MRI has provided important insights into the pathophysiology of multiple sclerosis (MS). However, conventional MRI scans furnish only gross estimates of the nature and extent of tissue damage associated with MS, and the data correlate poorly with measures of concurrent disability in patients. Recent advances in MRI technology have improved the correlation of MRI findings with clinical status and have increased the utility of MRI data as surrogate markers in monitoring disease progression and response to therapy. Newer MRI techniques, such as magnetization-transfer (MT) MRI, diffusion-weighted MRI, and functional MRI (fMRI), as well as proton magnetic resonance spectroscopy (MRS) and measures of brain and spinal cord atrophy, may help further elucidate MS pathology and may provide opportunities for new treatment approaches. CONVENTIONAL MRI MRI usually is recommended for diagnosing MS to confirm clinical findings and evaluate patients for other pathologies. Typically, the body is exposed to an external magnetic field that causes protons to align in an orientation parallel or antiparallel to the external magnet. A radiofrequency (RF) pulse transfers energy to the protons, which resonate with the pulse, causing some of the protons to alter their orientation. The RF pulse is discontinued, and the protons relax, returning to their starting point. Measurements of this relaxation phase are used to create images, which vary depending on the tissue being scanned.

Two relaxation times, T1 (longitudinal) and T2 (transverse), are important in using conventional magnetic resonance technology for the imaging of MS lesions. Contrast is influenced by the selected weighting of these relaxation times. T1 weighting uses a short delay between pulses, while T2 weighting uses a longer delay; this accentuates the differences in T2 relaxation time. Abnormalities seen with conventional MRI that are most often used to determine disease activity in patients with MS are hyperintense lesions visualized on T2-weighted images, hypointense lesions visualized on T1-weighted images, and gadolinium-enhanced (Gd+) hyperintense lesions visualized on postcontrast images (Table 1). T2-weighted images are used to assess edema and tissue destruction early in the inflammatory stage of MS. Later, when demyelination and gliosis occur, T2-weighted images are used most often to measure burden of disease, but they have limited sensitivity and specificity. There is generally a weak correlation between T2-weighted lesion load and concurrent clinical disability in patients with MS. Proton density (PD)-weighted scans, a type of T2 imaging, are obtained by minimizing T1 and T2 contrast effects and are used to distinguish periventricular lesions from the cerebrospinal fluid (CSF). Another widely used variant of T2 imaging is the "fluid attenuated inversion recovery" (FLAIR) sequence. FLAIR imaging suppresses the T2 hyperintensity of fluid and starkly differentiates the ventricles from periventricular white-matter lesions. FLAIR imaging also appears to make parenchymal hemisphere lesions stand out more prominently than does conventional T2; the ability to detect juxtacortical lesions is particularly improved. Because of concerns regarding the presence of artifacts, FLAIR imaging is not as useful as conventional T2 for evaluation of the spinal cord or posterior fossa. In these anatomic areas, PD or spin echo sequences are preferred. On T1-weighted scans, hypointense lesions that do not persist may indicate a reversible change, such as edema, whereas persistent lesions signify focal CNS damage, such as axonal loss and demyelination. Persistent hypointense T1-weighted images correlate more closely with disability than do T2-weighted images and are known as "black holes." These persistent T1 lesions may be useful markers of disease progression; however, further study is required to validate their usefulness. Gadolinium enhancement is used to estimate inflammation-induced permeability changes of the blood-brain barrier. The ability to distinguish between active and inactive lesions makes gadolinium enhancement the most clinically relevant MRI measure for ongoing inflammatory activity in patients.
with MS.10-12 NEWER MRI MEASURES Table 2 shows the newer MRI techniques.2,5,13,14 MT MRI This technique compares proton interactions in an unrestricted environment, such as water, with proton interactions in a restricted environment, such as tissue.2 With MT MRI, an off-resonance pulse is applied to tissue, which saturates the magnetization of protons.2 Next, magnetization is transferred from these protons to more mobile protons, resulting in a reduction of the tissue signal. The degree of signal loss depends on the density of macromolecules in tissue. For example, a low MT ratio (MTR) indicates the reduced ability of macromolecules in tissue to exchange magnetization with water molecules, which indicates damage to myelin and axonal membranes. In a small study of 5 patients with MS, investigators used serial MTR measurements to observe structural changes in those with new Gd+ lesions.15 Changes in MTR correlated with the degree of gadolinium enhancement in the MS lesions. In another study of 10 patients with MS, MT MRI of new Gd+ lesions was used to characterize lesions with variable durations of gadolinium enhancement.16 Results indicated that the duration of enhancement in MS lesions may be related to the severity of the ongoing demyelinating process as assessed by the MTR. Using serial MT MRI in the same patient group, investigators determined that the changes in normal-appearing white matter (NAWM) occur before lesions become evident on conventional MRI scans.17 One postmortem study correlated the extent of axonal loss and demyelination with the MTR of lesions and normal white matter.18 A substantial decrease in the MTR of MS lesions was indicative of severe tissue damage. A 5-year longitudinal study of 30 patients with MS revealed a continuous, gradual decline in MTR that was undetected by conventional MRI.19 The investigators further suggested that the early detection achieved with MT MRI could be used to predict the disease progression of MS. Diffusion-weighted and diffusion-tensor MRI With diffusion-weighted MRI, in vivo measurements of the molecular motion of water can be made and reduced to a diffusion coefficient.2 The pathologic elements of MS can alter the permeability and geometry of structural barriers as well as the in vivo diffusivity of water.2,20 In some brain tissues, such as white matter, molecular mobility is not the same in all directions.2 This property, called "anisotropy," results in a diffusivity that varies with the direction of measurement.20 Fractional anisotropy (FA) is a commonly used measure of isotropy deviation and is thought to reflect the structural integrity and alignment of cellular structures within fiber tracts.21 In diffusion-tensor MRI, diffusion-weighted images along 6 noncolinear directions of gradients are collected and analyzed. Studies of water diffusion in MS have consistently demonstrated a higher diffusion coefficient in the NAWM of patients with MS than in the NAWM of members of a control group.20,22 Abnormalities in diffusivity and FA histograms have been found in patients with different MS disease phenotypes.22 For example, changes in normal-appearing gray matter are more obvious in patients who have secondary progressive MS than in patients who have relapsing-remitting MS (RRMS) or primary progressive MS (PPMS).22,23 Consistent with the heterogeneity of MS lesion pathology are the variable FA values in macroscopic MS lesions.18,24 The results of numerous studies on diffusion-tensor MRI are in agreement regarding the utility of this in vivo technique. Diffusion-tensor MRI may greatly improve our understanding of the underlying mechanisms of MS damage and repair, because edema, inflammation, demyelination, remyelination, gliosis, and axonal loss most likely will have different effects on the size, integrity, and orientation of fluid-filled spaces.20 Proton MRS Unlike conventional MRI, which provides anatomic information based on water signals, proton MRS works by suppressing the signal from water and fat protons and, instead, detects and measures the amounts of other hydrogen-rich compounds, such as N-acetylaspartate (NAA), choline, creatine, and lactate.25 NAA is associated with neurons and neuronal processes in the normal adult brain. Decreases in NAA concentrations are thought to occur as a result of axonal dysfunction.2 Phosphocholine and glycerolphosphocholine, components of membrane phospholipids, are released during active myelin breakdown.2 Decreased creatine concentrations have been found in acute demyelinating lesions. Higher than normal lactate concentrations in tissue partly reflect the metabolism of inflammatory cells.2 Proton MRS of brain tissue lesions in patients with MS has demonstrated a decreased concentration of NAA.26 Other studies also have demonstrated a significant negative correlation between NAA changes and clinical disability in patients with isolated acute demyelinating lesions.27 These results suggest that axonal damage may be an immediate cause of functional impairment in patients with MS and that the relative NAA concentration in the brain may be a useful marker of disease progression.28,29 Increased concentrations of choline, creatine, and lactate typically are associated with a decrease in NAA concentrations.2 Preliminary data show an increase in creatine and phosphocreatine concentrations and a decrease in NAA concentrations in the brains of patients who have PPMS, compared with the brains of patients who have RRMS.30 Proton MRS has improved our understanding of MS because it enables quantification of axonal pathology by measuring NAA in MS lesions and in NAWM.2 fMRI This technique measures
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signal intensity related to blood oxygenation levels in the brain; it is used to study neuronal mechanisms that underlie CNS function and to define abnormal patterns of brain activation caused by disease.2 One method under development relies on blood oxygenation level-dependent contrast, which measures a change in the signal strength of water protons in the brain produced by venous blood deoxyhemoglobin paramagnetic effects.31 Challenges to the clinical use of fMRI include the interpretation of blood oxygen level signal intensities, the technical difficulties associated with equipment operation, and the cooperation of patients. In one study, the quantity and pattern of brain activity during the Paced Auditory Serial Addition Test and a recall test were found to be significantly more different in patients who had RRMS and no deficits or mild deficits on neuropsychological testing than they were in healthy controls.32 Activation of specific brain areas during both tests correlated with T2 lesions in patients with RRMS, and fMRI activity was greater in patients with higher cognitive function than in those with lower cognitive function. SPINAL CORD MRI Spinal cord imaging is technically challenging, owing to the thin, longitudinal anatomy of the spinal cord, as well as to artifacts that are introduced by voluntary and involuntary motions.33,34 MRI scans of the spinal cord provide useful information for diagnosing MS when MRI scans of the brain and clinical status are equivocal.35 Conventional techniques for imaging spinal cord lesions include high-intensity T2-weighted imaging, spinal cord enhancement, and measurement of spinal cord atrophy. Newer methods that are currently being investigated include magnetization transfer, diffusion-weighted imaging, and proton spectroscopy.34 MEASURE OF ATROPHY A variety of MRI techniques can be used to measure whole-brain atrophy in patients with MS.2,36 One of the more commonly used methods is the brain parenchymal fraction (BPF), which is defined as the ratio of brain parenchymal volume to the sum of brain and ventricular CSF volumes.37 This method has 2 advantages: first, normalization of the brain parenchymal volume relative to brain size reduces interindividual variation in brain size; second, BPF has high test-retest reproducibility.37 A potential disadvantage of BPF is its failure to account for CSF volume external to the outer surface of the brain; CSF volume can increase with progressive brain atrophy or loss of gray-matter volume.38 More recently, "structural image evaluation using normalization of atrophy" (SIENA) has been used to analyze longitudinal (temporal) brain changes.39 SIENA is a 3-dimensional method that should not be applied to 2-dimensional images. Fully automated and reliable, it can be applied to data acquired with different pulse sequences.39 Although used less frequently in the routine assessment of patients with MS, measurement of spinal cord atrophy using MRI is an emerging area of interest.40 Evidence suggests that the brain and spinal cord atrophy observed in these patients may begin at disease onset (Figure).37 This is supported by a longitudinal study showing increased brain ventricle size and decreased brain width in patients with MS.41 In a postmortem study of 70 randomly selected cases of MS, spinal cord involvement was evident in 99%.42 Atrophy suggests that the CNS responds to tissue destruction by shrinkage and reorganization, visible at the edges of the brain and spinal cord.43 In lesions associated with MS, a considerable loss of axonal density and volume, as well as loss of myelin, occurs.43-45 Small atrophic changes in various brain structures can be quantified, and such regional atrophy can be correlated with disability.46 dementia,47 and lower-than-average scores on neuropsychological tests.48,49 As demonstrated in a controlled study of 60 patients with MS,50,51 a strong correlation appears to exist between the level of the expanded disability status scale (EDSS) score and brain stem and upper spinal cord atrophy (r = 0.7; P 80%) of the development of clinically definite MS within the next 7 to 10 years. Also highly predictive of the subsequent development of clinically definite MS is the appearance of 2 or more Gd+ lesions at baseline and the presence of either new T2 lesions or new Gd+ lesions 3 months or more after a clinically isolated demyelinating event. In contrast, patients with a CIS are less likely to develop clinically definite MS when their baseline MRI findings are normal. Although a prognosis cannot be offered with certainty, the additional information provided by MRI, along with clinical assessment, permits a reasonably more reliable and earlier prognosis for some patients. The availability of disease-modifying therapies, such as interferon beta (IFN-beta), provides an opportunity to initiate early treatment to slow disease progression. Data from the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS), for example, have shown that in patients with a first demyelinating event, initiation of treatment with IFN-beta-1a reduced the probability of developing clinically definite MS by as much as 44% (P = .002).61 MRI in established MS To assess the degree of pathology associated with active MS, measurements of disease activity usually are obtained by using conventional MRI methods, such as gadolinium enhancement and T2-weighted lesion volume.7,62 The typical clinical measurements of disease activity are relapse rate and disability, according to EDSS measurements. MRI and clinical assessment indirectly measure underlying MS pathology and provide fundamentally different information from one another.4 For example, the frequency of...
identifying Gd+ lesions on MRI is much greater than the frequency of clinical relapse,63 which implies that the pathologic activity of MS is greater than what can be measured using clinical end points.2 The number and volume of T2-weighted lesions can be substantial, even in the absence of overt MS symptoms. In addition, there appears to be little difference in the number and dynamics of T2-weighted lesions in patients with a CIS compared with those who have early RRMS.4 It is known that atrophy increases temporally during MS progression; however, the rates of brain and spinal cord atrophy at different disease stages are not necessarily consistent.45 Ultimately, further longitudinal study of representative patient populations is needed to clarify the evolution of brain and spinal cord atrophy.2 MRI in MS treatment monitoring Available data demonstrate that disease-modifying therapies such as corticosteroids, IFN-beta, and glatiramer acetate (GA) reduce the frequency of Gd+ lesions and the rate of T2-lesion volume accumulation, both surrogate markers for CNS inflammatory activity in MS.4 Intravenous methylprednisolone (IVMP) temporarily reduces Gd+ lesions and slows atrophy and lesion volume accumulation.64 The efficacy of IVMP was assessed in a retrospective analysis of an open-label cross-over trial of IFN-beta-1b involving 26 patients with RRMS who were selected based on review of an MRI database and who had received IVMP 1 g/d for 3 to 5 days (without taper to oral corticosteroids), following an acute exacerbation.65 Serial monthly MRIs were performed in the 26 patients during treatment with IFN-beta-1b (study period, 6 to 36 months); 12 of these patients were evaluated at the baseline stage (duration, 7 to 48 months) of the open-label trial (ie, the natural history group). At 3 months after IVMP treatment, the number of Gd+ lesions observed was significantly reduced in both the IFN-beta-1b and natural history groups.65 MRI studies also are used to assess the efficacy of other disease-modifying therapies in MS. In a randomized placebo-controlled trial involving 341 patients with RRMS, MRI data (proton density or T2-weighted images) were collected annually for up to 5 years.66 Patients received either IFN-beta-1b 1.6 million IU, IFN-beta-1b 8 million IU, or placebo subcutaneously every other day for 3 to 5 years. At the 5-year follow-up, both IFN-beta-1b dosages resulted in a reduction in the annual lesion accumulation activity index relative to placebo (P = .001). In a large, phase 3, randomized trial, intramuscular IFN-beta-1a, 30 mg once weekly, significantly decreased the number of new and enlarging Gd+ brain lesions shown on annual MRI examinations conducted over 2 years (P lesser than or equal to .024).67 A randomized, double-blind, placebo-controlled MRI study indicated that patients with RRMS treated with GA had 29% fewer total Gd+ lesions over 9 months68; the number and volume of T2-weighted lesions decreased significantly and the relapse rate was reduced in the GA-treated group (P = .012), which paralleled the decrease in gadolinium-enhancement frequency. MRI measures also were being used to assess the clinical efficacy of natalizumab, which was recently approved for MS but was voluntarily withdrawn from the market in late February. Clinical studies were halted following reports of 2 serious adverse events in patients receiving natalizumab in combination with IFN-beta-1a (see Mental Notes, page 7). However, an earlier (phase 2) trial of natalizumab had demonstrated significant reduction in the mean number of new Gd+ lesions compared with placebo. A nearly 90% decrease in lesions was seen (P


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