ABSTRACT

Conventional magnetic resonance imaging (MRI) techniques are important tools in the diagnosis and management of patients with multiple sclerosis (MS), but they reveal only a small part of the overall disease process. Lesion burden on T2-weighted MRI correlates to some extent with disability during the early stages of the disease, but is less sensitive to increasing disability among patients with more advanced disease. New approaches are required to assess neurodegenerative changes that occur at even the earliest stages of MS but become the predominant pathophysiology in the progressive stages of MS. Diffusion tensor imaging (DTI) is an MRI technique that allows quantification of tissue water molecules that are restricted in their direction of motion by central nervous system (CNS) white-matter tracts. DTI provides several measures that can be used to assess the integrity of axons and myelin, and these DTI indices correlate significantly with histologic measures of CNS injury. Magnetization transfer imaging provides a relatively specific measure of lipid-associated macromolecules, and is therefore sensitive to changes in myelin, perhaps before typical lesions appear on conventional MRI. Optical coherence tomography (OCT) uses infrared light to calculate the thickness of the retinal nerve fiber layer, which consists of axons that form the optic nerve. Several studies have demonstrated that OCT is able to visualize and quantify neurodegeneration in patients with MS. New imaging technologies may provide opportunities to examine neurodegeneration in patients with MS and to assess the neuroprotective effects of new MS therapies. (Adv Stud Med. 2009;9(2):48-52)

Magnetic resonance imaging (MRI) is widely used in the diagnosis and long-term monitoring of patients with multiple sclerosis (MS). Although conventional MRI techniques are important for the identification of inflammatory episodes that contribute to the clinical relapses of MS, these methods reveal only a small part of the overall disease process. Several new imaging techniques that are now being developed may allow clinicians and researchers to visualize and quantify structural changes caused by gradual and irreversible neurodegeneration. New techniques, such as diffusion tensor imaging (DTI), magnetization transfer imaging (MTI), and optical coherence tomography (OCT), are likely to be of great importance in the assessment of neuroprotection in future clinical trials and in the long-term assessment of neurologic injury among patients with MS.

CONVENTIONAL MRI IN THE ASSESSMENT OF MS

Conventional MRI techniques are important tools in the diagnosis and management of MS, but are also associated with significant limitations. Lesion burden...
on T2-weighted MRI correlates to some extent with disability during the early course of the disease. However, after progression of disability corresponding to an Expanded Disability Status Scale score of approximately 4, T2 lesion burden remains relatively unchanged despite the continued progression of disability. The poor correlation between disability and conventional MRI measures of disease activity may reflect the capacity of intact central nervous system (CNS) circuits to compensate for neuronal loss. However, it is also clear that many patients exhibit spinal cord or brainstem lesions on MRI that are clinically silent even though they are located in CNS regions that might be expected to produce clinical manifestations. T2 lesions therefore appear to lack specificity for at least some of the tissue-level changes that are clinically important in MS, and many patients continue to exhibit long-term functional decline and accumulating disability despite MRI findings that remain relatively stable.

Recent research has focused on the development of new techniques to examine neurodegeneration of the CNS. These techniques will contribute to a more complete understanding of the disease processes that occur in MS and will also be important in evaluating new drugs. However, whereas gadolinium-enhancing lesions have been a successful surrogate marker for CNS inflammatory activity when evaluating anti-inflammatory therapies, it has been a less successful measure of neuroprotection. The development of novel validated imaging markers of neuroprotection would therefore be an important advancement both in patient management and the drug development process. Although T1 precontrast black holes are considered a somewhat specific marker of axonal pathology, they are seen in most lesions at the time of enhancement, and therefore can only be judged as tissue damaging if they persist as black holes for 6 months after the contrast-enhancing stage. In addition, T1 black holes eventually involute and are filled in as cerebrospinal fluid space or neighboring healthy tissue, which confounds their longitudinal analysis. It would therefore be desirable to have new imaging techniques that are capable of detecting and quantifying axonal injury before it becomes permanent.

**DTI and MTI**

Most MRI technologies measure the diffusion of water protons. When permitted to move freely, water molecules diffuse in an isotropic (spherical) manner. However, water molecules in CNS white-matter fiber tract bundles are not free to diffuse isotropically, but are restricted in their direction of motion along the length of the fiber tract. As a result, the diffusion of water molecules in white-matter tracts is anisotropic (elliptical). DTI allows quantification of this anisotropic distribution of water molecules and can be used to examine the integrity of white-matter pathways within the CNS. DTI provides several measures that may be of importance in assessing CNS integrity, including fractional anisotropy (estimated by the diffusion of the principal eigenvector in the parallel plane divided by the diffusion of the 2 orthogonal vectors in the perpendicular planes), axial diffusivity (the tendency of water molecules to move parallel to axons; a proposed measure of axon integrity), and radial diffusivity (the tendency of water molecules to move perpendicular to the direction of the axon; a proposed measure of the integrity of both axons and myelin).

Animal model studies have attempted to relate these DTI measures to neuro-axonal damage. In one model, axons that originate in spinal dorsal roots are transected between the dorsal root ganglion and the axon entry point to the spinal cord. This transection results in the axonal degeneration of the ascending spinal nerve pathway, which is accompanied by a secondary breakdown of myelin. DTI identifies significant abnormality of axonal structure before lesions are evident on T2 imaging, with axial diffusivity revealing axonal injury as early as 38 hours after neuronal transection. DTI measures are also significantly correlated with histologic measures of CNS injury, such as neurofilament staining and the accumulation of β-amyloid precursor protein. Similar results have been observed in an animal model in which inflammatory demyelination was induced by injection of cytokines into the spinal cord, resulting in a focal myelitis that resembles transverse myelitis in humans. These studies have demonstrated that high-resolution DTI is able to visualize subtle anatomic differences in portions of the spinal cord that are distant from the site of the focal myelitis, and to identify tissue abnormalities in CNS regions that appear normal when visualized using conventional MRI.

In human subjects, automated DTI techniques have been developed to examine alterations in specific CNS white-matter tracts, including the optic radiations, corpus callosum, and corticospinal tracts. These
studies have demonstrated significant correlations between cognitive abnormalities and DTI measures of the corpus callosum in patients with MS (Calabresi PA, Unpublished observations). DTI has also been used to demonstrate subtle abnormalities of the optic radiations that are not evident using T2 imaging, including retrograde alterations in the optic radiations in response to optic neuritis, and correlations between tissue abnormalities of the optic radiations and the optic nerves.

In contrast to DTI, MTI identifies changes in water molecules associated with macromolecules, such as those that occur in lipid-rich structures, and is somewhat more specific than other techniques for the presence of myelin. Studies in patients with MS who underwent serial monthly MRI evaluations have demonstrated significant alterations in MTI approximately 1 to 2 months before the appearance of gadolinium enhancement. In the spinal cord, MTI abnormalities of the lateral columns in patients with MS have been shown to correlate significantly with impaired motor function (eg, diminished ankle strength), whereas dorsal column MTI abnormalities significantly correlated with impaired vibration sensation. In this study, the correlations between the MTI signal and quantitative measures of tract-specific disability were much higher than what has been seen in previous studies, suggesting that MTI may provide more relevant information than T2 signal changes alone.

OCT

Optic neuritis is common in patients with MS, yet often produces changes to the retina or optic nerves that are microscopic and difficult to visualize using conventional MRI techniques. In addition, autopsy studies of optic nerve and retina samples from patients with MS have demonstrated reduced axonal densities in patients with MS. Optic nerve pathology may provide a sensitive measure of global neuro-axonal loss in patients with MS.

Optical coherence tomography has recently emerged as a potentially important method for the assessment of neurologic injury in patients with MS. OCT quantifies the back-scatter of infrared light off the retinal layers in the back of the eye to calculate the thickness of the retinal nerve fiber layer (RNFL), which consists of the axons that coalesce to form the optic nerve. The OCT scan provides separate readings of the RNFL for 4 quadrants of the optic disc (temporal, superior, nasal, and inferior regions), calculates the mean thickness of the RNFL for each quadrant, and also provides a fundus photograph.

The use of OCT to visualize and quantify neurodegeneration in patients with MS has recently been evaluated in several studies. Fisher et al have examined the relationship between OCT and subtle visual abnormalities that occur after optic neuritis. When tested using conventional high-contrast letter acuity charts, approximately 90% of patients recovered apparently normal vision following an episode of optic neuritis. However, many patients exhibited persistent impairment when tested under low-contrast conditions (Figure 1). A loss of RNFL thickness of approximately 6 to 7 µm corresponded to a 2-line difference in low-contrast visual acuity using the vision charts shown in Figure 1. These persistent impairments reflect residual microscopic damage that ensues after an episode of optic neuritis. In addition, diminished RNFL has been described even in patients with MS who have no history of optic neuritis when compared...
with disease-free control subjects, suggesting that sub-clinical optic neuritis occurs more frequently than was previously thought to be the case.\textsuperscript{18,20,21}

In order to be useful as a measure of neurologic injury in clinical trials, OCT must be highly reproducible when administered by different investigators or by the same investigator at different times. One recent study examined the reproducibility and comparability of RNFL thickness measurements that were obtained for patients with MS or control subjects at 3 study centers.\textsuperscript{19} The 3 centers produced highly consistent measures of RNFL thickness in both patients with MS and control subjects. Compared with healthy control subjects, mean reductions of RNFL thickness of approximately 10 to 15 \( \mu \)m were noted for all 3 study sites.

Other research has examined RNFL thickness as a function of MS type and duration of illness. Significantly decreased RNFL thickness values have been reported in patients with secondary progressive MS (SPMS) compared to control subjects,\textsuperscript{20,21} and have also been described in patients with primary progressive MS (PPMS), even when there is no history of optic neuritis (Calabresi PA, Unpublished observations). One study compared RNFL thickness values for normal control subjects versus patients with relapsing/remitting MS, PPMS, and SPMS. As shown in Figure 2, the mean RNFL thickness values were significantly lower than the control value for all 3 MS groups, with the greatest loss of thickness among patients with SPMS.\textsuperscript{21} In a study that examined the relationship between RNFL thickness and the duration of MS, patients were subdivided on the basis of whether or not they had a history of optic neuritis (Johns Hopkins University MS Center, Unpublished observations). After controlling for patient age, the RNFL thickness decreased as a function of increasing disease duration for patients with or without a history of optic neuritis. The rate of loss was somewhat higher for patients without a history of optic neuritis, presumably because those with optic neuritis started at a lower point due to RNFL loss from their previous episode. Finally, RNFL thickness has also been shown to significantly predict brain atrophy in patients with MS (Figure 3).\textsuperscript{21} Thus, it is possible to some extent to assess global brain volume loss in patients with MS by examining the RNFL thickness.

The use of OCT for the assessment of patients...
with MS is associated with potential advantages and disadvantages. OCT is a rapid, office-based procedure that may be administered in approximately 10 minutes. The typical cost of an OCT device is approximately $50 000 to $70 000, compared with $1.5 to $2 million for an MRI scanner. OCT provides a specific measure of CNS axons that correlates well with visual function. However, the reproducibility and reliability of OCT have not been demonstrated in a large number of patients with MS. The rate of change in RNFL thickness over time is not well established, and it is not clear how a measure of RNFL at a particular moment in time predicts later retinal changes. In addition, the results may be confounded by edema.24 Although OCT appears to provide an important tool to assess CNS function and structure in patients with MS, additional research is required to determine how to incorporate OCT into clinical decision making.

**Conclusions**

Multiple sclerosis is characterized by inflammatory demyelination and axonal degeneration. The inflammatory component of MS is highly variable from patient to patient, and is influenced by factors such as genetic predisposition, the involvement of specific immune cell populations, and the tissue response to inflammatory mediators. Conventional MRI methods do not provide the specificity required to distinguish the inflammatory and neurodegenerative aspects of the disease. DTI and OCT are potentially useful techniques to quantify axonal damage in MS, whereas MTI appears to be the most promising specific measure of myelin. These new imaging techniques may provide the opportunity to examine the disease processes of MS at the tissue level and to assess new MS treatments with neuroprotective effects.

**References**