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Endovascular Treatment of Cerebrospinal Venous Insufficiency Safe, May Provide Benefit in MS

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Authors and Disclosures

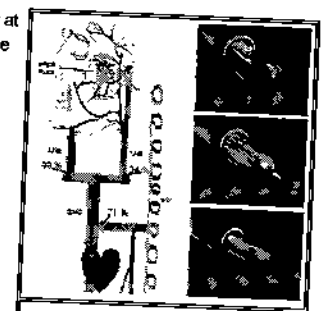
December 3, 2009 — New data from a pilot open-label study suggest that endovascular treatment of strictures in extracranial cerebrospinal veins is safe in patients with multiple sclerosis (MS) and may provide some neurological benefit for these patients, researchers conclude.

The controversial approach, which has recently been making headlines in consumer media outlets, proposes that narrowing in the veins draining the brain, called chronic cerebrospinal venous insufficiency (CCVI), may be an early step in the disease process causing MS, and further, this narrowing may respond to simple angioplasty.

Lead author Paolo Zamboni, MD, director of the Vascular Diseases Center at the University of Ferrara, Italy, emphasized that the current report should be viewed as an interesting finding that urgently requires replication by other groups.

"What we know is that MS is very complex and multifactorial," Dr. Zamboni told *Medscape Neurology*. "We have identified an unknown factor and possible treatment for this factor."

The study is published as an online article in the December issue of the *Journal of Vascular Surgery*.



Left: location of venous stenosis with relative rate found in CCVI associated with multiple sclerosis. Right: the minimally invasive technique of balloon angioplasty eliminates the stricture in the cerebral venous system.

CCVI and MS

In a previous study published online in December 2008, Dr. Zamboni and colleagues assessed venous outflow routes in 65 patients with clinically definite MS (CDMS) and 235 control patients using a combined transcranial and extracranial color Doppler high-resolution examination. They reported that CDMS and venous outflow abnormalities were "dramatically" associated, with an odds ratio of 43 (95% confidence interval, 29 - 65; $P < .0001$).

Venography showed the presence of multiple severe extracranial stenoses affecting the principal venous segments in the patients with MS but not the control patients. "This provides a picture of chronic cerebrospinal venous insufficiency with 4 different patterns of distribution of stenosis and substitute circle," the authors write. "Moreover, relapsing-remitting and secondary progressive courses were associated with CCVI patterns significantly different from those of primary progressive ($P < .0001$)" (Zamboni P, et al. *J Neurol Neurosurg Psychiatry* 2009;80:392-399).

In an editorial accompanying that publication, Claude Franceschi, MD, from Saint Joseph and Pitié-Salpétrière Hospitals in Paris wrote that, "in light of the association between such a previously overlooked vascular picture and MS, a further stimulating research field is opened by this article. This should be addressed in understanding the contribution of venous drainage to the different aspects of inflammation, autoimmunity and neurodegeneration characterising the intriguing puzzle of MS" (Franceschi C. *J Neurol Neurosurg Psychiatry* 2009;80:358).

Dr. Zamboni stressed that this association between venous stenoses in main extracranial veins and MS is not contradictory to what is already known about the disease. "What I've found is a previously unknown factor, widely diffuse in my MS population, which could trigger or facilitate both immune reaction and inflammation," he told *Medscape Neurology*. "If you have elevated pressure and difficulty of drainage in the brain, you have the possibility of extravasation of blood components crossing the blood–brain barrier, and this could trigger inflammation and also immune reaction."

Restenosis a Problem

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In the current report, the researchers describe the safety and early outcomes in these same patients after endovascular treatment of stenoses in the internal jugular vein and the azygous vein.

Of the 65 patients, 35 had relapsing-remitting disease, 20 had secondary-progressive disease, and 10 had primary progressive MS. All underwent percutaneous transluminal angioplasty to address strictures in these veins. All procedures were done as day surgery under local anesthesia, and no operative or postoperative complications were seen, including vessel rupture, thrombosis, or adverse effects from contrast.

Postoperative headache was reported in 6 patients, which resolved spontaneously, and minor hemorrhages with hematoma occurred at vascular access sites "occasionally," the authors report.

After the procedure, venous pressure was significantly lower in the internal jugular and azygous veins ($P < .001$). Stenoses in these venous pathways "were never found to be isolated," the researchers note, but always combined in the internal jugular, azygous veins, or lumbar system in 4 main patterns of distribution.

At a mean follow-up of 18 months, the risk for restenosis after intervention was higher in the internal jugular vein, Dr. Zamboni noted, with a patency rate of 53% compared with 96% in azygous veins (95% confidence interval, 3.5 - 72.5; $P < .0001$).

Patency at follow-up depended on the type of obstruction faced, including membranous obstructions, twisting, and hypoplasia. A stent was placed in 1 patient to resolve a twisted vein, but a second case not treated with a stent retwisted, the authors note.

Using the patients as their own control, the researchers found improvement with treatment on some clinical outcome measures after the intervention, particularly for the relapsing-remitting patients. In this group, 27% were relapse-free before surgery and 50% were so after treatment ($P < .001$). Gadolinium-enhancing lesions on magnetic resonance imaging (MRI) fell from 50% to 12% on a blinded assessment ($P < .001$).

Significant improvement over the preoperative assessment was seen at 1 year on the Multiple Sclerosis Functional Composite again for relapsing-remitting patients ($P < .008$), but not among those with a secondary or primary progressive course.

Physical quality-of-life measures also improved significantly in relapsing-remitting MS patients and in primary-progressive patients, with a positive trend among those with secondary progressive disease. Mental quality of life also was significantly improved for the relapsing-remitting and primary progressive groups, but not for those with secondary progressive MS.

The authors conclude that although improved endovascular techniques are needed to approach the internal jugular vein, "the results of this pilot study warrant a subsequent randomized control study."

It is possible that the addition of stents to this endovascular approach that he calls the "liberation procedure" may improve outcomes, Dr. Zamboni noted. "However, the results are really interesting, if you think that all treated patients were already under the best treatment for MS and had adjunctive neurological benefits from the liberation procedure compared to the previous 2 years."

Mixed Response From Neurology Community

Asked for comment on these findings, Lily Jung, MD, from the Swedish Neuroscience Institute, Seattle, Washington, speaking on behalf of the American Academy of Neurology, was cautious in her assessment. She feels some of the strong claims in the current report are not supported by the data.

For example, the number of patients in the report is small, "and to make the correlation between the patterns of venous obstruction and the categories of MS is a real stretch," Dr. Jung said. Assessment was done by unblinded neurologists, which is "not ideal." She also noted that the MRI results used different techniques, different protocols, and different study intervals.

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"The bottom line is that my colleagues and I have been flooded by calls and emails from patients who have been led by the publicity around this article to believe that there is a cure for MS, and to make such a claim with such preliminary results is premature," Dr. Jung said. "We would welcome some randomized, controlled, double-blinded studies to look at the issue, but before then would not be encouraging our patients to jump in with both feet to do this procedure, which has significant risks and has not been proven to be safe."

As a vascular interventionalist, Dr. Zamboni says he is keen to collaborate with neurologists in the setting of MS, but acknowledged that his work has had a mixed response from the neurology community. Some, he says, have been excited and at least curious, which in his view is important in research. Researchers from institutions including Stanford, Harvard, SUNY Buffalo, and others have asked to discuss the technique so that they may attempt to reproduce these findings in their own populations.

"To the contrary, of course, I've also found big opposition, but I think that probably it is a prejudgement, and they have not read the paper carefully," he said. "But it's not important. What is important is to have other people interested in doing the research and understanding more."

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The first step will be to understand how widespread the presence of CCVI is among patients with MS, he said. "We need to test patients very rapidly to have the epidemiological data, which are very important."

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Already, Dr. Zamboni is collaborating with Robert Zivadinov, MD, and colleagues at Buffalo General Hospital in New York on an open-label, MRI-blinded study of 16 relapsing-remitting patients with MS with confirmed strictures in the cerebrospinal venous outflow routes. Half — 4 randomly selected patients in Italy and 4 in New York — will undergo early intervention to address the blockages at 3 months, and 8 patients will have a delayed procedure at 6 months of follow-up.

Safety and preliminary efficacy will be monitored using MRI and clinical examination, and outcomes will be compared at 1 year. Dr. Zamboni and Dr. Zivadinov presented their protocol at the 25th Congress of the European Committee for the Treatment and Research in Multiple Sclerosis earlier this year in Düsseldorf, Germany.

In Buffalo, Dr. Zivadinov is also conducting a larger epidemiological study aimed at determining the prevalence of CCVI among their MS patients.

Dizzying Excitement, Desperate Hope

Although Dr. Zamboni has published previously on this procedure, a news report by a national Canadian news organization with an associated documentary on the same network recently profiled this work, generating a dizzying excitement for many patients in Canada, where MS rates are among the highest in the world. Their subsequent comments on various Internet news and patient sites reflect a desperate hope that this new approach may provide those with MS a possible alternative to lifelong drug therapy and the steady encroachment of disability.

In a public statement issued December 1, the National Multiple Sclerosis Society cautioned that the findings are preliminary. "Many questions remain about how and when this phenomenon [CCVI] might play a role in nervous system damage seen in MS, and at the present time there is insufficient evidence to prove that this phenomenon is the cause of MS."

However, the society also notes that it is very interested in seeing more data on this procedure and is prepared to put its money where its mouth is, calling for research proposals to generate that data.

"If confirmed, these findings may open up new research avenues into the underlying pathology of MS, as well as potential new approaches to therapy," the statement notes. "The National MS Society has invited research proposals to investigate this lead, and is in active discussions with the MS Society of Canada about the possibility of collaborative funding of [CCVI] research."

The authors have disclosed no relevant financial relationships.

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