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Perspectives on Multiple Sclerosis

Robert I. Grossman and Joseph C. McGowan

There is no question that MR imaging is presently the best method for imaging multiple sclerosis (MS); yet, even today, MS remains a clinical diagnosis, with the relationship between clinical course and MR findings still problematic (1, 2). MR imaging appears to be the most important test performed in the diagnostic workup of MS; it has much greater impact than CSF analysis and evoked potential testing (3). It is far more sensitive than a clinical examination in revealing disease activity, as MR abnormalities are found five to 10 times more often than clinical abnormalities detected by standard neurologic examination (4–8). In this review, we briefly summarize the clinical and pathologic hallmarks of MS and discuss the MR findings in this disease, examining the strengths and weakness of conventional imaging protocols in relation to their clinical utility. Additionally, we consider how newer imaging techniques may add to our understanding of this most interesting and challenging disorder.

Clinical Diagnosis

MS is primarily a disease of young adults, with peak age of onset at about 30 years; however, it does occur in children and adolescents (3% to 5%) and in persons over the age of 50 years (9%) (9–15). As noted, the diagnosis of MS is presently based on clinical and paraclinical criteria alone. These parameters were initially proposed to select patients for treatment trials (16, 17). The criteria designed by Poser et al (17) in 1983 establish two major groups: definite MS and probable MS, each with two subgroups, clinical and laboratory supported. Clinically definite MS is defined by the occurrence of two attacks and clinical evidence of two separate lesions, or by two attacks with clinical evidence of one lesion and paraclinical evidence of another, separate lesion. Clinically probable MS is defined by the occurrence of two attacks and clinical evidence of one lesion, one attack and clinical evidence of two separate lesions, or one attack and clinical evidence of one lesion and paraclinical evidence of another, separate lesion. Paraclinical evidence includes CSF, CT, or MR imaging data. MR imaging is by far the best paraclinical test, depicting abnormalities in 95% of patients with clinically definite MS (18). This number probably understates the

sensitivity of MR imaging, as the study does not include state-of-the-art spinal cord imaging. Combined brain and spinal cord imaging can increase the sensitivity to almost 100% (19).

MS is a disease characterized by a variety of clinical courses. Terminology regarding clinical classification can be confusing and even contradictory (20). Relapsing-remitting MS is the most common course of the disease, initially occurring in up to 85% of patients. Exacerbations are, at the beginning, followed by remissions, but over a period of years, additional exacerbations result in incomplete recovery. Within 10 years, 50% (and within 25 years, 90%) of these patients enter a progressive phase, termed secondary-progressive (or relapsing-progressive) MS, in which deficits are progressive without much remission in the disease process (21). Less commonly, MS is progressive from the start. This classification was first distinguished in 1952 and has been termed primary-progressive (or chronic-progressive) MS (22). These patients (5% to 10% of the MS population) may present at a later age, with progressive neurologic findings, including paraparesis, hemiparesis, brain stem syndromes, or visual loss. Patients in this group typically have a more severe disability; they may have occasional plateaus and temporary improvements, but they do not have distinct relapses. Patients with primary-progressive disease tend to have less lesion load, fewer new lesions on monthly T2-weighted MR images, and fewer enhancing lesions as compared with patients with secondary-progressive disease, despite progressively declining neurologic status (23, 24). Progressive-relapsing MS, a rare clinical course, is defined as progressive disease with clear acute relapses, with or without full recovery, and with the periods between relapses characterized by continuing disease progression (2). Some investigators lump all these groups together into a category called chronic-progressive MS; however, Lublin et al (2) believe the term should be abandoned because of its vague nature and the variable clinical courses and corresponding MR patterns (2, 25). Benign MS describes cases in which, after initial clinical symptomatology, no clinical progression is seen for a period of approximately 10 to 15 years. Conversely, a rapidly progressive course leading to significant disability or death shortly after disease onset has been termed malignant MS (2).

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In addition to these well-described clinical patterns, there is the dilemma of the monosymptomatic patient. This presentation consists of a single episode of neurologic deficit, such as optic neuritis, transverse myelitis, or brain stem syndrome. Seventy-seven percent of patients presenting with an isolated brain stem syndrome have been reported to have asymptomatic brain lesions (26). Miller et al (27) reported that progression to MS occurs in about 57% of patients with isolated brain stem syndrome and in 42% of patients with spinal cord syndrome. Jacobs et al (28) found that 50% of patients with optic neuritis had lesions in their brain 3 weeks to 7 years after their attack. The risk of MS developing after optic neuritis has been estimated to be between a few percent to 75% or more. The presence and the number of asymptomatic lesions on MR images markedly increase the risk of progression to MS, not only in patients with optic neuritis but also in those with isolated brain stem or spinal cord lesions (29–34). Patients with isolated acute syndromes and no asymptomatic brain lesions are at lower risk of progressing to MS (27). MR imaging thus possesses good predictive power in patients who have clinically isolated syndromes suggestive of MS (32, 35).

Clinical evaluation of MS most commonly relies on the Expanded Disability Status Scale (EDSS) devised by Kurtzke in 1955 (and improved in 1983) to evaluate isoniazid (36, 37). It is an ordinal system from 0 to 10, with incremental 0.5-unit steps (except at 1.0), designed to categorize deterioration in the pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, and cerebral (mental) functions, as well as to characterize any other neurologic finding attributed to MS. The test has been criticized for being insensitive, for being heavily weighted to motor disability, and for having substantial intra- and interrater variability (38–40). Controversy regarding clinical outcomes measures also pertains to the evaluation of neuropsychological dysfunction, which until recently was not appreciated as an important cause of disability and usually not examined in a sensitive manner, and to fatigue, which is not significantly linked to EDSS score.

From this brief discussion it is obvious why MR imaging is attractive. It is independent, objective, and can depict the entire nervous system. Nevertheless, attempts to associate T2-weighted imaging findings with EDSS scores have been weak or nonexistent (23, 41–43). The challenge is to develop better, more specific MR techniques that produce clearly significant correlations with clinical measures and that ultimately lead to predictions of outcome. If newer techniques, such as magnetization transfer, MR spectroscopy, and so on, prove to be robust, they will be implemented as more precise markers of disease progression as well as be used in treatment trials.

Pathologic Characteristics

The pathologic characteristics of MS are manifested by a chronic inflammatory process resulting in

myelin loss. Histopathologic hallmarks of the disease include multifocal lesions showing inflammation, lymphocytes and macrophages, demyelination, gliosis, attempts at remyelination, and relative sparing of axons (44). However, the sparing of axons has recently been challenged in a provocative article by Trapp et al (45), who found transected axons to be common and hypothesized that these could be responsible for neurologic impairment. Active histologic lesions show loss of myelin, infiltration with lipid-laden macrophages (Gitter cells), perivascular inflammatory cuffing with T- and B-cell lymphocytes, and plasma cells associated with perivascular demyelination. Reactive astrocytes, containing nuclear atypia, are observed within and on the border of plaques. Depletion of oligodendroglia has been seen in some patients early in their disease course, whereas in other cases there appears to be preservation of the oligodendroglia, suggesting that the pathogenesis of demyelination in MS may vary among different patients and may change over time within the same patient (46). Attempts by the oligodendroglia at remyelination have been observed in both acute and chronic plaques (47–49). The extent of this process can vary from a narrow rim around silent lesions to a zone of macroscopic satellites contiguous with demyelinated lesions, the latter being known as shadow plaques (50). What is not understood is the relationship, if any, between attempts at remyelination and clinical recovery. Inactive plaques are hypocellular without perivascular inflammation. The borders of these lesions are discrete, gliosis is present, and there may be axonal loss (45).

The histopathologic correlates of the various clinical courses are still not fully understood. Excellent correspondence has been reported between contrast enhancement and macrophage infiltration, but the association is weaker with perivascular lymphocyte infiltration (51). Blood-brain barrier (BBB) disruption and demyelination appear to be linked, but how strongly remains open to debate. In general, the longer the course of the disease, the greater the accumulation of MS lesions, which can average between 8% and 10% a year from baseline in relapsing-remitting MS (42, 43).

Brain Disease

The MR findings in MS include high-intensity abnormalities on T2-weighted images, with diameters ranging on the order of several millimeters to several centimeters. Lesions can occur throughout the brain and spinal cord. Histologically active lesions may have any of several MR characteristics (51). In one postmortem study, 5% of plaques were confirmed to occur in the cortex, although this is probably a low estimate (52). In a recent study, Catalaa et al (53), who used a semiautomated computer program to detect individual lesions, found that approximately 6% of lesions were cortical and 5% were in the deep gray matter. Involvement of U fibers has also recently been reported and may contribute to cognitive impairment (54). Lesions may display mass effect that

can mimic a tumor, and they have been associated with seizures (tumofactive MS) (55–58). There have also been rare reports of hemorrhage into demyelinating lesions (59, 60). The shape of these hyperintensities may be variable; however, ovoid lesions are believed to be more specific for MS, their morphology has been attributed to inflammatory changes around the long axis of a medullary vein (Dawson's fingers) (61). It has been suggested that high-intensity lesions at the callosal-septal interface, best seen on sagittal MR images, have a 93% sensitivity and a 98% specificity in differentiating MS lesions from vascular disease (62).

Hypointensity of T2-weighted images in the thalamus, basal ganglia, cortex, and subcortical white matter has been described in patients with MS and is thought to represent nonheme iron deposition as part of a generalized degenerative process (63, 64). Peripheral high intensity on T1-weighted images has been reported and correlated with marked macrophage infiltration (51, 65–67).

Atrophy has been observed in the spinal cord, corpus callosum, cerebellum, and throughout the brain in patients with MS (68–70). In a recent study, progressive cerebral atrophy was identified in cases of MS without increasing disability; additionally, correlation was found between brain atrophy and worsening disability in a cohort of patients studied over an 18-month period (71).

N-acetyl aspartate (NAA), a neuronal marker, is commonly decreased within MS lesions (72–81). It has also been noted that NAA is decreased in regions of brains with probable microscopic disease, suggesting the occurrence of diffuse axonal volume loss in all regions of the brain, with the extent of NAA decrease possibly related to clinical classification (77, 82–84). It is possible that NAA measurements may be a more specific measure of disease than lesion load, particularly in secondary-progressive MS (82, 85). Brain volume loss and NAA measurements in MS are becoming important parameters, perhaps more critical than T2 lesion load, for determining disease categorization, progress, and therapeutic efficacy.

Hypointensity was reported on T1-weighted images by Uhlenbrock et al (86), who associated these abnormalities with scars as opposed to inflammation and found them to be more common in MS than in subcortical arteriosclerotic encephalopathy. A later study of 35 patients with confirmed MS by Poser's criteria found hypointense lesions on 91% of T1-weighted imaging examinations. These authors concluded that many lesions visible on T2-weighted images were visible on T1-weighted images as regions of low signal intensity with a more or less distinct boundary (86). Results in a study of biopsy'autopsy samples indicated that T1 hypointensity could be observed in both active and inactive lesions, where active lesions were defined as those showing at least moderate macrophage infiltration and mild perivascular inflammation on histopathologic examination (51). Subsequently, it was reported that in MS lesions identified as areas of hyperintensity on T2-weighted images,

intensity on corresponding T1-weighted images was correlated ($r = .6; P < .01$) with magnetization transfer ratio, suggesting that T1 hypointensity might reflect in some way the grade of lesion (87). The authors speculated that hypointense plaques, including the central portion of a ring-enhancing lesion and the entire volume of some nonenhancing lesions, represented the most demyelinated region of MS lesions. Van Walderveen et al (88) reported a correlation between degree of disability and T1-hypointense lesion volume in 19 patients, with disease described as ranging from clinically probable MS to clinically definite MS, which was significantly stronger than that between disability and lesion volume on T2-weighted images. These authors suggested that T1 lesions were more relevant to disability than were T2 lesions. The lesions were subsequently dubbed black holes and were studied more extensively in an investigation of disease progression. Baseline disability was found to be related to T1 lesion load, and in patients with secondary-progressive MS, the rate of accumulation of black holes was significantly related to the rate of disease progression (89).

Still to be determined is whether apparent differences in information obtained with T2- and T1-weighted imaging represent real variation in sensitivity or specificity of the MR imaging examination in MS. Clearly, fewer lesions are observed in most patients by using standard T1-weighting parameters, which have been developed and optimized primarily for delineation of morphology rather than for detection of disease. Issues to be addressed through future study may include the optimization of T1-weighted imaging for the purpose of disability classification and the underlying physical basis for the presence of a lesion on a T2-weighted image but not on the corresponding T1-weighted image.

Differential Diagnosis

Many other lesions exhibit an appearance similar to that of MS on conventional MR images. Most commonly, the challenge is to distinguish MS from the high-intensity abnormalities associated with vascular disease and hypertension. Usually, these lesions are seen among older patients. The broad differential diagnosis of multiple high-intensity areas in the white matter includes tumor; inflammation (infectious and noninfectious origin); vascular diseases, including vasculitis, hypertension, and infarction; and demyelinating diseases. Specific pathogenetic entities and anatomic variants to consider include enlarged Virchow-Robin (perivascular) spaces (these usually follow CSF in intensity on all imaging sequences), migraine, hypertension, vascular disease (including vasculitis), acute disseminated encephalomyelitis, Lyme disease, chronic fatigue syndrome, aging, collagen vascular diseases, trauma, toxic exposure, sarcoid, Behcet disease, and HIV.

MR Imaging Criteria for the Diagnosis of MS

MR imaging criteria for the diagnosis of MS appear predominantly in the neurologic literature and are typically based solely on conventional proton density- and T2-weighted images. Paty et al (18) proposed that four or more lesions (Paty A criteria) or at least three lesions with one lesion bordering the lateral ventricles (Paty B criteria) are strongly suggestive of MS. The criteria suggested by Fazekas et al (90) include three or more lesions with the presence of at least two of the following characteristics: size greater than 5 mm, periventricular, and infratentorial. Although lesions in the centrum semiovale tend to occur with aging and other processes, periventricular lesions do appear to be more specific for MS. Lesions around the temporal horn and fourth ventricle as well as in the cerebellar peduncle and midbrain also appear more specific for MS but have a low rate of occurrence. Yetkin et al (91) reported that 2% to 4% of healthy patients had high-intensity periventricular abnormalities that could not be distinguished from MS, while Barkhof et al (92) proposed that the presence of juxtacortical lesions in patients with monosymptomatic neurologic disease was a highly specific prognosticator of progression to MS.

A comparison of Fazekas and Paty criteria, referring to best-case scenarios, respectively, revealed higher specificity (96% versus 92%) and increased positive predictive value (65% versus 50%) but less sensitivity (81% versus 90%), with most false-positive findings occurring in patients over the age of 60 years (93). Another study by two experienced neuroradiologists, without using rigid criteria, designed to study specificity of MR imaging in the diagnosis of MS (true-negative results in proportion to all non-MS studies) reported results of between 95% and 99%, with improved specificity when age and sex were considered (91). Sensitivity in this study was 66% to 83%, depending on the control group used. There was a significant prevalence of high-intensity abnormalities in the brains of healthy persons, with this number varying depending on the particular report and the cohort's age (94, 95). In one study of healthy volunteers, white matter abnormalities were noted in 11% of subjects aged 0 to 39 years, in 31% aged 40 to 49 years, in 47% aged 50 to 59 years, in 60% aged 60 to 69 years, and in 83% of those 70 and older (96). Rudimentary MR imaging criteria may have a role in ranking differential diagnoses; however, with all the caveats related to high-intensity abnormalities, the use of MR imaging criteria alone is open to criticism and fraught with error.

Serial imaging can clearly aid in the diagnosis of MS, particularly in monosymptomatic patients. New lesions identified on MR images more than 1 month after initial presentation indicate clinically probable MS on the basis of Poser's criteria. The same may be said for enhancing lesions (see below), where new enhancement most likely indicates new or recurrent activity over time and is considered to be evidence of probable MS.

Contrast Enhancement in MS

Contrast material depicts abnormalities of the BBB in patients with MS (97). Contrast-enhanced examinations are more sensitive than either clinical examination or T2-weighted MR imaging in detecting disease activity, and can potentially separate clinical groups (24, 98, 99). Increased sensitivity enables the detection of a treatment effect in smaller patient cohorts over shorter periods of time, and has been used as a parameter in monitoring the efficacy of betaseron treatment (100–102). The normal window of enhancement is from 2 to 8 weeks; however, plaques can enhance for 6 months or more (24, 103). Enhancement cannot be viewed as an all-or-none phenomenon; rather, it is dependent on the time from injection to imaging, the dosage of contrast agent, the magnitude of the BBB abnormality, and the volume of the accumulation space (104–106). Delayed imaging (usually 15 to 60 minutes after injection) increases the detection of enhancing MS lesions (107, 108). Triple doses of contrast agent (0.3 mmol/kg) or a single dose (0.1 mmol/kg) with magnetization transfer to suppress normal brain tissue can increase the number of detectable MS lesions (109, 110). Silver et al (111) found that a triple dose of contrast material increased lesion detection by 75% as compared with a single dose, whereas magnetization transfer combined with a 20- to 40-minute scan delay increased the number of enhancing lesions detected with single-dose contrast agent by 47% and with triple-dose injection by 27%. Magnetization transfer with a 40- to 60-minute delay after triple-dose contrast injection resulted in the detection of 126% more enhancing lesions than in standard single-dose imaging.

Not only is there a gradient with respect to the BBB abnormality but there is also controversy as to how strongly the BBB abnormality is linked to the inflammatory and subsequent demyelinating processes. Enhancement may precede the development of high T2 signal intensity and clinical symptoms, which suggests that the BBB abnormality is the seminal event in the inflammatory cascade (104, 112). Yet we know there is disease in the normal-appearing white matter that cannot be detected with the resolution available with standard imaging and contrast techniques (113–116). It is also unlikely that all the inflammatory changes occur in the 2- to 8-week window of enhancement. Miki et al (117) found a negative correlation between enhancing lesion volume and duration of disease, suggesting that the BBB abnormalities are less important over time. Furthermore, when the disease evolves to the secondary-progressive stage, decreasing levels of enhancement are observed in spite of increasing neurologic deficits, again suggesting a diminished role of the BBB abnormality. Recent experimental work by Dousset et al (V. Dousset, University of Bordeaux, France; personal communication), who used ultrasmall iron oxide particles to image macrophages in experimental autoimmune encephalomyelitis in rats, suggests that inflammatory cells may cross

an intact BBB by diapedesis. This result is consistent with the reports of "abnormal" normal-appearing white matter without concomitant enhancement and of progressive disease with diminishing levels of enhancement. BBB abnormalities are associated, in many macroscopic lesions, with inflammatory change. However, inflammatory changes in MS are not always detected by enhancement, particularly when the level of inflammation is low. Last, primary-progressive MS displays little enhancement despite progressive neurologic decline, suggesting an alternative pathologic process most likely dissociated from BBB abnormality, such as primary neuronal loss.

Increasing the dose of contrast material, using delayed scanning, and employing magnetization transfer are not without costs. Triple-dose studies are more expensive, producing more false-positive lesions (ie, small vessels) and/or flow artifacts (ie, around the brain stem and posterior fossa), and delayed scanning interferes with patient throughput. The magnetization transfer pulse can generate images that reveal nonenhancing MS lesions to be of high signal intensity, increasing the possibility of mistaking them for contrast-enhancing lesions. It is necessary to obtain a precontrast T1-weighted magnetization transfer image and to compare it with a postcontrast image if the use of magnetization transfer is implemented.

Spinal Cord Disease

MS can affect the spinal cord alone (5% to 24% of cases) or, more commonly, both the brain and the spinal cord (19, 118–122). Approximately 60% of spinal cord lesions occur in the cervical region. In one study, the majority of patients had only one spinal lesion (122), while in another large study, 56% of patients had more than one spinal lesion (121). Spinal cord MS tends not to involve the entire cord, is peripherally located, generally does not respect boundaries between white and gray matter, and can range in length from 2 to 60 mm, with 90% of lesions spanning less than two vertebral body segments (121, 122). Spinal cord swelling associated with lesions occur in 6% to 14% of cases, while atrophy ranges from 2% to 40% (121–123). The majority of lesions in patients referred for imaging of spinal cord MS symptoms show enhancement (122). In terms of clinical categories, spinal cord lesion load is highest in relapsing-remitting and secondary-progressive MS (123). Patients with primary-progressive disease have a higher proportion of lesion load within the spinal cord than do those with secondary-progressive disease; however, no association has been found between spinal cord lesion load and EDSS score (123), although clinical disability has been correlated with spinal cord atrophy (70, 123, 124).

Spinal cord imaging is important in the context of patients presenting with signs and symptoms of MS. Here it can increase the diagnostic sensitivity by revealing lesions in the cord in patients who have nor-

mal findings on brain MR images, as well as account for neurologic findings that were mistakenly attributed to MS. The latter can include compressive lesions, such as an intrinsic tumor or extrinsic compression from an extraaxial tumor, or disk/bone disease. It can increase the specificity of the diagnosis in patients with white matter abnormalities in the brain. In this case, brain lesions plus spinal cord lesions may increase the likelihood of MS. Moreover, false-positive lesions in the spinal cord occur rarely, if ever, whereas nonspecific high-intensity abnormalities in the brain are not uncommon, especially with aging (125). The acquisition of both brain and spinal cord images enables the physician to thoroughly and properly evaluate the clinical presentations in patients with MS. Negative findings on brain and spinal MR images, obtained with contemporary hardware and software, almost certainly rule out MS.

Several investigations have produced conflicting data regarding the best pulse sequence for imaging the spinal cord when intramedullary disease is suspected. For detecting MS lesions, cardiac-triggered dual-echo spin-echo images of the spinal cord in the sagittal plane are considered superior to magnetization transfer-prepared gradient-echo (GRE) images (126). Finelli et al (127) also found them useful because of their low sensitivity to flow artifacts. Fast spin-echo (FSE) techniques appear comparable to conventional spin-echo (CSE) with respect to lesion detection (128). Hittmair et al (129) compared CSE, FSE, short-inversion-time inversion recovery (STIR) FSE, and fluid-attenuated inversion recovery (FLAIR) FSE in spinal cord MS, and found the STIR-FSE sequence to be the best choice. These authors also reported that for T2-weighted FSE imaging, shorter TEs were advantageous for spinal cord imaging and that T2-weighted FSE imaging was superior to T2-weighted CSE imaging. FLAIR-FSE has been reported to be not very useful for spinal MS (129–131). Fast-FLAIR sequences did not depict as many lesions in the spinal cord as compared with FSE images in the posterior fossa and spinal cord, which are important sites related to disability (131, 132).

What is the differential diagnosis in a patient with a clinical condition suggestive of MS and with high-intensity lesions in the spinal cord that may enhance? It should include vascular lesions (particularly dural arteriovenous malformation, producing venous hypertension and subsequent venous infarction) as well as other vascular malformations and arterial lesions. In addition, collagen vascular diseases (such as lupus) can produce myelitis, and other inflammatory diseases (such as sarcoid and acute disseminated encephalomyelitis) can also involve the spinal cord. Other considerations include intrinsic spinal cord neoplasms and infections, both viral and bacterial, which can all masquerade as spinal MS. An appropriate history and CSF analysis, as well as careful examination of the MR images, are important in differentiating these lesions.

How to Use MR Imaging

From the discussion above it is clear that MR imaging has a dominant role in ruling in or ruling out MS. In patients presenting with clinical signs or symptoms of MS, imaging of both the brain and spinal cord is very important. The examination should include T1- and T2-weighted sequences and contrast-enhanced images. The purpose of the examination is to attempt to explain the clinical findings. As stated above, there is a long differential diagnosis for MS; therefore, a correct diagnosis at this time depends on the imaging data, clinical information, and, in some cases, laboratory tests. High-intensity abnormalities without enhancement can be seen normally in the population under 50 years old; therefore, false-positive findings can occur in this healthy population and also in those with diseases that mimic MS. Knowledge of the variations in the appearance of MS as well as appropriate clinical information can lead to the correct diagnosis in most cases.

Examination of comparative data regarding various pulse sequences aids in the choice of techniques. FSE and CSE sequences produce quantitatively equivalent images with respect to detection of high-intensity lesion (133, 134). Important advantages of the FSE sequence in MS is the ability to acquire contiguous thin sections with high signal-to-noise and contrast-to-noise ratios in times comparable to those required for CSE sequences, which yield thicker sections. Lesion volume averaging is thus decreased. FLAIR imaging, in which an inversion pulse with an appropriate inversion time is coupled to a long TE readout, can yield heavily T2-weighted images in which CSF is nulled (135). FLAIR imaging serves to increase the conspicuity of lesions that are at the interface between brain and CSF, including cortical/subcortical lesions, which are generally difficult to discern with CSE imaging. Similarly, FLAIR is useful for distinguishing periventricular lesions from adjacent brain. This method improves sensitivity, increasing the number of lesions depicted (136, 137). The inverting pulse can be combined with an FSE pulse sequence, which provides improved lesion detectability, lesion conspicuity, and lesion-to-CSF contrast, as compared with CSE imaging (138, 139).

A quantitative comparison of CSE, FSE, and fast-FLAIR brain images in the depiction of MS lesions by size and site was undertaken by two groups of observers, with CSE as the standard of reference (140, 141). The results indicated that FSE images depicted 16% more lesions than CSE images, most of which were found in the cortical/subcortical area, and that fast-FLAIR images depicted 28% more lesions than CSE images, with the difference again in the cortical/subcortical area. Fewer lesions were detected in the posterior fossa. The comparison of fast-FLAIR and FSE sequences showed no significant differences in lesion depiction. The conclusion from this data was that FSE or fast-FLAIR sequences could be used in place of CSE imaging, and that, indeed, because of their

speed and increased sensitivity to lesions, each would be preferable to CSE for imaging MS.

New Techniques

Contrast in conventional MR imaging reflects primarily differences in relaxation times and proton density. New techniques offer the possibility of improving either or both sensitivity and specificity through exploitation of other parameters that can generate MR contrast. Sensitivity is improved in cases in which a disease affects a parameter, such as a diffusion characteristic, while relaxation times are essentially unchanged. In this case, a disease or injury process that is occult on conventional images may be detected on the novel scan. Specificity gains are possible when the new technique distinguishes forms of the disease that are indistinguishable on conventional images.

Many newer techniques involve quantitative imaging, by which the tissue or region of interest (ROI) may be characterized by a numerical index. These include studies based on magnetization transfer contrast, diffusion-weighted contrast, and functional MR imaging. New applications of MR spectroscopy have also been presented, and, in some cases, applied to the study of MS. Some of these methods may lead to an increased understanding of the disease, and additionally may provide more sophisticated tools for its monitoring and evaluation. Some represent relatively mature technology, which may now be considered for applicability to treatment trials and diagnostic use, while others are in less-advanced stages of development. Reference has already been made to some of these techniques. In the following sections we summarize nonconventional methods deemed most promising for application to MS.

MR Spectroscopy

MR spectroscopy has been increasingly applied to the study of MS and offers the potential to identify chemical compounds in CNS tissue and MS plaques. Of primary interest currently is proton MR spectroscopy, which, like most imaging techniques, is primarily applied to studies of the brain. The proton MR spectrum is characterized by at least three peaks, representing the compounds creatine, which is associated with cellular energy metabolism, choline, associated with cell membranes, and NAA, which is considered to be a marker of neuronal integrity. Lactate is not detectable in the normal spectrum but may be seen with inflammation. Other peaks may be found in proton spectra, particularly those acquired at short TEs, including inositol, the methyl group of lipids, and the so-called marker peaks associated with γ -aminobutyric acid (GABA), glutamate, and glutamine (76, 81, 142). The appearance of the latter peaks in the adult MR spectrum may be associated with pathologic conditions. MR spectra are acquired by using primarily one of two volume localization techniques, point-resolved spectroscopy (PRESS) and stimulated-echo acquisition mode (STEAM). Analysis is car-

ried out to obtain either relative metabolite measurements (peak area ratios) or absolute metabolite concentrations with the use of a variety of techniques. Spectroscopic images may also be acquired by using methods that are hybrids of conventional spectroscopic and imaging techniques.

In MS, the proton spectrum may be altered substantially from normal. Decreased NAA, which has been associated with neuronal loss (143), has been used to probe the natural history of the disease. In a longitudinal study of seven patients, decreases in the ratio of NAA to creatine resonances were noted at 12 and 18 months after initial measurements, which were themselves lower than the values obtained in age-matched control subjects (144). This analysis, as well as many similar studies based on metabolite ratios, was predicated on the assumption that the magnitude of the creatine resonance is stable, an assumption that may be invalid (145). Further caution is warranted given that the presence of edema in any given volume will also reduce NAA concentrations. However, the results of ratio analysis are consistent with the observation that NAA has been found to be reduced when absolute concentration is estimated or calculated in MS (146) or in any disease process that results in neuronal loss. NAA has also been found to be reduced absolutely in MS plaques studied postmortem with high-resolution proton spectroscopy.

Increased choline levels have been suggested to result from myelin breakdown or inflammation (147), suggesting a role in the detection of abnormal membrane metabolism. Using short-TE spectroscopy (TE = 30), one of two lipid resonances was detected in the MS-affected brain (81, 148) and further shown to decrease with time in individual lesions (84). Analysis of lipids may be of use for assessment of demyelination in MS.

Further evidence of disease-mediated changes in spectroscopic findings was provided by an *in vitro* study of CSF, in which lowered levels of lactate and glutamine were detected in MS patients as compared with control subjects, suggesting altered astrocytic metabolism (149). A prior study had found slight increases in lactate concentration along with higher fructose, lower creatine, and lower phenylalanine in contrast to profound changes detected in dementia (150).

To investigate the relationship between MR spectroscopic findings and clinical disability, Davie et al (146) studied 22 patients with MS, half with clinical evidence of severe cerebellar involvement, along with eight patients with autosomal dominant cerebellar ataxia (ADCA) and 11 control subjects. NAA levels were found to be significantly reduced in the groups with cerebellar involvement and ADCA, while they were static over 9 months in the MS patients, suggesting that axonal loss is implicated in the persistent clinical disability seen in patients with MS. A recent MR spectroscopy/PET study documented decreased NAA in combination with increased glucose utilization in most lesions as well as in the normal-appearing white matter of that patient cohort with stable disease

(151). MR spectroscopy has been reported to provide a window on the mechanism of clinical disability; specifically, a strong correlation was found between NAA level (ipsilateral/contralateral ratio) and EDSS score in a population with relapsing-remitting MS (152). These results are consistent with the hypothesis that axonal loss leads to disability.

Current research is aimed both at acquiring data from smaller, single volumes of interest and at producing image maps of large regions. A spectroscopic imaging study in 28 patients with MS found that NAA was diffusely and abnormally low in regions of high and low lesion probability as assessed by T2-weighted imaging (82). The authors speculated that the extralesion abnormality represented the presence of microscopic disease or wallerian degeneration along projection pathways of axons traversing the lesions. A promising new technique for application to MS employs 1-D Hadamard spectroscopic imaging and 2-D chemical-shift imaging to achieve 3-D multivoxel proton spectroscopy (153). In a pilot application of this method, lesions in one MS patient were distinguished on the basis of NAA and choline content, with decreased NAA and choline seen as consistent with chronic, nonenhancing plaques (Fig 1). One known enhancing lesion showed elevated choline levels and normal NAA, consistent with tissue that has yet to suffer neuronal damage (Fig 1).

Magnetization Transfer

Magnetization transfer is a contrast mechanism based on the supposition that macromolecular protons can be examined indirectly through their effect on the visible water proton spins by exploiting the exchange of magnetization (154). To obtain magnetization transfer contrast, the investigator effects selective partial saturation of the spins associated with macromolecules (such as myelin) by applying RF pulses that most effectively saturate spins with high T1/T2 ratios (155). The most straightforward method for accomplishing this is with the use of pulsed, off-resonance RF (156), although equivalent on-resonance techniques can be used to the same end (157). Magnetization transfer contrast has been described as qualitatively resembling T2-weighted contrast (154) and has found some diagnostic applications when used simply to generate visible contrast; specifically, in MR angiography (158). However, the magnetization transfer data may also be normalized and quantified (providing that an appropriate control scan is obtained) through the calculation of the magnetization transfer ratio (159). Analysis of this normalized data has included ROI analysis and calculation of histograms, which provide a global index of magnetization transfer abnormality with potential application to the monitoring of MS disease progress (160, 161) (Fig 2).

Initial results have shown decreased magnetization transfer in MS, including in plaques and in normal-appearing white matter, and in animal models of experimental allergic encephalomyelitis (159). These

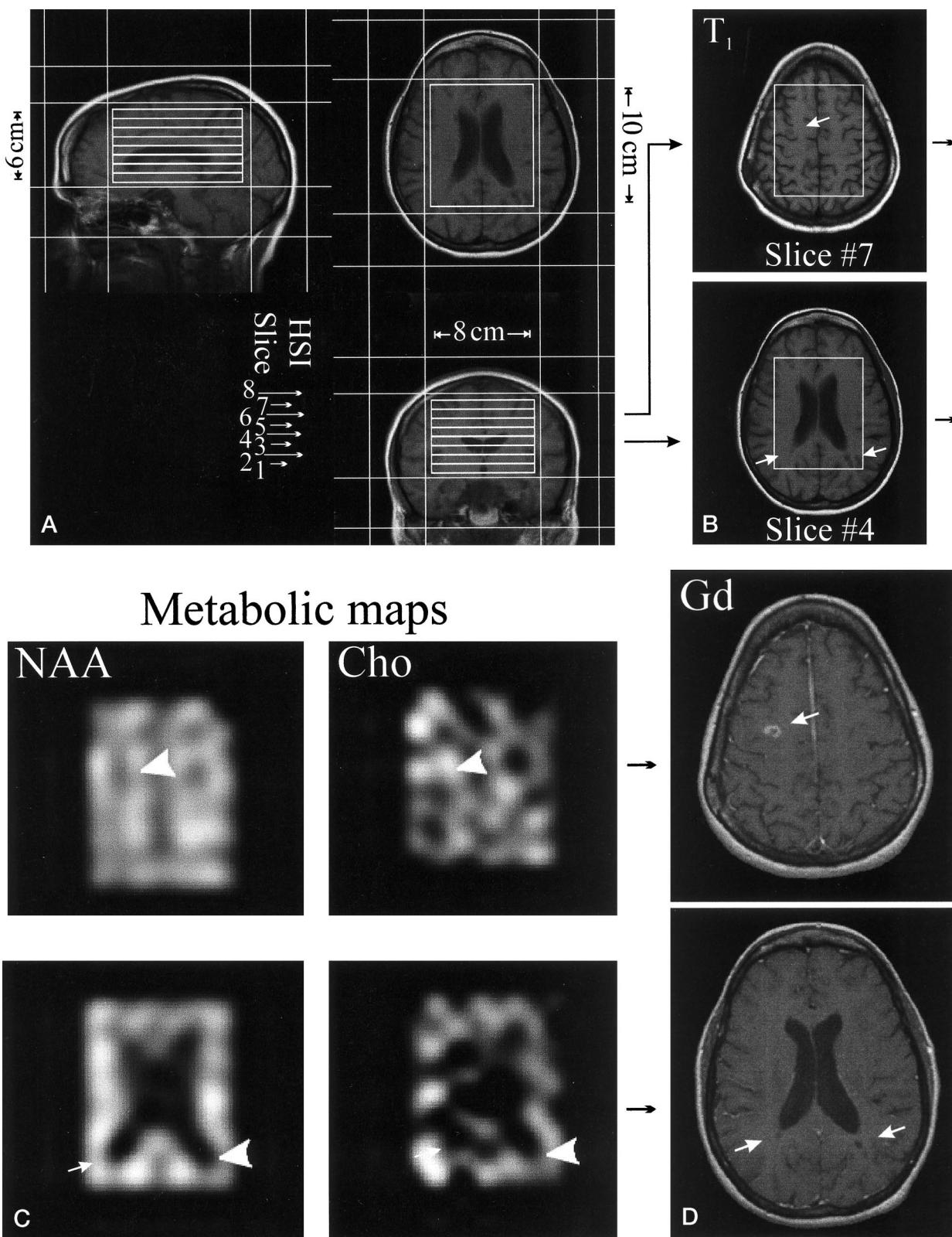


FIG 1. 1-D Hadamard spectroscopic imaging and 2-D chemical-shift imaging (HSI/CSI) resulting in 3-D multivoxel proton spectroscopy in a patient with clinically diagnosed MS.

A, Spectroscopic image shows locations acquired in a single HSI/CSI series (45 minutes).

B, Corresponding T₁-weighted image of two selected sections.

C, Metabolite maps representing absolute magnitudes of NAA and choline.

D, Contrast-enhanced images corresponding to the metabolite maps and the T₁-weighted images. On section (slice) 4, two areas of T₁-hypointensity (arrows), representing MS lesions, do not enhance and are presumed to represent chronic plaques. Metabolite maps show decreased NAA and choline in these regions. On section (slice) 7, an enhancing lesion (arrow) shows markedly increased choline but only slightly reduced NAA, consistent with relative sparing of neuronal tissue.

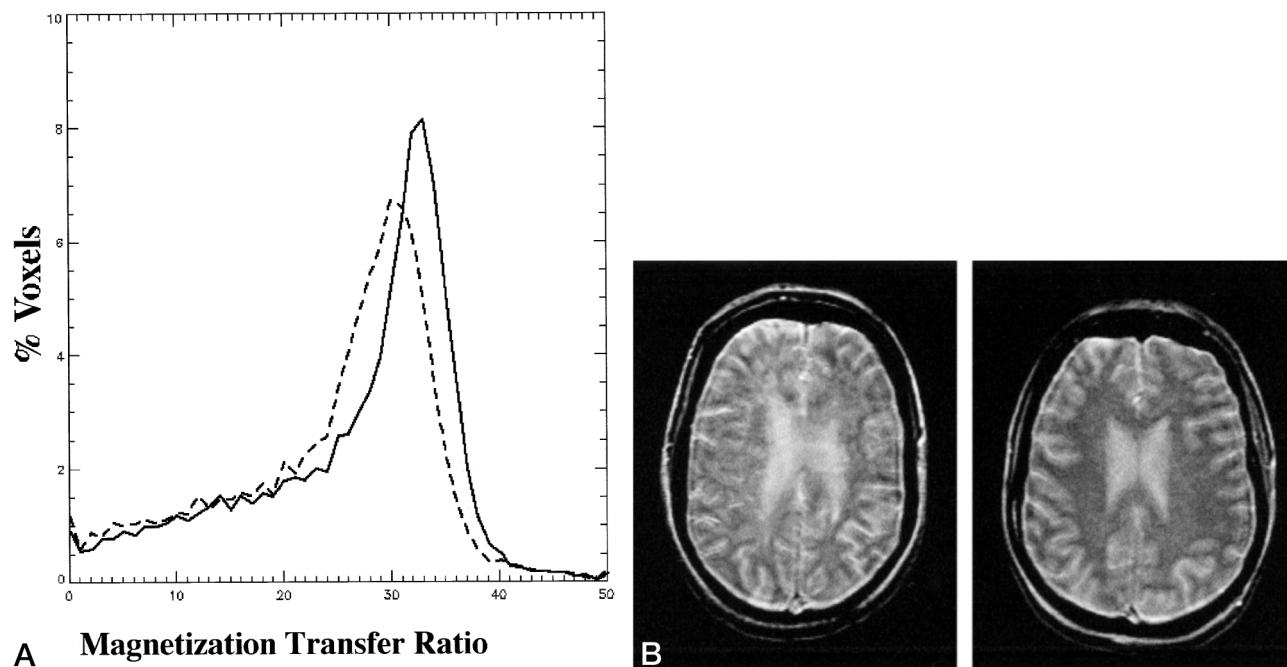


FIG 2. Magnetization transfer images in normal brain and in the brain of a patient with clinically diagnosed MS, with corresponding single-section histograms. Acquisition parameters for the 3-D GRE magnetization transfer image include 106/5 (TR/TE), a flip angle of 12°, and a magnetization transfer pulse of 50°. A single pronounced peak corresponds to white matter with normal magnetization transfer ratio, and is seen to be reduced and left-shifted in MS, representing the effects of magnetization transfer ratio reduction in plaques and in normal-appearing white matter. Similar results have been obtained in whole-volume analyses with and without segmentation.

were complemented by a study in wallerian degeneration, which showed that magnetization transfer could be used as a marker of structural change at the molecular level that was below the sensitivity of conventional MR imaging (162). Filippi et al (116) confirmed a decreased magnetization transfer ratio in frontal normal-appearing white matter in MS patients as compared with the same region in control subjects. In 29 patients (54 lesions) Petrella et al (163) found that magnetization transfer ratio was highest in homogeneously enhancing lesions, lower in nonenhancing lesions, and lowest in the central portion of ring-enhancing lesions, suggesting possible evolutionary patterns. A relationship with clinical disability has only been established in one study, in which magnetization transfer ROI analysis was used (164); however, newer techniques, such as histogramic analysis combined with segmentation, have displayed potential advantages in long-term follow-up studies (161).

Magnetization transfer methods, and indeed all quantitative imaging techniques, are limited by the reproducibility of the scanning equipment, which is affected by coil tuning and loading as well as by acquisition parameters. Such considerations have limited the usefulness of some techniques to the analysis of pooled data rather than to diagnostic appraisal of a single patient. Recognizing that clinical scanners are designed to produce images that will be read qualitatively, the investigator must take extra care when obtaining data to be used for quantitative analysis. Current efforts are directed toward identifying sources of variance in magnetization transfer meth-

ods and eliminating those under experimental control, with the eventual expectation of specificity gains through quantitative analysis.

T2 Decay Analysis

As noted, the assumption that CNS tissue is homogeneous with respect to relaxation times is known to be inaccurate. Another method, besides magnetization transfer, for exploiting this observation is the analysis of T2 decay fit to a composite of several exponential functions. This so-called T2 decay curve analysis has been investigated in relation to a variety of disease processes, including MS. Data for this analysis may be gathered by using a multiecho sequence, in which the data necessary to reconstruct a single image section is acquired many times during one TR (165). By using this sequence it is possible to obtain points on the T2 decay curve from approximately 10 milliseconds out to seconds (166). The data are analyzed via fitting to several exponential curves. A particular challenge of such multiexponential fitting is the difficulty of establishing a unique solution, particularly when only a few points of the observed decay are relevant to the rapid component of relaxation. With the use of this technique, several components of T2 relaxation have been identified in CNS tissue; namely, a rapid component on the order of 15 to 30 milliseconds, a primary component at 70 to 100 milliseconds, and a long component on the order of seconds. The latter is associated with CSF, while the 70-millisecond component is typically observed for

brain tissue and is assigned to intra- and extracellular water (167–169). Other investigators have observed monoexponential decay in lesions, attributed primarily to extracellular water with T2 rates in excess of 200 milliseconds (170). The rapid component is of perhaps greatest interest in the study of MS and has been suggested to represent water compartmentalized within myelin bilayers (169). However, this component is the most difficult to study, limited by the temporal resolution of the MR image. It has been hypothesized that T2 decay analysis will establish new markers for myelin in order to characterize MS disease, and the study of such potential markers is a focus of current efforts.

Diffusion Properties

Diffusion-weighted imaging is based on the well-known sensitivity of the MR imaging examination to motion. It represents a fundamental advance in that it allows the investigation of motion on the molecular scale, much smaller than the scale of the image resolution. Diffusion imaging is performed by the application of very strong paired gradient pulses, which serve to dephase and rephase spins that are stationary. Spins that move, even on the order of diffusion distances, are not rephased and are detected as a signal decrease (171). Ever since diffusion-weighted imaging was applied to the diagnosis of stroke (172), its use has rapidly become widespread. Larsson and collaborators (173) indicated that water self-diffusion was higher in MS plaques than in normal-appearing white matter and higher in acute plaques than in chronic plaques. Subsequently, Christiansen et al (174) confirmed the presence of elevated ADC in acute plaques, and also detected increased self-diffusion in normal-appearing white matter. This finding was interpreted as due to an increase in the extracellular space with edema and demyelination. In a recent study, a volume-selective technique allowed the investigators to focus on individual lesions for diffusion measurements, which again confirmed elevation of the apparent diffusion coefficient (ADC) in all plaques. They found that ADC was significantly elevated in normal-appearing white matter for patients with a benign disease course only. No relationship between ADC and disability was found (175).

Measurement of Lesion Load

Measurement of volumetric lesion load is another area of active research with applications to MS that have been discussed above. A related technology, registration, is commonly pursued for development in parallel with this work. Finding optimal sequences that can be implemented across institutions and on different MR imaging platforms is a difficult enterprise. In one study, comparison of CSE and FSE sequences for measurement of lesion volume using a semiautomated contour technique indicated that mean lesion load was slightly higher with the CSE sequence. However, intraobserver variability was sig-

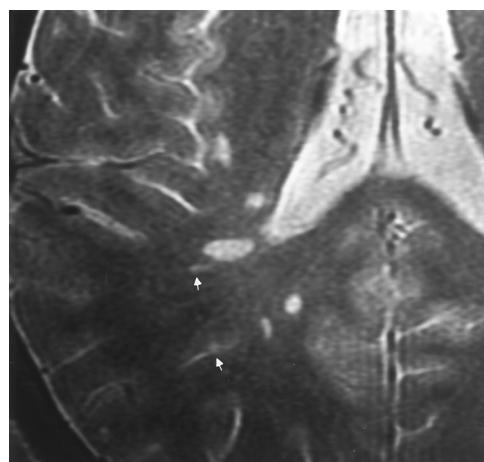


FIG 3. FSE axial image of the brain obtained at 4.0 T shows nodularity along the Virchow-Robin spaces (arrows), which we believe represent small MS lesions. Acquisition parameters include 4000/90, 256 × 512 matrix, 22-cm field of view, 3-mm-thick sections, an echo train length of 8, and an acquisition time of 4.38 minutes.

nificantly higher for FSE than for CSE. Although FSE sequences are quicker and the total lesion volume measurements are similar to those obtained with CSE, the authors concluded that the poorer reproducibility of FSE raised doubts about the use of FSE to replace CSE in clinical trials (176). New possibilities with regard to sensitivity of lesion detection are potentiated by the advent of imaging at magnetic fields of 4.0 T. Preliminary results from studies of MS patients at this ultrahigh field suggest that lesion detection is enhanced (Fig 3).

From an engineering perspective, manual, automated, or semiautomated algorithms designed to obtain volumetric data must perform tasks of recognition and delineation of diseased tissue in a robust and reproducible manner. Manual tracing, as was applied in the 1993 interferon- β clinical trial (42), has been reported to achieve intraobserver variability as low as 6%, although the variability in other studies has been significantly higher. Still, a retrospective analysis of trial data with additional simulated noise established that the treatment effect on lesion load would have been detectable with noise variability as high as 40%, a demonstration that the manual outlining technique was clearly robust in this application (42). Subsequent techniques rely to a lesser degree on human operators, and include threshold based techniques. These have achieved greater intrarater reliability than have purely manual algorithms, but they have yielded results that are highly dependent on the chosen threshold (88, 177, 178). More recent developments have included feature space partitioning (cluster analysis) in the algorithms, which have employed a variety of strategies for operator involvement and noise effect mitigation (179–185). Difficulties of these techniques arise from the heterogeneous nature of some lesions, partial volume effects, and nonlesion materials that can present lesionlike contrast under some conditions. Results of these studies suggest that while the

computer may optimally delineate lesion extent, some degree of human input is often necessary to discriminate true lesions from false-positive findings. Some new and promising techniques are based on the principle of fuzzy connectedness, which attempts to incorporate graded composition and "hanging togetherness" into the description of objects identified as lesions as well as white matter and other structures (186, 187). These techniques are designed to overcome the limitations of artificially imposed hard thresholds and to make feasible a greater degree of automation. The goal of a completely automated technique that is robust and reproducible has yet to be realized and remains the focus of current efforts.

Functional MR Imaging

The observation that local cerebral hemodynamics are closely associated with neuronal activity in the brain has contributed to the current interest in functional MR imaging. Techniques based on blood oxygen level-dependent (BOLD) contrast have been used to probe the hemodynamic response of the brain to activation corresponding to tasks and challenges (188). BOLD contrast is based on the observation that the magnetic properties of deoxyhemoglobin change dramatically with oxygenation. Specifically, the susceptibility of hemoglobin goes from positive in the deoxy form to negative in the oxygenated form. At concentrations found in venous blood vessels, a distortion in the magnetic field surrounding the vessel is produced, which can be detected as a small signal loss on an MR image. This same effect accounts for the observation that T2-weighted signal intensity is decreased in some stages of acute hemorrhage (189).

When a brain region is activated, an increase in blood flow (without a commensurate increase in oxygen extraction) results in a temporary increase in the concentration of oxyhemoglobin, leading to an increase in MR imaging signal intensity on a susceptibility-weighted pulse sequence. Both conventional GRE and echo-planar imaging pulse sequences have been used to detect brain activation, with echo-planar imaging offering advantages of temporal resolution, and conventional GRE contributing advantages of spatial resolution.

A preliminary study using functional MR imaging in eight patients with MS has shown that the cortical activation responses were much larger as compared with those in healthy subjects, and frequently involved both contralateral and ipsilateral cortices. Future work to explore activation patterns in a longitudinal study is suggested.

Conclusion

MR imaging has had a profound influence on the diagnosis of MS. In fact, today it would be virtually inconceivable to make the diagnosis of MS without a confirmatory MR study. Although the diagnosis of MS remains predominantly clinical, it is not impossible to envision MR imaging criteria emerging, in the

near future, as an alternative to clinical diagnosis. As noted, many of the MR imaging techniques considered to be in active development are being investigated for application to both the diagnosis and characterization of MS disease. These efforts may be expected to increase the body of knowledge regarding the natural history of MS, to add to our diagnostic capabilities, and to contribute to the testing and monitoring of new therapeutic agents and procedures. Subclassification of MS by MR imaging or MR spectroscopic criteria is clearly on the horizon, and no therapeutic trial is now complete without MR imaging data. Clearly, treatment in the near future will be rationalized on the basis of MR imaging markers of disease, and MR imaging research may indeed unravel the pathogenesis of this disorder.

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