Experimental Multiple Sclerosis Vascular Shunting Procedure Halted at Stanford

Last August, 51-year-old multiple sclerosis (MS) patient Holly Shean was flying home to Arizona after undergoing an experimental surgical endovascular procedure at Stanford School of Medicine, during which two self-regulating stents were inserted to open a stenosis in her right jugular vein.

Her surgeon believed the stents could restore normal blood flow from the brain and alleviate some of her symptoms, a procedure developed by an Italian researcher but one that has never been evaluated for safety and efficacy in a clinical trial.

Shortly after her return, Shean suffered a fatal hemorrhage to her brain stem while on coumadin following the procedure. Although her family has stated publicly that her death was not due to the experimental procedure – noting that her mother suffered a similar stroke – many experts, including some of the surgeon’s colleagues at Stanford, are openly critical that the procedure was being performed without adequate evaluation.

Shean’s death marked a turning point in what has become one of the mostcontentiously debated issues in MS today: chronic cerebrospinal venous insufficiency, or CCSVI.

Dr. Paolo Zamboni, a vascular surgeon at Italy’s University of Ferrara, began studying what became known CCSVI in 2002. Using Doppler ultrasound and venograms, he and his colleagues reported that 100 percent of MS patients they had studied had stenoses or malformations of the internal jugular and/or azygous veins. They theorized that these blockages constrict the flow of blood, causing a reflux back into the brain and/or spine, leading to edema and inflammation. This, they reasoned, might cause the immune response and lead to the lesions that are the hallmark of MS.

Zamboni and his colleagues then began inserting endovascular stents or balloons to open the blocked or malformed veins, a technique they named “the liberation procedure.” They report being able to correct the problem in 100 percent of patients, relieving symptoms in many.

In the December, 2009 Journal of Vascular Surgery, Zamboni published results of a study of the procedure in 65 patients with either relapsing/remitting, primary progressive or secondary progressive MS. Using sonograms to detect abnormalities of venous drainage, they reported significant functional gains in patients with relapsing/remitting (RR) disease, and better quality of life scores after one year in patients with RR and primary progressive disease.

But because their research has yet to be confirmed by others, or replicated in a randomized, blinded or controlled study, most neurologists, and even Dr. Zamboni himself, have repeatedly emphasized the need for major clinical trials to test the paradigm.

On December 10, the National Multiple Sclerosis Society released a position statement on CCSVI in response to the findings:

“To get the quickest answers and most reliable results about benefits and risks of any surgical procedure that might attempt to address blood flow in or out of the brain, it is crucial that such surgery be performed only as part of controlled trials, especially since there have been anecdotal reports of surgical attempts to treat CCSVI in people with MS resulting in adverse events, including one reported death,” according to the group.

Nevertheless, driven largely by word-of-mouth demand from patients, many of whom follow CCSVI developments on the Internet patient forum www.thisisms.com, several endovascular surgeons in the U.S. began evaluating patients for stenoses in the past year. Among them is Dr. Michael Dake, who returned to Stanford University in 2008 as a professor of cardiothoracic surgery and chief of the Catheterization and Angiography Center, at Stanford Medical Center. He began evaluating MS patients and confirmed Dr. Zamboni’s findings about the high prevalence of stenoses, and then began performing the endovascular procedure. Word quickly spread among patients that the procedure was being performed in the United States. Many sought evaluations from Dr Dake and more than 35 patients underwent procedures.
**Event Horizon**

In November, three months after Holly Shear’s death, a second serious adverse event occurred. A jugular vein stent that had been placed in another patient with MS-like symptoms dislodged into the right ventricle, requiring emergency open heart surgery to remove the device.

Several days later, on December 5, Dr. Dake’s patients were notified that he was suspending all scheduled procedures until a planned clinical trial was launched, sometime in early 2010. At least six hopeful MS patients with surgery scheduled for December were told that they will be contacted when the trial begins – between January and March, 2010 – and that their cases would receive priority.

Stanford Medical Center spokesman Paul Costello said that at this stage, a clinical trial is not definite.

“As interest in the procedure has grown, Dr. Dake and Stanford have determined that the initiation of a clinical development program leading to a possible clinical trial will be the next step, as we examine the possible risks and benefits of the procedure for patients with multiple sclerosis.”

**‘Outside the Box’**

As word of Zamboni’s CCSVI theory and the liberation procedure spread, an avalanche of interest developed among MS patients, and patient forums today are flush with comments and endorsements by patients who have undergone the procedure at Stanford, or are interested and have questions.

Patients appear to be the leading advocates of CCSVI, and their comments routinely chide neurologists for failing to endorse the theory and surgical procedure, citing everything from “turf protection” to the influence of major pharmaceutical companies.

There is little discussion of the fact that the theory has yet to be confirmed by other researchers or that safety and efficacy of the liberation procedure yet to be evaluated in randomized and blinded trials, noted Dr. John Richert, executive vice president for research and clinical programs at the National Multiple Sclerosis Society.

It has not even been established if such stenoses can be detected sufficiently with available technology to guide endoplasty procedures, he said. The Food and Drug Administration does not regulate procedures using approved medical devices – as are all of those being used in CCSVI treatment.

“When dealing with a disease like MS, where we don’t know the cause or have many therapeutic options, it’s important to think outside the box,” he commented. “Dr. Zamboni is doing this, but his techniques need to be confirmed.”

There are still many unanswered questions, he continued.

“All of the evidence today is preliminary. There is not even enough evidence to say that obstruction of veins might be a factor in MS, or to determine when this obstruction may occur in the course of disease. That said, we feel the findings are important enough that we need to move forward with clinical trials, and the MS Society is willing to provide funding.”

He applauded Stanford’s decision to stop performing any more procedures outside of a clinical trial.

**Objectivity Urged**

Dr. Jeffrey Dunn, associate director of Stanford’s MS center, was cautious in commenting on his colleague’s work, but he called on other neurologists to speak out about the potential “dangers” of the unproven procedure.

“After sustained and explicit calls to suspend this unproven procedure, we succeeded on December 5. But this issue has become one of international scope, and well beyond Stanford’s borders now, he said. “Despite our local efforts . . . patients remain insufficiently aware of the active and serious risks, and our colleagues have felt insufficiently equipped to defend their cautionary advisories.

“We should not seek to make these adverse events unknown – we should actively seek to make them more known – and in so doing assist our colleagues in addressing ongoing patient inquiries and in protecting patients . . . If I can do anything to protect MS patients from the potentially devastating effects of false hopes or the risks of invasive and unproven treatment, I am happy to do so,” he stated.

His colleague Dr. Larry Steinman, the George A. Zimmermann Professor of Neurology and Neurological Sciences, Pediatrics and Genetics at Stanford, also emphasized that the procedure should only be done as part of an IRB-approved experimental protocol.

“The invasive shunting procedure is entirely experimental for its application to multiple sclerosis,” he said. “Only by testing this hypothesis under rigorous experimental conditions will we learn whether or not the hypothesis has validity.”

It has been known for over a century that there are abnormalities in the cerebral veins in MS, particularly in the white matter of MS brain, he continued, and perivascular infiltrations of lymphocytes in the brain are a hallmark of acute inflammation, and hence the target for some of the most potent approved MS drugs.

“This intervention focusing on stenting the extracranial veins draining the brain ought to be studied under carefully designed and fully approved experimental protocols so that we maximize our understanding, and either prove or disprove Dr. Zamboni’s hypothesis,” Steinman said.
“Finally, it appears that there are very different standards for testing established drugs for new indications versus testing established procedures for new indications.”

**First Clinical Trial**

Dr Robert Zivadinov, associate professor of neurology and Director of the Buffalo Neuroimaging Analysis Center at the Jacobs Neurological Institute, University of Buffalo, NY, was a coauthor of the original Zamboni paper and its follow-up in 2005. He is also principal investigator for the first U.S. clinical trial of CCSVI.

“If we can prove our hypothesis, that cerebrospinal venous insufficiency is the underlying cause of MS, it’s going to change the face of how we understand MS,” he said.

Media coverage of CCSVI and its potential has been “unrealistic” and premature, he added.

“We are three to five years away from the possible treatment options. Even with Dr Zamboni’s new paper (*J Vasc Surg*) there was very little improvement in patients, and it calls for caution – a reasonable approach. But I wouldn’t have invested so much of my time, personally, if I didn’t believe there might be something to all of this.”

The growing influence of Internet patient forums and networks in clinical research, by raising awareness of trials and helping recruitment, is illustrated by the response the institute has already received. More than 8000 MS patients are on the waiting list for the new trial, Dr Zivadinov said.

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**LONG AGO**

in the Annals...

IMMUNOREACTIVE MYELIN BASIC PROTEIN IN THE CEREBROSPINAL FLUID IN NEUROLOGICAL DISORDERS

WHITAKER JN, LISAK RP, BASHIR RM, FITCH OH, SEYER JM, KRANCE R, LAWRENCE JA, CH’IEN LT, O’SULLIVAN P

JANUARY 1980

ABSTRACT

Cerebrospinal fluid from 582 persons was analyzed by a double-antibody radioimmunoassay for the presence of material cross-reactive with peptide 43-88 of human myelin basic protein (BP). In a group of 104 patients with multiple sclerosis (MS), 23 of 33 individuals clinically judged to have had an exacerbation within two weeks prior to the time CSF was obtained had detectable material ranging from 2 to 200 ng/ml. In the remaining 71 MS patients who were stable or had had an exacerbation more than two weeks before, only 1 patient had a marginally elevated level of immunoreactive material. CSF from 53 persons with cerebrovascular disease was studied, and 13 of 29 with recent infarctions had values of 2 to 540 ng/ml. The degree of elevation in strokes generally paralleled the predicted volume of the lesions, but the amounts detected did not correlate quite so closely temporally with onset as they did with the periods of active disease in MS. Of the remaining 425 patients, 29 had immunoreactive material of 2 to 400 ng/ml in their CSF. Most of these patients with detectable material had acute diseases known to affect the myelin sheath. Eight of 10 persons with acute disseminated encephalomyelitis had no detectable material. The presence in CSF of material cross-reactive with BP peptide 43-88 does not have diagnostic specificity for MS but can be used as a means for determining recent myelin injury. The type of BP peptide formed and mechanisms for clearance of BP and BP peptides may be important in determining the biological consequences following release of this potentially immunogenic material from the central nervous system.