

A

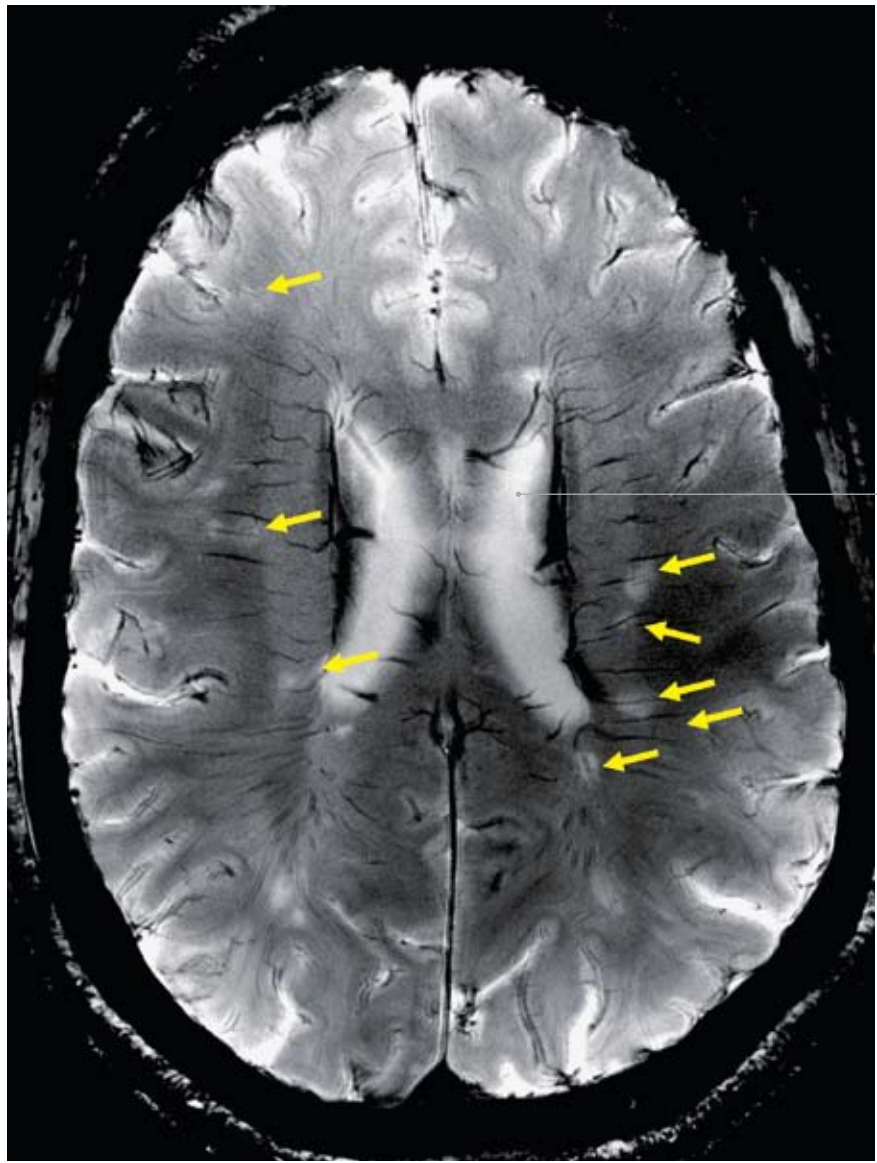
▲ SCAN

Brain images obtained with the ultra-high-field 7-tesla MRI scanner at NYU Langone Medical Center reveal subtle abnormalities that cannot be seen with

conventional MRI. Images A and B are from a patient with multiple sclerosis and show subtle vascular abnormalities in very early lesions. Yellow arrows show inflammation

surrounding venous blood vessels in these lesions, suggesting that blood vessel abnormalities are linked to the development of early lesions in MS patients.

The 7-tesla magnet is 140,000 times stronger than the earth's magnetic pull. The Medical Center's 7-tesla MRI is one of a handful available for basic and clinical research in the U.S.



LATERAL VENTRICLES

B

▲ SCAN

Lesions are more abundant in image B, which was obtained from the periventricular region of the brain,

where MS lesions are often found. White arrows in image A point to abnormal iron deposits, which can be detected on 7-tesla MRI, indicating early

neuronal degeneration in deep gray matter (i.e., lentiform nucleus, head of caudate, and thalamus).

Predicting the Course of MS

Powerful tools are enabling researchers to search for markers that may help predict when, and how fast, the disease will progress.

BY GINA SHAW

What happens next?

→ That's the question that confronts patients, clinicians, and researchers when a diagnosis of MS is made.

To patients, it's an especially agonizing question because they are usually young when MS strikes—the average age of onset is 27. Will they have a limp? Will they need a wheelchair? Will it affect their mind? Or will they have few if any symptoms?

To clinicians and researchers, it's frustrating that they simply don't know.

Multiple sclerosis confounds scientists, explains Oded Gonen, Ph.D., professor of radiology, and physiology and neuroscience, because they are unable to predict the course of this disease. Conventional imaging techniques offer confusing information. The number of lesions identified does not always correlate with the degree of disability. Moreover, these techniques fail to identify some lesions that influence the severity of the disease.

Dr. Gonen and his colleagues at NYU's Center for Biomedical Imaging are addressing these problems by bringing to bear an arsenal of the world's most powerful and sophisticated imaging techniques to find markers in the brain that will signal how severe the disease will become.

It is a mission he first undertook at the suggestion of Robert I. Grossman, M.D., Dean and CEO, when both were at the University of Pennsylvania. Dr. Grossman has devoted the past 20 years to the development of novel radiologic methods to unveil and understand the hidden signs of MS and to assess patients' response to treatment. This endeavor has earned Dr. Grossman an international reputation as a preeminent researcher in this field. He became chairman of radiology at NYU in 2001, and again recruited Dr. Gonen to join him.

Dr. Gonen is applying spectroscopy to the study of MS. "We're looking for imaging holy grails that will tell us accurately, specifically, and early if there are changes to the brain of MS patients, and whether those are good or bad changes," says Dr. Gonen.

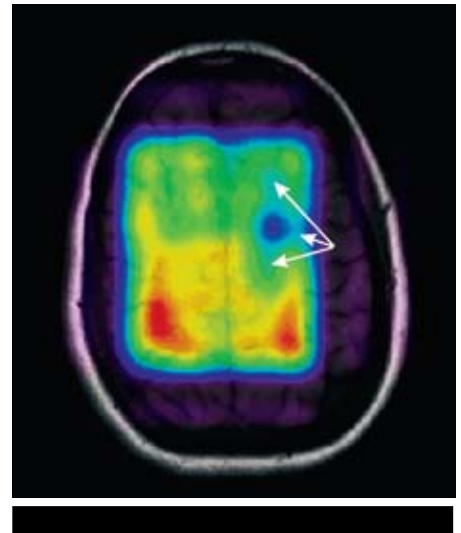
Dr. Gonen's studies are part of a decade-long collaboration with Dr. Grossman. Other researchers working in this area include Yulin Ge, M.D., associate professor of radiology, and Matilde Inglese, M.D., Ph.D., associate professor of radiology and neurology. All of their

studies are supported in part by the National Institutes of Health.

Dr. Gonen is using MR spectroscopy to study four major brain metabolites that may prove to be useful biomarkers of MS: n-acetyl aspartate (NAA), an amino acid found only in the neurons and axons of the brain and a key marker of neuronal health and integrity; choline, a marker of membrane construction and breakdown; and creatine and myo-inositol, which in combination are markers of energy and proliferation of glial cells." (Glial cells help to form myelin, and they also transmit signals in the nervous system.)

"What I'm trying to do is determine whether those markers predict what is going to happen clinically before it happens," Dr. Gonen says. "Growing deficits of NAA will probably be reflected in cognitive dysfunction, for example, and an increase in regional choline levels may indicate that a lesion is about to appear there that may or may not also cause a relapse."

Dr. Gonen's study is tracking 25 MS patients in the early stages of the disease, and 25 age- and gender-matched controls, for five years. Three years into the research, his findings indicate that early on in the disease, there is little detectable difference in NAA levels—the essential marker of neuronal death—between MS patients and normal controls. Since patients at this stage of the disease usu-



Brain metabolites such as n-acetyl aspartate (NAA) may prove to be useful biomarkers for MS. Seen here is an MRI of the brain of a female MS patient, overlaid with the metabolic distribution of NAA, obtained with proton MR-spectroscopy (MRS) displayed in the format of a heat map for enhanced color contrast.

Such images allow anatomic locations in the brain (from the underlying MRI) to be associated with metabolic activities (from the overlaid MRS). The white arrows point to a metabolic "hole," or deficit, over the visible lesion in the white-matter region of the brain as well as to a "halo" of NAA deficit surrounding it, which is not seen on the MRI.

ally have little cognitive dysfunction, this result jibes with his theories about NAA levels. He has found elevated levels of choline—the marker for the inflammatory stage of the disease, in which the myelin sheaths that shield the brain's axons are slowly destroyed.

"The first thing that happens in the disease, that's what I think you should develop drugs to stop. My findings indicate that with MS, it's not neuronal damage, but inflammation or maybe even an earlier process," Dr. Gonen says. "That suggests to me that if you're a drug developer, you should focus on an anti-inflammatory treatment for the early stages, and the brain will take care of neuronal preservation."

"We're looking for imaging holy grails that will tell us accurately, specifically, and early if there are changes to the brain of MS patients, and whether those are good or bad changes," says Dr. Gonen.



D ▲

Oded Gonen, Ph.D., (left) with Yulin Ge, M.D., and Matilde Inglesse, M.D., Ph.D., in front of the 7-tesla

MRI machine at NYU Langone Medical Center. The glowing orange and yellow globe in

the center of the 7-T head coil contains pure oil, which is used for calibrating the system.

Neuroradiologist Dr. Inglesse focuses on the clinical application of advanced MRI techniques in people with MS. She notes that imaging in common use today cannot detect prelesional injury, nor can it differentiate between lesions where there is merely inflammation and those that involve the death of axons. An axon is a critical part of a neuron because it transmits signals to other neurons. This is a critical distinction for the clinical picture because lesions where there is axonal loss are the only ones that lead to loss of function, such as a limp or cognitive problem.

“That’s why there’s this disconnect, this poor correlation between the number of lesions on the brain and the scores on rating scales used to measure disability,” says Dr. Inglesse.

Neuroradiologist Dr. Yulin Ge is focusing on inflammation. NYU is one of only a few major research centers in the country that have a 7-tesla MRI unit; most researchers are working with 3-tesla. (A tesla is a measure of MRI field strength—the higher

the number, the more detailed the image.) Using 7-T, Dr. Ge has been able to detect differences among lesions that appear identical on conventional MRI. “What we’re finding,” says Dr. Ge, “is that the *number* of lesions is less important, because most lesions are found in white matter. The gray matter damage—neuronal damage—plays more of a role in neurological dysfunction and disability. Using quantitative MRI, we are developing methods to analyze the total lesion load so that we can better understand brain atrophy and the effect of treatment on that atrophy.”

Dr. Ge is also using 7-T MRI to detect minuscule changes signaling that a lesion is about to develop. “We recently scanned MS patients and found that there are lots

of subtle vascular abnormalities which had never been seen before in such detail,” he says. “This vascular inflammation event is critical in the evolution of MS lesions. These findings not only highlight early lesion development, they will also be very important for monitoring treatment that might stop damage before it starts.”

It will take time, though, before these techniques are available outside the research setting. Dr. Gonen wishes he and his colleagues could speed up the process: “I would like to know the future now. It’s disheartening when your doctor puts you on a medication, five years elapse and you get worse, and the doctor says that it might have been the wrong medication all along. I don’t want patients to have to hear that.” ●