

CCSVI -- A New Phrenology?

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Question

Where does the evidence stand on CCSVI as a cause of MS?



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What is CCSVI?

In 2009, Paolo Zamboni, MD, a vascular surgeon, provided the first description of chronic cerebrospinal venous insufficiency (CCSVI) in a study of 65 patients with multiple sclerosis (MS) and 235 controls.^[1] Dr. Zamboni observed that CCSVI existed in 100% of those with MS, but none of the controls. Subsequent exploration of this controversial concept has provoked heated debate and consumed enormous resources of funding, research, and time.

The Five Criteria of CCSVI

Dr. Zamboni described 5 critical venous flow anomalies detectable by transcranial and extracranial color Doppler that could determine the existence of CCSVI.

1. Reflux in the internal jugular veins and/or vertebral veins in sitting and supine posture;
2. Reflux in the deep cerebral veins;
3. High-resolution B-mode evidence of proximal internal jugular vein stenosis;
4. Flow in the internal jugular veins and/or vertebral veins that is not detectable on Doppler; and
5. Reverted postural control of the main cerebral venous outflow pathways.

In Dr. Zamboni's study, the presence of any of the 5 criteria was significantly more likely in patients with MS than in controls ($P < .0001$).^[1] None of the control patients had more than 1 of the abnormal parameters, but all of the patients with MS had at least 2 of the parameters. Venography was performed in the 65 patients with MS and revealed unilateral or bilateral stenosis of the jugular veins (91%) and abnormalities of the azygous vein (86%). Findings on venography included agenesis, annulus, atresia, closed stenosis, membranous obstruction, septum and twisting. Venography identified 4 principal patterns of CCSVI that had different types of obstruction and venous flow. The patterns correlated with the type of MS.

There was no difference in the number of extracranial venous stenoses in patients with relapsing remitting MS treated with immunosuppressant therapy (N = 37) vs those not treated with immunosuppressant drugs (N = 18). None of the control patients without MS who were scheduled for venography for other reasons had stenosis in the azygous, internal jugular, or lumbar venous territories.

Limitations of Methodology

Methodologic problems with the original study include a heterogeneous study group. The 65 subjects with MS included 35 with relapsing-remitting MS, 20 with secondary progressive MS, and 10 with primary progressive MS, resulting in small numbers of each type of MS. In addition, full data for each patient regarding each of the 5 venous flow parameters was not presented, the 5 parameters were not validated, and venography procedures were not blinded.

Importance of Venous Flow

Until Dr. Zamboni's provocative paper, the study of venous function in the central nervous system had been relatively neglected.^[2] However, the possibility that intravascular stasis caused by chronic venous obstruction could lead to pericapillary iron deposition, subsequent tissue injury, and an autoimmune response resulting in MS represented an intriguing hypothesis.^[2] MS is characterized by perivenous white matter lesions, supporting the possibility of a venous etiology.^[3] Dr. Zamboni's work sparked interest in the concept of "vascular immunology" and revived interest in long-forgotten papers that suggested a link between MS and vascular pathology.^[4]

Dr. Zamboni immediately followed this study with an open-label therapeutic study of transluminal angioplasty of the stenoses identified in the same 65 patients.^[5] All of the patients survived with minimal complications. Venous pressures were similar in stenotic or normal vessels, but after treatment, venous pressures were significantly lower ($P < .0001$). However, restenosis in the internal jugular vein was 47% at 18 months, 16 times higher than restenosis in the azygous vein. Significantly more patients were relapse free (50%) compared with the year prior to the procedure

(27%; $P < .0014$), but the annualized relapse rate did not change. On MRI, the number of active gadolinium-enhanced lesions decreased from 50% to 12% ($P < .001$). Mental and physical quality of life improved significantly in patients with relapsing remitting MS. All of the clinical and radiologic assessments were unblinded, and there was no placebo or sham-treated MS control group.

Desperate Patients Seek Treatment

Despite the lack of agreement among experts regarding whether CCSVI exists, or if it does, whether it plays a role in the pathogenesis of MS, and if it does play a role, whether reversing it with angioplasty or stents might improve symptomatology, enthusiasm for CCSVI engulfed the MS community. Interest spread quickly, in large part because of vocal patient advocacy and Internet forums such as www.thisisms.com. There is even the Website, LiberationProcedureCCSV.com.

Michael Dake, MD, Professor of Cardiothoracic Surgery and Chief of the Catheterization and Angiography Center at Stanford Medical Center in Stanford, California, performed more than 35 endovascular procedures for CCSVI.^[6] However, after one patient on warfarin anticoagulation following placement of an internal jugular venous stent had a fatal brain stem hemorrhage and another patient required emergency heart surgery for a dislodged stent, all CCSVI procedures were suspended.

Because endovascular procedures for CCSVI are not approved in the United States or Canada, many patients seek treatment outside North America at their own personal expense. Patients may receive endovascular balloon angioplasty alone or in combination

with venous stenting.^[7] There is no central registry to track these patients, their results, or their adverse events. One patient treated in Costa Rica died from complications.

To accommodate these patients, TraveloMed, a medical tourism company, offers a "Liberation Treatment Package," including flight, hotel, local taxi, and treatment beginning at 4500 euros. Their Website encourages patients to "Sign up now to get the procedure done this month!"

A "nonprofit" venture, the CCSVI Clinic, also arranges a medical travel package. Balloon venoplasty and stenting are available for \$15,000 at Noble Hospital in Pune, India. Their Website includes a disclaimer, "CCSVI Clinic can accept no responsibility or liability whatsoever for medical procedures, advice, opinions and services provided by others."

Numerous testimonials to the success of these procedures have appeared on YouTube, including one from Ginger, who sought treatment in Poland. Other patients have sought treatment in Bulgaria, Costa Rica, India, and Mexico. Ginger enthusiastically describes improvement in her symptoms, but nothing to suggest a cure. Given the relapsing remitting nature of MS, it is impossible to determine from this and other anecdotal reports whether any improvement after CCSVI treatment is related to the procedure, a placebo effect, or simply the natural history of a relapsing-remitting disease. Nonetheless, many patients have embraced this treatment as an MS cure. Patients are so invested in this therapy that one woman who experienced transient improvement of her balance, fatigue, and mobility after treatment in India attributed the return of her symptoms 6 weeks later to a return of the "blockages" rather than a failure of the therapy.

To date, no testimonial to the success of CCSVI procedures for MS in the form of a randomized, controlled, clinical trial has appeared in any peer-reviewed publication. Until a prospective, randomized, sham treatment trial demonstrates the value of endovascular treatment for CCSVI, the Cardiovascular and Interventional Radiological Society of Europe has recommended that this treatment "should not be offered to MS patients."^[8]

Conspiracy Theory

Some patients endorse a conspiracy theory, believing that neurologists, the national MS societies of the United States and Canada, and pharmaceutical companies are suppressing CCSVI because a cure for MS would mean a loss of business and profits. According to one blogger whose wife has MS, "They [the MS societies] have become a new enemy that we have to fight against, in addition to MS, and we must be determined." As Ginger declared in her video, "We're going to win this."

Diagnostic Trials: Can the Results Be Duplicated?

In response to patient demand for treatment of CCSVI, the National Multiple Sclerosis Society allocated \$2.4 million for 7 pilot research studies. The MS Society of Italy also appropriated approximately \$1 million for CCSVI epidemiologic research. So far, no one has been able to duplicate Dr. Zamboni's astonishing results.^[9]

A study of 25 patients with MS and 25 controls demonstrated CCSVI in 84% of those with MS and none of the controls.^[10] Another study identified CCSVI in 63 of 70 (90%) patients, but there was no control group.^[11]

A blinded diagnostic research trial by Zivadinov and colleagues.^[12]

the Combined Transcranial and Extracranial Venous Doppler evaluation in MS and related diseases (CTEVD) trial, compared the frequency of CCSVI in a total of 499 patients, including those with MS (N = 289), a control group who had no neurologic disorders (N = 163), patients with other neurologic disorders (N = 26), and patients with clinically isolated syndrome (CIS; N = 21).^[12] CCSVI was present in 56.1% of patients with MS, in 42.3% of those with other neurologic diseases, in 38.1% of those with CIS, and in 22.7% of healthy controls. Sensitivity was 56.1%, specificity was 77.3%, the positive predictive value was 81.4%, the negative predictive value was 49.8%, and the odds ratio was 4.33 for CCSVI relative to controls. CCSVI prevalence was higher in patients with progressive MS and in those with neuromyelitis optica than in patients with relapsing remitting MS or CIS.

A triple-blinded sonographic study of 20 patients with MS and 20 healthy controls failed to replicate any of the findings in Zamboni's original study.^[3] None of the patients or controls fulfilled anomalous venous outflow criteria 1, 2, or 4. More controls (N = 16) than patients (N = 13) fulfilled criterion 3, and only 1 control subject fulfilled criterion 5. In a study of 56 patients with MS and 20 controls, none of those with MS fulfilled more than 1 of the 5 criteria.^[13] A case control study of 21 patients with relapsing remitting MS and 20 healthy controls evaluated with phase-contrast MRI found no differences between the 2 groups regarding internal jugular venous outflow, aqueductal cerebrospinal fluid flow, or internal jugular reflux. However, 3 patients with MS had internal jugular stenoses on MR angiography.^[14]

It could be postulated that if CCSVI is responsible for the development of MS, then it should be present in patients with CIS because clinically definite MS will develop in most of these

patients. However, a study of 50 patients with CIS identified only 8 (16%) who fulfilled CCSVI criteria. Selective venography in all 7 who agreed to the procedure failed to confirm any venous anomalies.^[15]

A Treatment Trial Is Underway

The first (and only) prospective, randomized, double-blind study of endovascular treatment of CCSVI for patients with MS, the Prospective Randomized Endovascular therapy in Multiple Sclerosis (PREMISe) trial is ongoing at the State University of New York in Buffalo. Researchers will randomly assign 20 patients to balloon endovascular treatment of CCSVI or a sham angioplasty, where patients will undergo catheter insertion but without balloon inflation. During the sham procedure, a video fluoroscopy of a different balloon angioplasty procedure will be shown in the operating room to provide realism. The patient will be blinded as will the clinician performing the clinical assessment following the procedure. The principal investigator is Adnan Siddiqui, MD, Assistant Professor of Neurosurgery at the University of Buffalo School of Medicine and Biomedical Sciences in Buffalo, New York.

Experts Weigh In

At the 2010 American Academy of Neurology (AAN) meeting in Toronto, Canada, the AAN hosted a press conference to provide information about CCSVI. Facilitated by stories on the Internet, interest was high, with more than 4000 people registered online and a packed conference room on site. Speakers included Paolo Zamboni, MD, Director, Vascular Diseases Center, University of Ferrara, Italy; Robert Zivadinov, MD, PhD, Director of the Buffalo Neuroimaging Analysis Center, Buffalo, New York; Andrew

Common, MD, Radiologist in Chief, St. Michaels Hospital, University of Toronto, Ontario, Canada; and Aaron Miller, MD, Professor of Neurology, Director of the MS Center at Mount Sinai, NY, New York. Dr. Miller is also the Chief Medical Officer of the National MS Society. At the end of the conference, Dr. Miller concluded, "How, when, and indeed whether CCSVI has any role in the treatment of MS remains to be seen."

Expert clinicians have been skeptical. For example, Randall Shapiro, MD, Clinical Professor of Neurology at the University of Minnesota in Minneapolis, likened CCSVI therapy to other MS "cures" that have come and gone, such as bee stings, colostrum, cobra venom, goat serum, hyperbaric oxygen, mercury amalgams, vertebral stenosis with surgery, and vitamin therapy. According to Dr. Shapiro, the proposed rationale of CCSVI as an MS etiology "would appear to defy logic and reason...."

Jeffrey Dunn, MD, Associate Director of Stanford's MS Center, commented on CCSVI procedures, "...Patients remain insufficiently aware of the active and serious risks, and our colleagues have felt insufficiently equipped to defend their cautionary advisories....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."^[6]

Victor Rivera, MD, Director of the Maxine Mesinger MS Clinic at Baylor College of Medicine in Houston, Texas, moderated a debate between Dr. Zivadinov and Mark Freedman, MD, Director of the Multiple Sclerosis Research Unit at Ottawa Hospital in Ottawa, Ontario, Canada, at the recent Consortium of Multiple Sclerosis Centers Annual Meeting in Montreal, Canada, June 1-4, 2011. Dr. Zivadinov suggested that CCSVI might contribute to MS in a

manner similar to environmental factors such as latitude, viral exposure, vitamin D levels, or genetic predisposition, but that CCSVI was not the sole cause of MS. Dr. Zivadinov conceded, "CCSVI is neither necessary nor sufficient to cause MS."

Animal models, which would be a logical part of the research process, have not been developed to aid in the diagnosis of CCSVI or to test the effects of endovascular treatment. According to Dr. Zivadinov, the development of a CCSVI animal model is "too difficult."

If intracerebral venous congestion leads to MS, disorders that cause cerebral venous congestion such as cerebral venous thrombosis, chronic obstructive pulmonary disease, idiopathic intracranial hypertension, or radical neck dissection that results in internal jugular vein removal might be expected to be associated with an increase in MS. However, they are not.^[13]

CCSVI Interventions

Although endovascular interventions may rarely result in life-threatening complications,^[6] the relative safety of endovascular treatment of 331 patients with CCSVI, including balloon angioplasty and stenting, has been reported.^[7] There were no deaths, cerebral strokes, or instances of stent migration. Stent thrombosis occurred in 2 (1.2%) patients, and 1 (0.3%) patient required surgical removal of an angioplastic balloon. Local bleeding occurred in 4 patients (1.2%), difficulty removing balloon or delivery system occurred in 4 patients (1.2%), unsuccessful catheterization occurred in 4 patients (1.2%), problems with stent placement occurred in 4 patients (2.3% of stents), transient cardiac arrhythmia occurred in 2 patients (0.6%), and minor gastrointestinal bleeding

occurred in 1 patient (0.3%).

Conclusions and Recommendations

The theory that CCSVI leads to venous congestion, increased pericapillary iron deposition, an autoimmune response, and MS is a tantalizing one, but it is scantily supported by objective data. More than a year, millions of dollars, and a myriad of publications later, Dr. Miller's assessment that the role of CCSVI in MS remains to be seen still holds true.

Dr. Zamboni may have invented a new phrenology, a seemingly rational series of observations and measurements that has no significant relationship to the physiology under study. The CTEVD study did reveal an increased prevalence of CCSVI in people with MS, but also found CCSVI in healthy controls, patients with CIS, and those with other neurologic diseases.^[12] CCSVI may be nothing more than normal anatomic venous variation coupled with nonspecific venous changes associated with the neurodegeneration of MS and other diseases. A sham treatment study is underway to clarify the value of reversing the features that define CCSVI.

Although further studies regarding the role of venous circulation in the etiopathogenesis of MS may be informative, endovascular "treatment" at this time is inappropriate. Patients requesting CCSVI procedures should be referred to centers doing clinical trials. Both Dr. Zamboni and Dr. Zivadinov endorsed this recommendation at the 2010 AAN press conference. Those who subject patients to endovascular procedures for CCSVI outside of clinical trials exploit the fears, hopes, and wallets of desperate patients and their families and put these patients at risk for procedure-related

complications that may, albeit rarely, be fatal.

Time will tell whether CCSVI represents a phenomenal medical breakthrough for patients with MS or a failed hypothesis.

Accumulating evidence suggests the latter.

References

1. Zamboni P, Galeotti R, Menegatti E, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2009;80:392-399. [Abstract](#)
2. Franceschi C. The unsolved puzzle of multiple sclerosis and venous function. *J Neurol Neurosurg Psychiatry*. 2009;80:358. [Abstract](#)
3. Mayer CA, Pfeilschifter W, Lorenz MW, et al. The perfect crime? CCSVI not leaving a trace in MS. *J Neurol Neurosurg Psychiatry*. 2011;82:436-440. [Abstract](#)
4. Putnam T. Studies in multiple sclerosis: encephalitis and sclerotic plaques produced by venular obstruction. *Arch Neurol Psychiatry*. 1935;33:929-940.
5. Zamboni P, Galeotti R, Menegatti E, et al. A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. *J Vasc Surg*. 2009;50:1348-1358. [Abstract](#)
6. Samson K. Experimental multiple sclerosis vascular shunting procedure halted at Stanford. *Ann Neurol*. 2010;67:A13-A15. [Abstract](#)
7. Ludyga T, Kazibudzki M, Simka M, et al. Endovascular treatment for chronic cerebrospinal venous insufficiency: is the procedure safe? *Phlebology*. 2010;25:286-295.
8. Reekers JA, Lee JM, Bellie AM, Barkhof F. Cardiovascular

and Interventional Radiological Society of Europe commentary on the treatment of chronic cerebrospinal venous insufficiency. *Cardiovasc Intervent Radiol*. 2011;34:1-2. [Abstract](#)

9. Khan O, Tselis A. Chronic cerebrospinal venous insufficiency and multiple sclerosis: science or science fiction? *J Neurol Neurosurg Psychiatry*. 2011;82:355. [Abstract](#)
10. Al-Omari MH, Rousan LA. Internal jugular vein morphology and hemodynamics in patients with multiple sclerosis. *Int Angiol*. 2010;29:115-120. [Abstract](#)
11. Simka M, KostECKi J, Zaniewski M, et al. Extracranial doppler sonographic criteria of chronic cerebrospinal venous insufficiency in the patients with multiple sclerosis. *Int Angiol*. 2010;29:109-114. [Abstract](#)
12. Zivadinov R, Marr K, Cutter G, et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. *Neurology*. 2011 Apr 13. [Epub ahead of print]
13. Doepp F, Friedemann P, Valdueza JM, et al. No cerebrocervical venous congestion in patients with multiple sclerosis. *Ann Neurol*. 2010;68:173-183. [Abstract](#)
14. Sundstrom P, Wahlin A, Ambarki K, et al. Venous and cerebrospinal fluid flow in multiple sclerosis: a case-control study. *Ann Neurol*. 2010;68:255-259. [Abstract](#)
15. Baracchini C, Perini P, Calabrese M, et al. No evidence of chronic cerebrospinal venous insufficiency at multiple sclerosis onset. *Ann Neurol*. 2011;69:90-99. [Abstract](#)

