

# Imaging Suggests Gray Matter Atrophy in MS

VITALS

**Major Finding:** Volumetric measurements of the cerebral cortex and hippocampus declined with disease duration in multiple sclerosis.

**Data Source:** Imaging study of 38 adults with relapsing-remitting multiple sclerosis.

**Disclosures:** None.

BY MICHELE G. SULLIVAN

BANGKOK, THAILAND — Far from affecting only white matter, multiple sclerosis seems to strike at gray matter as well, causing atrophy of brain structures that correlates with disease duration and declining cognitive function.

“Traditionally, multiple sclerosis has been considered a white matter disease, but recent literature suggests an involvement of the gray matter as well, causing atrophy of particular brain regions,” Asaf Achiron said at the World Congress of Neurology.

Mr. Achiron, a fifth-year medical student, presented the results of an imaging study of 38 adults with relapsing-remitting multiple sclerosis, in which he tracked volumetric changes in specific brain regions as the disease progressed. The research was part of the Arrow Project, a student/professor collaboration in Tel Aviv University. Mr. Achiron’s mentor, Dr. Ida Sarova-Pinhas, is a neurologist at The Chaim Sheba Medical Center, Tel Hashomer, Israel, and at Tel Aviv University.

The collaborators used a computerized

imaging program called FreeSurfer to determine thickness and volume of the cerebral cortices, thalamus, and hippocampi of their subjects.

FreeSurfer is a set of automated tools that can reconstruct the brain’s cortical surface from structural MRI data and overlay functional MRI data onto the reconstructed surface.

The study group consisted of 38 patients with relapsing-remitting MS, 24 of whom were women. Those with short disease duration (fewer than 5 years) were an average age of 33 years, with an average disease duration of 2 years. Those with longer disease duration (more than 5 years) were an average age of 36 years with an average disease duration of 11 years. Significant differences were found in the neurologic disability of those with shorter compared with longer disease duration.

In addition to undergoing MRI studies, the patients completed an online cognitive assessment called the Neurotrax Mindstreams Computerized Cognitive Battery ([www.neurotrax.com](http://www.neurotrax.com)). Mindstreams allows testing for mild cognitive impairment in the domains of memory, executive function, attention, visual spatial perceptions, verbal function, information processing motor skills, and mo-

tor skills. It also allows the assessment of patients who might have more severe cognitive deficits.

Mr. Achiron and Dr. Sarova-Pinhas found that, compared with patients with longer disease duration, patients with shorter disease duration had significantly larger volumetric measurements of the right cerebral cortex (274 vs. 245 cc) and left cerebral cortex (276 vs. 247 cc) and the right and left hippocampi (both 4.7 vs. 4.3 cc). While the differences were not significant, the right thalamus was larger in the group with shorter disease duration (7.4 vs. 7.0 cc), as was the left

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thalamus (7.8 vs. 7.4 cc).

“My feeling is that if we had a larger group, we might have reached significance,” in thalamic volume difference, Mr. Achiron said.

In the cognitive testing, patients with short duration of disease had significantly better scores in global cognition, visual spatial perception, and executive function than did those with longer disease duration.

“This loss of gray matter is a complement of the axonal loss and the genesis of symptomatic progression in MS,” Mr.

Achiron said. “Identification of these specific areas of loss has clinical relevance for understanding the associated cognitive changes.”

FreeSurfer software, developed by the National Institutes of Health, is available for free download at <http://surfer.nmr.mgh.harvard.edu/>. The page also contains a link to FreeSurfer Wiki, which walks new users through several tutorials using provided MRI images. The main FreeSurfer page also contains a link to a discussion board where users can field questions about the program and how it is best used.

The Arrow Project is a research program for medical students held in the Multiple Sclerosis Center at Sheba Medical Center, Tel Hashomer. Its aim is to strengthen students’ knowledge and

practice, and train them to be better physicians and researchers. Students are matched with a mentor and together, they choose a study topic and work on its design, literature review, and methodology.

This year, 10 students, including Mr. Achiron, are involved in the program (<http://medical-students.ny.sheba.co.il/>).

To watch a video interview of Mr. Achiron, go to [www.youtube.com/watch?v=2gfvYiwacaw](http://www.youtube.com/watch?v=2gfvYiwacaw).

## Lesions in MS May Resurge After Halting Natalizumab

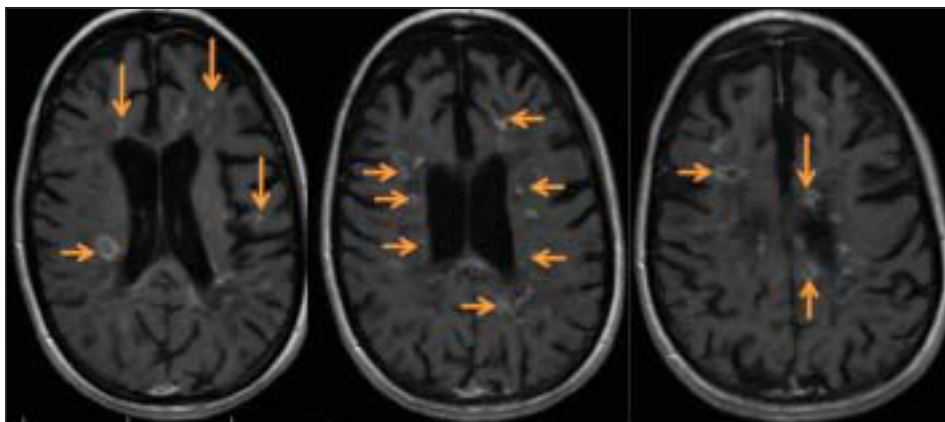
BY MICHELE G. SULLIVAN

BANGKOK, THAILAND — Patients with multiple sclerosis who abruptly discontinue natalizumab treatment may develop a sudden surge in the number of gadolinium enhancing lesions apparent on imaging, which seems to resolve by 9 months.

The phenomenon is probably a reaction to the sudden resurgence of lymphocytes into the brain—a central nervous system form of immune reconstitution inflammatory syndrome, Dr. Omar Khan said at the World Congress of Neurology.

Although the dramatic imaging changes aren’t accompanied by clinical deterioration, about 22% of the lesions did develop into nonenhancing T1 hypointensities, said Dr. Khan, director of the Wayne State University Multiple Sclerosis Clinical Research Center and Radiology Image Analysis Laboratory, Detroit. “Some patients may accumulate a lot of irreversible neuronal damage in this short period of time. And although it’s too soon to know for sure, my gut feeling is that over 3 or 4 years, there might be some consequences,” he noted.

Dr. Khan presented a case series of 11 patients with MS who had received natalizumab infusions before stopping the treatment abruptly. The reasons that were given for discontinuation included infusion site reactions, the development of neutralizing antibodies,



**When this 43-year-old woman discontinued natalizumab after the 17th infusion of the drug, she developed many areas of gadolinium enhancement, which were visible 3 months after discontinuation. Most areas of enhancement appeared in areas that previously were normal on T2 or FLAIR sequences before the patient started on the natalizumab treatment.**

changes in insurance coverage, and patient concerns about developing progressive multifocal leukoencephalopathy.

The patients’ mean age was 36 years. They had undergone a mean of 13 natalizumab infusions, although that number ranged from 8 to 21. Before taking natalizumab, their mean relapse rate was 1.6/year; the mean relapse rate at discontinuation of the drug was 0.1/year. All patients were negative for John Cunningham virus.

Before beginning natalizumab, the patients had a mean of 12 T2 lesions, two T1 lesions, and 20 gadolinium-enhancing lesions on MRI. Three months after stopping the drug, the numbers of lesions increased sig-

nificantly, to 17 T2 lesions, 13 T1 lesions, and 137 gadolinium-enhancing lesions. Overall, 93 of the lesions appeared in brain areas that were previously normal-appearing on imaging.

Before natalizumab discontinuation, the mean magnetization transfer ratio value of the gadolinium-enhancing lesions was 31%; at month 3, the mean value had dropped to 19%. “This is a pretty impressive decline, something telling us there might be some fairly intense inflammatory injury on these sites,” Dr. Khan said.

Despite the “alarming” scans, Dr. Khan said, the patients did not show corresponding clinical deterioration. Their mean Expanded Disability Status Scale (EDSS) was 3.2 at discontinuation, and did not increase significantly by 3 months.

By 9 months, however, the scans had almost universally improved. The mean number of T2, T1, and gadolinium-enhancing lesions had dropped and were not significantly different from the number of lesions seen at baseline.

Clinically, the patients remained stable, Dr. Khan said. Their mean EDSS at 9 months was 4.0—not significantly worse than it was at natalizumab discontinuation. The mean relapse rate also was not significantly different.

Dr. Khan said the study was independently funded and he did not have any financial declarations to make.

COURTESY DR. OMAR KHAN