Image of the Month

Magnetization transfer imaging (MTI) assays macromolecular protons through their intimate connection and interaction with surrounding tissue water.

"Anywhere it's applied, MTI is very sensitive to macromolecular makeup of the tissue," said Seth Smith, Ph.D., a postdoctoral fellow at the F.M. Kirby Imaging Center at Johns Hopkins University in Baltimore. In the case of patients with multiple sclerosis (MS), this means myelin. "MTI is a much more sensitive myelin marker than any other conventional imaging technique," he said.

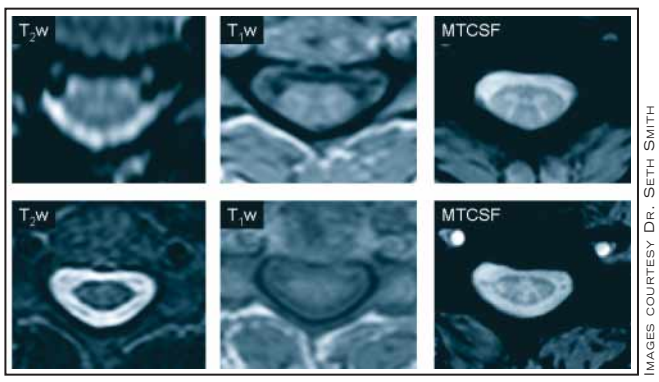
Conventional MRI targets only water, making it hard to assess the macromolecular subunits of CNS tissue, like myelin. With MTI, an initial off-resonance radiofrequency pulse is applied to the spinal column. This pulse selectively saturates the magnetization of protons attached to such macromolecules as myelin. Some of this magnetization is transferred to free protons in tissue, which reduces the intensity of the observed water signal. Since MT's effect depends on the density of macromolecules in the tissue, "it's a backdoor method for getting at the macromolecular structure," said Dr. Smith.

The researchers then calculate a slightly modified magnetization transfer ratio, based on the difference in the signal intensity with and without an MT prepulse, to quantify differences between patients with MS and healthy controls.

In the past, it was difficult to ascertain whether or not spinal cord lesions were a significant factor in MS. Conventional MR imaging did not reveal the amount of tissue damage that was actually present in the spinal cord, though inflammation can be seen. MTI reveals much more MS pathology. It is now hypothesized that a lot of the clinical deficit in MS arises from spinal cord damage. "When we use MT imaging, what we find is that every cord [from patients with MS] is damaged in some way," said Dr. Smith.

The presence of MS spinal lesions on MTI correlates better with the patient's symptoms at presentation than does the presence of brain lesions detected by MRI. A patient with MS brain lesions may be walking at presentation. However, "if I look at the spinal cord and see a bunch of lesions, I can guarantee that the patient is not walking well," said Dr. Smith.

The researchers have imaged patients of varying ages and at a spectrum of stages in MS: relapsing-remitting, secondary progressive, etc. Since it is difficult to get a patient before he or she has had an attack, information from such studies about the early stages of the disease may prove useful, said Dr. Smith. The researchers also are imaging MS patients periodically (3, 6, 12, and 24 months) to see if they can detect changes in the disease over time.



Images courtesy Dr. Seth Smith

Healthy spine by T2 and T1 3T MRI and MTCSF (top): While T2 and T1 MRI show slight cord atrophy in an MS patient, MTCSF shows hyperintensities in the lateral (green arrow) and dorsal (yellow arrow) column (bottom).

The researchers are seeking links between MS-induced changes on spinal MTI and brain MTI and the neurologic presentation of patients with MS. The correlation between spinal MTI and the neurologic presentation has been striking.

"We and others find in the brain there is little correlation with clinical presentation. However, the second we look at the spine, everything starts to correlate," said Dr. Smith. The spine is the main pipeline for nerves in the body, so "if you get a small lesion in something the size of a quarter, the effects could be massive."

MRI is used to confirm the clinical findings in patients suspected of MS. "We're hoping to make MTI more of a diagnostic tool," Dr. Smith said. A strong enough correlation between MTI spinal imaging findings and the neurologic presentation could lead to the primary use of MRI to diagnose MS and predict outcome.

MTI also has implications for therapy. Right now, patients with MS often are treated with axonal protection agents, but the effects may take a long time to be seen. "What we hope to see is, can we within a shorter amount of time see that there is any sort of change in the tissue due to therapeutic intervention," said Dr. Smith.

MTI scans can be done with most higher field MRI scanners using a surface/spine coil and each scan takes only 7 minutes using a 3T magnet. This implies that the technique could easily be integrated into an imaging center or hospital radiology department.

Dr. Smith's collaborators include Dr. Peter Calabresi; Peter van Zijl, Ph.D.; Craig Jones, Ph.D.; Eliza Gordon-Lipkin; and Kathleen Zackowski, Ph.D.

—Kerri Wachter

Over One-Third of MS Patients Report Missing Injections at Least Monthly

BY DOUG BRUNK
San Diego Bureau

San Diego — More than one-third of multiple sclerosis patients missed at least one injection of a first-line disease-modifying therapy over a 4-week period, results from a large multicenter study showed.

The most frequently reported reasons were forgetting to take the injection, not feeling like taking it, and being tired of the shot, Katherine A. Treadaway reported in a poster session at the annual meeting of the American Academy of Neurology.

The study marks the first time that adherence to all four first-line disease-modifying therapies (DMTs) approved for the management of multiple sclerosis—Avonex, Betaseron, Copaxone, and Rebif—were assessed in a multicenter patient population.

Patients who were most compliant with their medication schedule had a higher quality of life, lower rates of depression, and higher levels of hope. Neurologists "need to ask their patients if they're taking their medications and whether the medications are causing problems," Ms. Treadaway, a licensed clinical social worker at the Multiple Sclerosis Program and Clinical Center, of the University of Texas Southwestern Medical Center at Dallas, said in an interview. "Depression might also be something neurologists can ask about, because we want people to stay on the medications."

Ms. Treadaway and her associates at 17 sites nationwide recruited patients to participate in a Web-based survey to determine what factors influence adherence to DMT injection schedules. The survey included the Multiple Sclerosis Quality of Life-54 (MSQOL-54), the Beck Depression Inventory (BDI) Fast Screen, the Herth Hope Index, and questions about medication compliance. Study participants were surveyed at baseline, 4 weeks, and 8 weeks.

Adherence was defined as not missing an injection of a DMT in the last 4 weeks. Nonadherence was defined as missing at least one DMT injection in the last 4 weeks.

Of the 798 survey respondents, 77% were female and their median disease duration was 5 years.

Overall, more than one-third of patients were nonadherent, which remained consistent across all three time periods. Adherence rates were 61% at baseline, 63% at 4 weeks, and 64% at 8 weeks.

The top five reasons for nonadherence as reported by patients were forgetting to administer the injection (58%), not feeling like taking the injection (22%), being tired of taking the injection (16%), fatigue (12%), and inconvenience of the dosing schedule (8%). Study patients were allowed to report more than one reason for noncompliance.

Ms. Treadaway also reported that compared with adherent patients, nonadherent patients had significantly worse perceived quality of life based on the MSQOL-54, lower levels of hope based on the Herth Hope Index (39.5 vs. 38.2), and significantly higher depression scores based on the BDI Fast Screen (scores ranged from 2.5 to 3.4 on a scale of 1-21).

"I think education is a big key to keeping people on their [DMT] medications," she commented. "If they're satisfied and they feel like it's working, they're going to be more adherent."

Limitations of the study include its observational design and its reliance on patient self-reports, she noted.

The study was supported by an unrestricted grant from Biogen Idec Inc., which manufactures Avonex. Ms. Treadaway disclosed that she has received speaker honoraria from Biogen Idec and from Teva Neuroscience Inc., which manufactures Copaxone. ■

Study: Natalizumab Use Poses Limited Risk of PML

Los Angeles — There is limited risk of developing progressive multifocal leukoencephalopathy with the use of natalizumab, according to the results of a safety evaluation presented at the annual Digestive Disease Week.

Researchers from the Mayo Clinic in Rochester, Minn., and Cedars-Sinai Medical Center in Los Angeles evaluated patients who had taken the drug while participating in clinical trials of its use in treating Crohn's disease, multiple sclerosis, and rheumatoid arthritis.

Trials involving natalizumab (marketed as Tysabri) were halted in 2005 after there were two reports of patients who developed progressive multifocal leukoencephalopathy (PML) while taking combination therapy with natalizumab and interferon-β. A third report described a patient who was taking natalizumab alone and had previously taken the drug in combination with azathioprine.

Earlier this year, the FDA lifted is clinical hold on trials of the drug for multiple sclerosis. The agency has yet to announce a decision about wider marketing of the drug.

For the safety evaluation, the researchers screened participants in the two suspended studies and a completed 2004 study of multiple sclerosis. The majority of patients from the original studies participated in the safety evaluation.

No additional cases were found to have the JC virus, which has been associated with PML, according to the researchers. They found that the absolute risk of developing PML after taking natalizumab was about 0.1%.

Since only three patients developed PML, it was difficult for researchers to identify any risk factors for the rare disorder, said lead study author Dr. William Sandborn of the Mayo Clinic. Dr. Sandborn is a consultant for Elan, which jointly markets the drug with Biogen Idec. The companies funded the safety evaluation.

However, Dr. Sandborn noted that the patients who developed PML had taken natalizumab in combination with either interferon-β or azathioprine, and physicians were likely to use the drug as monotherapy until the risk factors were better understood.

It is unclear whether a screening strategy would be effective for PML, according to the researchers.

—Mary Ellen Schneider