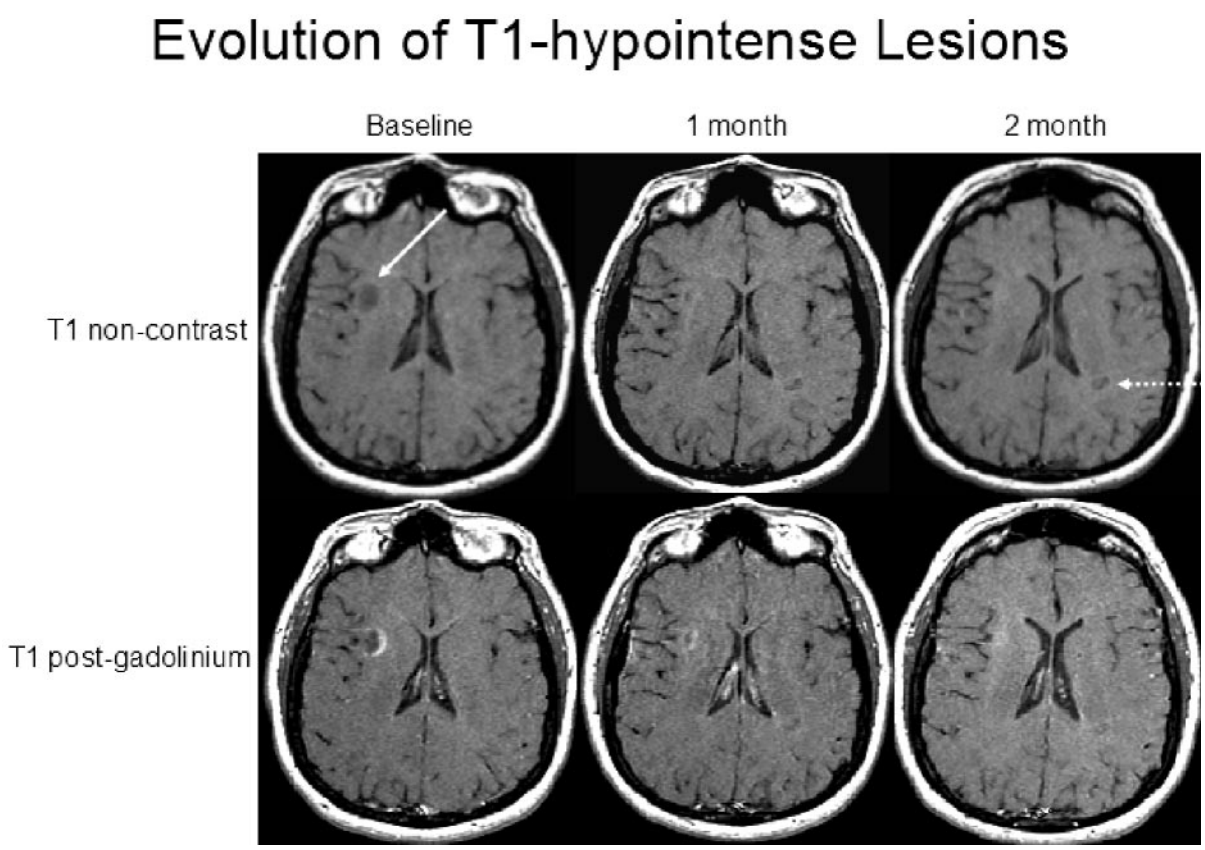

FIG. 2. Evolution of T1 hypointensities ("black holes"). A 48-year-old woman with RR MS received serial MRI during the pretreatment screening period of a clinical trial. Noncontrast (upper row) and post-contrast (lower row) images are shown. Scans were obtained at baseline, 1 month, and 2 months later. Note the ring-enhancing lesion appearing at baseline that has corresponding T1 hypointensity (solid arrow). The ring enhancement has an incomplete or open ring that is typical of MS.[10] The T1 hypointensity resolves 2 months later. A second T1 hypointensity develops over 2 months (broken arrow).

alterations at a distance related to disruption along connected pathways that traverse focal lesions, and Wallerian degeneration along highly organized pathways may be reflected in altered diffusion tensor eigen values.[21] These distributed effects may help to explain some of the quantitative change that is rather consistently found in conventional MRI-defined NAWM.

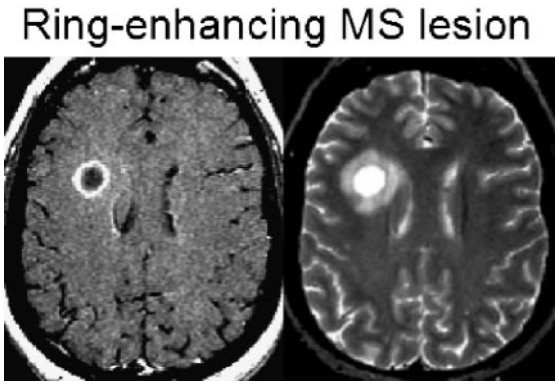

FIG. 3. T1-weighted post contrast (left) and CSE T2-weighted (right) images of a 48-year-old woman with RR MS show a ring enhancing lesion and corresponding complex appearance on the T2 image.

MRSI defines dynamic metabolite changes compatible with alterations in mobile lipids in cortical gray matter.[22] These observations are consistent with the known occurrence of cortical plaques.[23] However, intracortical and subpial lesions have yet to be adequately resolved by conventional MRI at up to 3 Tesla, or with other available advanced methods. Recently, postmortem MRI at 8 Tesla has identified some purely intracortical lesions (K. Rammohan, personal communication).

With this overview of lesion development and evolution as defined by MRI, we can turn to a consideration of the various conventional and advanced imaging approaches applied to MS, with particular attention to their current use or potential use in the assessment of MS disease modifying therapeutics.

Hyperintense lesions on T2-weighted images

Technical aspects. The intensity of tissue signals is influenced by proton density and the rate at which nuclear MR signals decay in the static magnetic field of the scanner following application of a radio-frequency excitation pulse as characterized by T1 (longitudinal relaxation time) and T2 (transverse relaxation time). These three parameters (proton density, T1, and T2 relaxation

times) determine the MRI appearance; their relative influences are affected by scanning parameter changes. Proton density and T2-weighted images are generated with long repetition time (TR). At relatively short echo time (TE), the image appearance is mainly determined by proton density, whereas at relatively long TE, the T2 effect is increased. FLAIR uses an inversion pulse followed by a variable signal recovery time to maximize the contrast between tissues with different T1 values. Most clinically used FLAIR inversion pulses are designed to null the signal from CSF at a long TE to provide a high degree of T2 weighting to increase lesion conspicuity, particularly for those lesions that abut CSF pathways.

Neuropathology. The lesions of MS show considerable histopathologic heterogeneity, in part related to evolution of individual lesions over time and (possibly) to fundamental differences in patient-specific pathogenesis of lesions.[24] However, with the possible exception of large ring-enhanced lesions, lesion appearance and patterns seen by conventional MRI have thus far failed to consistently distinguish among these histopathologic subtypes. The extent of MRI-defined T2 hyperintense lesions seen on postmortem imaging clearly can approximate the extent of lesions found on direct histopathologic tissue examination.[25,26] Postmortem MRI allows for the detection of regions of microscopic inflammation or active demyelination otherwise missed by visual inspection of the tissue.[27,28] Moreover, there are considerable MRI-defined lesion abnormalities that exceed the sensitivity of histopathologically defined plaque burden.[29] These discrepancies are readily explained by the basis of the signal generated by T2-weighted image as described above, which is highly sensitive to the tissue mobility of protons, but influenced to a lesser extent by the underlying processes that give rise to altered tissue water content and proton mobility. Thus, hyperintensities on T2-weighted images in patients with MS are nonspecific for the relative degree of underlying inflammation, edema, demyelination, axonal damage, Wallerian degeneration, and gliosis.

Clinical correlation. Both cross-sectional and short-term longitudinal correlations between T2-hyperintense disease burden (T2 BOD) and clinical impairment are generally poor.[30–32] The possible reasons for this are numerous and readily attributed to the lack of pathologic specificity for the extent of tissue destruction and the well known limitations of existent clinical rating systems, including the benchmark Expanded Disability Status Scale (EDSS).[32] One of the main reasons for the lack of correlation is that MRI often shows hemispheric involvement in areas that are clinically silent. However, the biologic burden of the disease is probably reflected better by the MRI findings. Despite these limitations, more focused attention may provide some hope that better correlations may be possible if restricted over appropriate phases of the disease. T2 BOD is quite variable among patients when evaluated at the earliest clinically recognized stage of the disease, with a clinically isolated demyelinating syndrome (CIS) highly suggestive of the type seen in relapsing-remitting (RR) MS patients. Even so, it is at this stage that differences in T2 BOD have strong predictive value for distinguishing the subsequent short-term clinical course. The best available data suggest that about a third of patients presenting with CIS will have negative cerebral MRI and about 40% will have fewer than two lesions. In the Early Treatment of Multiple Sclerosis (ETOMS) study of CIS,[33] independent of treatment, conversion to clinical definite MS (CDMS) occurred in 41% of patients with at least one Gd-enhancing lesion or 9 T2-hyperintense lesions, *versus* 11% of those without either. The best data on follow-up at 5 or more years after presentation come from subjects gathered nearly two decades ago.[34] A number of reports have concentrated on similar patients followed for shorter intervals. CIS patients with normal cerebral MRI at presentation have only a 5% risk of another clinical attack (progressing to CDMS) in the next 1-5 years; those with cerebral lesions have a considerably higher risk. The risk remains below 50% until the cerebral T2 BOD exceeds 1.2 ml; corresponding to about six lesions each of about 5 mm in diameter at 5-mm slice thickness.[35] The risk of progression to CDMS within 10 years with a negative MRI at presentation remained low at 11%, but 2 or more lesions conferred nearly a 90% risk of conversion.[36] Of those with an abnormal MRI scan, 31% developed disability equivalent to an EDSS score of at least 6.0 within 14 years, and the EDSS score at 14 years correlated moderately with the increase in lesion volume in the initial first 5 years ($r = 0.61$).

International panel MRI criteria for dissemination in time require one or more new Gd-enhanced lesions at least 3 months after the initial clinical event or a new T2-hyperintense lesion identified at least 3 months after a baseline set of images obtained after the presenting clinical event had stabilized or resolved.[1] Admittedly, these time intervals are somewhat arbitrary. They were originally developed because most new Gd-enhanced lesions will no longer enhance after 6–8 weeks, and that new lesions continue to appear for some days to weeks in association with a single clinical attack.[37] Subsequent data have generally supported the utility of follow-up MRI at 3 months to refine the predictive value of early MRI for conversion to CDMS.[38,39]

Two clinical trials of different preparations of interferon β (IFNB)-1a indirectly address the sensitivity of the international panel MRI criteria for dissemination in space in the early diagnosis of MS. The Controlled High Risk Avonex Multiple Sclerosis trial studied patients with monosymptomatic CIS.[40] Entry criteria were restricted to subjects with at least two clinically silent

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