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Harry Scull Jr./Buffalo News

Study could hold key to MS treatment

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Buffalo researchers early next year expect to report the initial results of the first major study of a controversial new theory that multiple sclerosis is caused by blockages in the veins that drain the brain.

If proven correct, the novel theory could overturn the current understanding of how to diagnose and treat a disabling and incurable disease that attacks the nervous system.

Advocates of the new theory contend that angioplasty, the same procedure used to open clogged arteries around the heart, could repair the blockages.

If so, it could change the lives of the 2.5 million people worldwide — 500,000 in the United States — with MS, many of whom are desperate for better therapies and intensely monitoring the work here.

In the few months since news reports announced the study, the Buffalo research team has fielded thousands of telephone calls from patients and has become the focus of MS-related Web sites, chat rooms and blogs on the Internet.

The frenzied reaction, including claims that there already is a cure and the pharmaceutical industry is trying to suppress it, contributed to multiple sclerosis organizations around the world recently urging caution while awaiting the results of more studies.

“The idea looks encouraging, but even if it turns out to be right, people need to remember that miracles don’t happen overnight. We have to prove it first,” said Dr. Robert Zivadinov, the principal investigator.

Zivadinov, director of the Buffalo Neuroimaging Analysis Center, is careful not to hype the new theory as groundbreaking medicine. Multiple sclerosis is a complex disorder, and skeptics raise questions that have not yet been answered.

But Zivadinov and others also view the early evidence as compelling and are excited about the potential prospects for patients and for the MS medical programs in Buffalo that might get a head start in pioneering a new treatment.

“We’re two to four years away from being able to say whether this can be recommended as a treatment and understanding its value,” Zivadinov said. “This is the nature of science. We need data.”

Body attacks itself

Multiple sclerosis is a mysterious disease that is difficult to diagnose and different in each person. It’s not known why, but the body attacks itself. Cells in the immune system that normally fight such foreign invaders as bacteria instead damage myelin, the fatty substance that surrounds nerve fibers similar to the way insulation protects electrical wiring, as well as the nerve cells.

Scars created by multiple sclerosis disrupt the messages between the brain and other parts of the body that control muscle movements — everything from seeing to urinating to walking.

Most multiple sclerosis patients initially develop a relapsing-remitting form of the disease characterized by unpredictable attacks followed by periods of recovery. Many eventually slip into a progressive phase of decline in which disabling symptoms steadily worsen.

There is no cure for MS, but in the last 26 years, a handful of medications have come to market to treat the exacerbations and slow the course of the disease. Research by the late Dr. Lawrence D. Jacobs, a Buffalo neurologist, played a key role in the development of Avonex, the drug most widely prescribed to treat relapsing MS.

The available drugs offer an option that didn’t exist before, but they have shortcomings. They can cause side effects and stop working. More than anything, they don’t help against the progressive form of the disease.

“We’re always trying to postpone the second part of multiple sclerosis — the progression. We get to a point that we can’t get past,” said Dr. Bianca Weinstock-Guttman, director of the Baird MS Center at the Jacobs Neurological Institute.

The Neuroimaging Analysis Center is also part of the institute, which is part of the University at Buffalo Neurology Department and located at Kaleida Health's Buffalo General Hospital.

A link to iron

The chief proponent of the new theory is Dr. Paolo Zamboni, director of the Vascular Diseases Center at the University of Ferrara in Italy, who in 2002 looked into the possibility that malfunctioning veins might damage the central nervous system. He shook up the MS community in late 2008 with a study that tested the theory in 65 patients with multiple sclerosis and 235 people who were healthy or suffered from different neurological disorders.

Others in the past had suggested a similar link, but the idea never gained traction, as research focused on the role of the immune system.

Zamboni developed sophisticated Doppler ultrasound techniques to detect abnormalities in the veins in the brain and neck, a key technical advance, and found a dramatic association between MS and obstructed blood drainage in the veins draining the brain.

He called the pattern chronic cerebrospinal venous insufficiency, or CCSVI, and suggested that the narrowing of the veins caused blood flow to reverse itself back into the brain. The backward flow, he theorized, allows immune system cells to cross the body's protective blood-brain barrier and damage nerve fibers.

He also suggested that the damage involved the buildup of iron deposits in veins. The body needs iron, but too much of it is linked to brain disorders.

If correct, Zamboni's theories will upset current thinking on MS. But experts say the work requires more scrutiny.

Because everyone in his research had MS, it's not clear if the blocked veins were the cause of the multiple sclerosis or a consequence of having the disease. The study also was small and lacked some of the safeguards demanded of major research projects before a new idea gains acceptance.

"This is the main reason to plan sooner a study with an indubitable level of evidence," said Zamboni, who has urged other researchers to test his ideas.

Replicating results

The Buffalo Neuroimaging Analysis Center took up the challenge.

Zivadinov's team, which was conducting research on iron in the brain in MS, will try to replicate Zamboni's findings in a much larger group of patients and in a randomized controlled trial, the gold standard of medical research.

Zivadinov plans to recruit 1,100 patients with all types of MS, including children, 300 healthy volunteers and 350 people with other neurological diseases.

Using Doppler ultrasound, which uses sound waves to evaluate blood as it flows through a vessel, the researchers will look for blockages in veins of the neck and brain. Participants also will complete an extensive questionnaire to identify potential MS risk factors.

In another part of the study, patients will undergo MRI exams of their brains to measure iron deposits. The Buffalo researchers are the first to explore iron in the brain in connection with vein abnormalities diagnosed by Doppler ultrasound. They will also see if MRI is a reliable way to identify abnormalities in veins.

It's hoped the larger, more diverse set of patients can shed light on when the vein abnormalities in multiple sclerosis begin — evidence suggests they may be congenital — and why some people show the radiological signs of MS but don't exhibit symptoms of the disease.

“If you’re born with CCSVI, why does it take years to get multiple sclerosis?” asked Zivadinov. “Is it linked to the amount of iron in the brain? Are there triggers, such as smoking or vitamin D deficiency?”

The Buffalo team is also collaborating with Italian researchers, including Zamboni, on a second study in which 16 multiple sclerosis patients — eight from Buffalo and eight from Italy — were assessed in Buffalo using MRI and then had their blockages cleared in Italy by angioplasty. They expect to report the findings early next year.

Whether the new approach offers a new treatment is the fundamental question for patients.

“We’re very encouraged but can’t say it’s a 100 percent thing yet,” said Zivadinov.

Hope for a new therapy

Zamboni and his colleagues treated 65 other multiple sclerosis patients with angioplasty, calling it the liberation procedure, as part of a pilot study published this month. It offered mixed results.

In half of the patients with clogged jugular veins, for instance, the narrowing reoccurred in the months following the procedure. Zamboni suggests the solution may be to use stents, metal devices to prop open vessels, although this will require technical advances to make stents designed for veins.

The patients with progressive MS did not show improvement in function 18 months after angioplasty. But the procedure, which is considered experimental for MS patients, showed significant success at alleviating exacerbations in patients with the relapsing form.

Zamboni, who used a stent in one patient in the study, said the findings are not good enough to routinely offer angioplasty to MS patients, but do warrant larger, scientific trials. Balloon angioplasty and stents carry risks, and at least one MS patient died and one other has suffered severe complications following use of a stent to open a vein, according to physicians who follow the research.

A Stanford University surgeon, Dr. Michael Dake, was the first physician outside of Italy to treat this vein blood flow problem with stents. He recently stopped offering the procedure but is working with the school on a possible study involving stents for MS, said Stanford spokesman Paul Costello.

Hospitals and medical schools generally require physicians to obtain permission from review boards before trying experimental therapies on patients.

National MS societies are taking a wait-and-see approach to the vein condition in MS patients while offering grants for research. The Buffalo study, which is seeking a grant and private donations, will cost an estimated \$5 million.

“We don’t understand the cause of MS and don’t have optimal treatments. Therefore, we need to think outside the box,” said Dr. John R. Richert, executive vice president of research and clinical programs at the National Multiple Sclerosis Society.

“You can’t blame people with MS from grabbing on to this,” he said. “Unfortunately, our field is full of therapies that looked promising in the early stages but didn’t hold up.”

Strange disease

Individuals like Melinda Kontos, who is among the 4,000 with MS in the Buffalo Niagara region, would welcome an alternative treatment.

The disease forced her to quit playing the violin and teaching music because of pain, double vision and falling episodes.

Now, after disappointing results with medications, she has gone three years on the drug Tysabri without an exacerbation and can play the violin again. She hopes to remain stable, but MS is unpredictable.

“Every day is different,” she said. “This is an incredibly strange disease.”

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