Magnetic resonance imaging (MRI) techniques offer a window into the pathologic processes of multiple sclerosis (MS) and other neurologic conditions. Each technique possesses advantages and disadvantages (Table), yet they all involve the indirect measurement of changes in the molecular content of central nervous system (CNS) tissues, especially water. Several clinical trials have shown that MRI techniques are useful for evaluating degeneration in MS and for monitoring the effects of treatment. Recent evidence also suggests MRI techniques may be useful for monitoring the regeneration of CNS tissue with emerging therapies, such as stem-cell transplantation.

Hyperintense T2-weighted lesions can be observed at any stage of MS and can provide a measure of total white-matter lesion burden. Several other methods are available to visualize and quantify the pathologic effects of MS in the brain and spinal cord, including magnetization transfer imaging (MTI), diffusion-weighted imaging (DWI), and magnetic resonance spectroscopy (MRS).

### TECHNIQUES TO MONITOR NEUROLOGIC INJURY IN MS

**T1 BLACK HOLES**

Gadolinium contrast-enhancing lesions on T1-weighted images reveal areas of blood-brain barrier disruption that are associated with areas of acute inflammation and edema. T1 hypointense lesions, or “black holes,” are typically transitory. About 70% to 80% of these lesions are associated with a contrast-enhancing lesion and are no longer apparent on follow-up scans performed 1 month after first visualization. Persistent black holes correspond approximately to the loss of axonal density in white matter; however, black holes can represent lesions in evolution that encompass all stages of tissue damage, including edema and inflammation, demyelination, gliosis, and remyelination. No universally available automated tools exist to quantify the number and volume of black holes, and they do not provide information about the state of normal-appearing white matter (NAWM). Black holes may disappear from the MRI image for several reasons, including the resolution of edema or inflammation, remyelination, or partial-volume effects (which occur when the lesion is smaller than the slice thickness of the scan). Parenchymal interstitial pressure and hydrostatic pressure from the ventricles may also collapse a small black hole.
An extensive discussion of MRI and measure of cerebral atrophy has been presented by Dr. Rudick. Cerebral atrophy represents the summation of both microscopic and macroscopic disease processes in the MS brain and spinal cord. Measures of the rate of progression of cerebral atrophy may vary depending on the MRI pulse sequence and image analysis software used to acquire and process the MR images. Care must therefore be taken when comparing and interpreting the results from different studies using measures of atrophy in clinical trials as outcome measures.

**Magnetization Transfer Imaging**

MTI measures the exchange of magnetization between free water molecules and water molecules bound to protein and is expressed quantitatively as the magnetization transfer ratio (MTR). MTI provides a quantitative measure of CNS structural damage that correlates well with axon loss, edema, Wallerian degeneration, gliosis, atrophy, and demyelination. Conventional MRI measures (i.e., lesion burden, contrast-enhancing lesions) have a generally poor correlation with clinical outcomes because they do not distinguish inflammation from demyelination or detect small pathologic changes. MTR values have been described as a more sensitive and specific measure of pathology in NAWM and of small pathologic changes than conventional MRI. Longitudinal studies have shown that the MTR decreases 1 to 12 months before the appearance of contrast-enhancing lesions, with a pronounced drop in MTR at the time of lesion enhancement. In a prospective study of patients with MS who were followed up for approximately 5 years, baseline MTR values in NAWM were highly correlated with changes in Expanded Disability Status Scale (EDSS) scores (Figure 1). MTR is also able to differentiate lesions that appear similar to one another on conventional MRI (Figure 2).

MTR measures can encompass the entire brain and spinal cord, including white and gray matter and occult disease in NAWM. However, MTR values for NAWM and lesions may vary depending on the manufacturer of the device, software and hardware upgrades, and the specific methodology used.

**Diffusion-Weighted Imaging**

DWI measures the extent to which water molecules diffuse freely within tissue. In the CNS, water diffusion is most restricted within myelin and least restricted in cerebrospinal fluid. The diffusion of water is expressed as the apparent diffusion coefficient (ADC), which increases when tissue is damaged. Diffusion changes may occur before acute blood-brain barrier changes are visible on conventional MRI. One difficulty with DWI as a measure of neurodegeneration or neuroprotection in MS is that healing and degeneration may produce DWI images that may be indistinguishable from each other because they cause similar changes in water diffusibility. DWI is sensitive to subtle changes in pathology, especially in NAWM, that may not be apparent on conventional MRI scans. In a serial DWI study of 5 patients with MS, a steady increase in the ADC was noted during the months that preceded the appearance of gadolinium-enhancing lesions, compared with matched white matter from the contralateral side in the same patient (Figure 3).

DWI can also be used to measure fractional anisotropy, or differences in the direction of motion of water molecules. Fractional anisotropic maps can be used to describe anatomic structures within the CNS. For example, water molecules move faster along axons than across them, allowing anisotropic maps to delineate fiber pathways in the CNS. DWI can be used to detect Wallerian degeneration of axons in the CNS, which may be of interest in clinical trials that are evaluating neuroprotective strategies. DWI has relatively limited spatial resolution and therefore may not be useful in evaluating small lesions.

**Magnetic Resonance Spectroscopy**

MRS makes it possible to visualize metabolic properties of CNS tissue. Several tissue metabolites can be studied using MRS, including the specific neuronal marker as the apparent diffusion coefficient (ADC), which increases when tissue is damaged. Diffusion changes may occur before acute blood-brain barrier changes are visible on conventional MRI. One difficulty with DWI as a measure of neurodegeneration or neuroprotection in MS is that healing and degeneration may produce DWI images that may be indistinguishable from each other because they cause similar changes in water diffusibility. DWI is sensitive to subtle changes in pathology, especially in NAWM, that may not be apparent on conventional MRI scans. In a serial DWI study of 5 patients with MS, a steady increase in the ADC was noted during the months that preceded the appearance of gadolinium-enhancing lesions, compared with matched white matter from the contralateral side in the same patient (Figure 3).

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N-acetyl aspartate (NAA), choline and choline-containing compounds, creatine, lactate, and lipids. In CNS injury, choline is generally elevated as the result of the release of choline-containing compounds from cell membranes. Lactate may be increased as a result of anaerobic metabolism or influx of inflammatory cells within a lesion. In patients with MS, NAA is decreased in lesions but also in NAWM adjacent to or distant from lesions. MRS provides a quantitative method to assess neuronal injury and has also been shown to correlate with a clinical course of MS better than T1 or T2 lesion volumes. MRS measurement of NAA has been shown to be highly correlated with EDSS scores (Figure 4). The disadvantages of this method are that it is time-consuming and possesses relatively low spatial resolution.

**IMAGING IN STUDIES OF NEUROPROTECTION**

Neuroprotection can be defined as an “an effect that results in salvage, recovery, or regeneration of the nervous system or its cells, structure, or function.” In MS, neuroprotection can be thought of as encompassing 3 distinct approaches, each with its own therapeutic strategy and appropriate imaging methods: salvage (preventing cell loss after injury), recovery (stimulating healing and increasing neurologic function), and regeneration (replacing or restoring damaged tissue). Each strategy has been investigated in studies that used magnetic resonance approaches to measure injury and the response to treatment.

**SALVAGE**

Salvage of tissue in MS could refer to the prevention of processes, such as neuron or oligodendrocyte loss, Wallerian degeneration, and decreasing inflammation. MRI techniques have been used to visualize Wallerian degeneration in patients who were recently diagnosed with MS and thinning of the cerebral cortex in patients with more advanced disease. These methods may be useful for clinical trials of patients who are receiving treatment to slow the progression of MS.

**RECOVERY**

Recovery refers to the use of strategies such as improving remyelination, increasing axon or dendrite sprouting, improving blood-brain barrier healing, and so on. Several clinical studies have used MRI methods to evaluate the effects of treatment on recovery from neurologic injury in patients with MS. Richert and colleagues used serial MTI images to evaluate MS lesions.
during a baseline period followed by treatment with interferon (IFN)-beta-1b or treatment of acute exacerbations with intravenous methylprednisolone for an average of 12 months. Improvement or recovery in MTR values back to baseline in MS lesions was pronounced with short-term steroid treatment and with IFN-beta-1b compared with lesions that developed during the baseline period. According to the investigators, this may reflect the fact that high-dose steroids produce a more rapid closing of the blood-brain barrier than enhancing lesions that developed while patients were taking IFN-beta-1b, although there was no difference in the length of time of enhancement between the treatment groups.

The effects of treatment with IFN-beta-1b on metabolic recovery were examined over the course of 12 months in patients with relapsing-remitting MS (RRMS). The ratio of NAA to creatine, an index of neuron-specific function, significantly increased with IFN-beta-1b treatment but decreased in control patients with MS (Figure 5). In a study that compared the immunomodulating drug glatiramer acetate with placebo in patients with RRMS, the number of new lesions that evolved into T1 black holes during 9 months of treatment was significantly lower among patients taking glatiramer (15.6% of new lesions) than those taking placebo (31.4%; P = .002).

Riluzole, a drug that reduces the activity of the excitatory amino-acid neurotransmitter glutamate, was examined using MRI measures of disease progression in patients with primary progressive MS. Patients were first studied for 1 year without treatment, during which the investigators noted an approximately 2% decrease in cross-sectional spinal cord area at the C2-C3 boundary. In the second year, during which patients received treatment with riluzole, spinal cord size stabilized, with a loss of 0.2%. The total T2 lesion load was not affected by riluzole treatment. The authors suggested that neuroprotective agents such as riluzole may have relatively little effect on the formation of new lesions but may produce a more specific sparing of axon loss. (Excitotoxic white-matter injury is described in detail by Drs Raine and Stys).

**Regeneration**

Several strategies have been proposed to produce regeneration of injured CNS tissue. Some possibilities include increasing stem-cell division, stimulating remyelination by progenitor oligodendrocytes, stimulating differentiation of stem cells, and the use of growth factors.
A recent study examined whether the administration of neural precursor cells (which can differentiate into neurons, astroglia, or oligodendroglia) could improve histologic or functional outcomes in an animal model of MS (experimental autoimmune encephalomyelitis [EAE]). Whether administered by intracranial or intravenous administration, neural precursor cells differentiated into myelin-forming cells and reestablished myelination. Astrocytic scar formation was also reduced in the animals that received neural precursor cells. Some preliminary studies suggest it may be possible to track the movement of these cells to their target sites. This has been demonstrated in a primate MS model in which EAE was induced by sensitizing marmosets to myelin proteins. Mononuclear cells, including T-cells, B-cells, monocytes, and stem cells, were labeled by transfecting them with iron oxides to decrease the signal intensity on T2 weighted MRI (J. Frank et al, unpublished observations). These cells could be visualized entering the spinal cord and reducing the extent of T2 lesion area over the course of several weeks after their administration.

**SUMMARY AND CONCLUSIONS**

The goal of slowing or repairing neurologic injury in MS could be met by several different approaches, such as removing inflammatory mediators, decreasing edema, increasing survival of injured axons, redistributing Na+ channels, reducing reactive gliosis, improving remyelination, or enhancing functional cortical adaptation. MRI techniques offer several different approaches to visualizing changes in CNS structure and function as a result of progressive neurologic injury and to assessing the effects of treatments on neurologic function.

**REFERENCES**