Title: Diagnosis and Treatment of Chronic Cerebrospinal Venous Insufficiency in Multiple Sclerosis

**PROFESSIONAL**

Original Effective Date: January 30, 2012
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**INSTITUTIONAL**

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**DESCRIPTION**

Chronic cerebrospinal venous insufficiency (CCSVI) may be associated with multiple sclerosis (MS), although this is controversial and an active area of research. Correction of CCSVI has been attempted via percutaneous venoplasty. The intent of this procedure is to relieve MS symptoms by improving venous drainage of the central nervous system. Correction of CCSVI by this method may be referred to as the “Liberation Procedure.”

**Background**

Multiple sclerosis (MS) is generally considered a chronic inflammatory demyelinating disease of the central nervous system (brain, spinal cord, optic nerve) felt to be triggered by an autoimmune response to myelin. However, in part due to the periventricular
predilection of the lesions of multiple sclerosis, vascular etiologies (chronic cerebrospinal venous insufficiency [CCSVI]) have also been considered. An animal model for MS was developed by injecting obstructing agents into the venous sinuses. This etiology, and treatment approach for MS had not been actively pursued for many years; recent reports by a European researcher have renewed interest in this topic.

The core foundation of this vascular theory is that there is abnormal venous drainage from the brain due to outflow obstruction in the draining jugular vein and/or azygos veins. This abnormal venous drainage, which is characterized by special ultrasound criteria, is said to cause intracerebral flow disturbance or outflow problems that lead to periventricular deposits. In the CCSVI theory, these deposits have a similarity to the iron deposits seen around the veins in the legs in patients with chronic deep vein thrombosis. Those studying this theory have promoted balloon dilatation, with or without stenting, to treat the outflow problems, thereby curing CCSVI and by the same token alleviating MS complaints.

The following 5 criteria were defined by Zamboni et al. as features of CCSVI. In order to make the diagnosis of CCSVI, at least 2 of the 5 criteria need to be present:

1. Reflux constantly present (for a duration >0.8 s) in the supine and upright positions at the level of an internal jugular or vertebral vein. This parameter was evaluated during a short breath-hold following normal breathing and not under Valsalva maneuver.
2. Reflux at the level of veins of the deep cerebral system (for a duration >0.5 s). This was evaluated with the patient in the sitting and supine positions, and venous flow was enhanced by inviting the patient to breath in.
3. Stenosis (<0.3 cm), valve abnormalities and septa on B-mode imaging.
4. Absence of flow at the level of the internal jugular or vertebral vein despite numerous deep inspirations.
5. No increase in the diameter of the internal jugular vein when changing from an upright to a supine position (lack of ∆).

POLICY
The identification and subsequent treatment of chronic cerebrospinal venous insufficiency (CCSVI) in patients with multiple sclerosis is considered experimental / investigational.

RATIONALE
The most recent update covers the period of April 2012 through March 2013.

Diagnosis of CCSVI and Association with Multiple Sclerosis
Recent interest in the role of chronic cerebrospinal venous insufficiency (CCSVI) in multiple sclerosis (MS) followed reports from a European vascular surgeon, Zamboni and colleagues. Zamboni used ultrasound and catheter-based venography to describe venous insufficiency in the
internal jugular veins, vertebral veins, and deep cerebral veins of MS patients and described the finding as CCSVI. (1) Using 5 ultrasound criteria (described above), Zamboni defined the condition of CCSVI. In initial research reports, Zamboni and colleagues reported both sensitivity and specificity of 100% in separating MS patients from controls when applying these criteria. (2)

Since the development of the Zamboni criteria for CCSVI, there have been numerous research studies that have attempted to compare the rate of CCSVI in MS, normal patients, and patients with other neurologic diagnoses. The following review includes some of the largest of these studies, as well as any relevant systematic reviews.

A systematic review of the association between CCSVI and MS was published in 2011 by Laupacis et al. (3). This review included 8 studies that used ultrasound to diagnose CCSVI by the Zamboni criteria and compared the rate of CCSVI in patients with MS to those without MS. These studies were mostly small, with the median number of patients with MS of 50. There was a large degree of heterogeneity across studies in the rate of CCSVI among MS patients. Two smaller studies reported a rate of 0% for CCSVI in a total of 20 and 56 patients with MS. In contrast, the original study by Zamboni et al. reported a 100% rate of CCSVI in 109 patients with MS. A small study of 25 patients also reported a very high rate of CCSVI at 84% (21/25). There was no obvious reason identified for this large discrepancy in CCSVI rates; the authors hypothesized that the most likely reason was variability in ultrasound technique and interpretation. There was a significant association of CCSVI with MS in combined analysis, with an odds ratio of 13.5 (95% confidence interval [CI]: 2.6 to 71.4). There was a large amount of heterogeneity in this measure as well, with a reported I² of 89%. Several sensitivity analyses were performed, with marked variability of the odds ratio from a low of 3.7 to more than 58,000, depending on the analysis. However, in all cases the association of CCSVI with MS remained significant.

A systematic review published in 2011 (4) that included a smaller number of studies (n=4) came to similar conclusions. The rate of CCSVI in MS patients ranged from 7-100%, and the rate in non-MS patients ranged from 2-36%. There was a significant association between CCSVI but with a high degree of heterogeneity (I²=96%) and an odds ratio for association that had extreme variability, from approximately 2 to more than 26,000.

The largest study performed to date is a U.S. study by Zivadinov and colleagues that used ultrasound to evaluate CCSVI in 499 subjects. (5) A subject was considered CCSVI-positive if 2 or more venous hemodynamic (VH) criteria were fulfilled. The authors’ studies of transcranial and extracranial echo-colored Doppler (ECD) were carried out in 499 enrolled subjects: 289 with MS, 163 healthy controls (HC), 26 other neurologic diseases (OND), and 21 with clinically isolated syndromes (CIS). Prevalence rates for CCSVI were calculated in 3 ways: first, using only the subjects for whom diagnosis was certain (i.e., borderline subjects were excluded); second, including the borderline subjects in the no CCSVI group; and finally, taking into account subjects who presented any of the VH criteria. CCSVI prevalence with borderline cases included in the no CCSVI group was 56.1% in MS, 42.3% in OND, 38.1% in CIS, and 22.7% in HC (p<0.001). The CCSVI prevalence figures were 62.5% for MS, 45.8% for OND, 42.1% for CIS, and 25.5% for HC when borderline cases were excluded (p<0.001). The prevalence of one or more positive VH criteria was the highest in MS (81.3%), followed by CIS (76.2%), OND (65.4%), and HC (55.2%) (p<0.001). CCSVI prevalence was higher in patients with progressive than in nonprogressive MS (p=0.004). The authors concluded that their findings were consistent with an increased...
prevalence of CCSVI in MS but with modest sensitivity and specificity. They also noted that their findings point against CCSVI having a primary causative role in the development of MS.

Zivadinov et al. also reported on a substudy (6) from the original study (5) to explore any relationship between CCSVI and intracranial MS pathology as determined by magnetic resonance imaging (MRI). This substudy included 228 MS patients (162 relapsing-remitting and 66 secondary-progressive MS subtypes) and 73 HCs who had MRI imaging within 30 days of ultrasound imaging for CCSVI. In the MS group, 131 (57.5%) patients were considered CCSVI-positive and 21 (9.2%) were considered having borderline CCSVI. In the HC group, 19 (26%) were CCSVI-positive and 6 (8.2%) had borderline CCSVI. CCSVI was not significantly correlated with MRI imaging results on lesion burden and brain atrophy in MS patients and HCs. There was also no association between CCSVI and MRI imaging markers of inflammatory and neurodegenerative processes.

In an additional report from the Zivadinov study, (5) Weinstock et al. analyzed data from the MS subjects to examine the association between CCSVI and disability status, as measured by the Kurtzke Expanded Disability Status Scale (EDSS) and MS severity scale (MSSS). (7) CCSVI was not associated with disability status. However, there was an association between CCSVI and secondary or progressive MS versus nonprogressive MS, which included relapsing-remitting MS (p=0.004, OR: 2.34, CI: 1.3-4.2).

Barreto et al. conducted a single-center, prospective, case–control study of 206 MS and 70 non-MS patients to examine rates of CCSVI using color and spectral Doppler, B-mode imaging, with neurosonologists blinded to patients’ clinical characteristics. (8) Rates of CCSVI and extracranial or intracranial venous flow rates were not significantly different between MS and non-MS patients. In MS patients, CCSVI was found in 3.88% versus 7.14% of non-MS patients.

Floris et al. (9) used the Zamboni criteria to assess 74 patients with a diagnosis of MS and 34 healthy controls. All patients underwent Doppler ultrasound of the neck and transcranial Doppler ultrasound. A total of 34 patients were identified with CCSVI. The rate of CCSVI in MS patients was numerically higher than in normal controls (55% vs. 35%), but this difference did not reach statistical significance (p=0.09). There were 12/74 patients 16% in the MS group who had normal ultrasound exams and an additional 28% (21 patients) who had some abnormalities on ultrasound but did not meet the criteria for CCSVI.

Centonze et al. (10) evaluated CCSVI by the Zamboni criteria in 84 patients with MS and 56 healthy controls. The rate of CCSVI was 50% in the MS patients versus 36% in controls (p=0.12). These authors also reported that there were no differences between MS patients that did and did not meet the criteria for CCSVI on demographic and clinical characteristics. There were also no differences between MS patients that did and did not meet CCSVI criteria in terms of disease severity, functional status, or quality of life. Doepp and colleagues evaluated 56 patients with MS and 20 controls and found that none met the criteria for CCSVI using ultrasound. (11)

Conclusions. The relationship between CCSVI and MS is unclear. The initial reports of excellent discrimination of MS patients from non-MS patients using CCSVI ultrasound criteria have not been replicated in subsequent studies. There is an extremely large variability in the literature in the rate of CCSVI among MS patients, ranging from 0-100%. Many of these studies report higher
rates of CCSVI in MS patients, but others do not. Systematic reviews have reported that the combined odds ratio for an association is significantly increased; however, there is a very large degree of heterogeneity in these studies that has not been explained. If there is an association, it is unclear whether this is a causative factor for MS or whether the ultrasound findings are a result of MS and/or related processes.

**Treatment of CCSVI with Percutaneous Venoplasty**

There are no trials with concurrent controls that report on outcomes of percutaneous venoplasty compared to alternatives. There is one small controlled trial of 15 patients comparing immediate venoplasty versus delayed venoplasty, and there are several single-arm case series that report on outcomes and adverse events of this procedure. One review and some of the larger case series are reviewed below.

In a 2012 Cochrane review, Van Zuuren et al. found no randomized controlled trials on the treatment of CCSVI in MS patients. (12) While there are ongoing clinical trials, the reviewers concluded the efficacy or safety of percutaneous transluminal angioplasty for CCSVI treatment in MS patients could not be determined.

Hubbard et al. prospectively followed 259 MS patients treated with venous angioplasty for CCSVI. Patients completed the Multiple Sclerosis Impact Scale (MSIS-29) 1 month before, and 1 and 6 months after angioplasty. (13) MSIS-29 scores significantly improved at each evaluation after angioplasty on both the physical and psychological scales (p<0.01). Symptoms recurred in 15 patients (6.3%).

In a case series of 65 patients with MS and CCSVI, Zamboni et al. reported clinical improvement following catheter-based venoplasty. (2) Patients were subdivided by MS clinical course into relapsing remitting (n=35), secondary progressive (n=20), and primary progressive (n=10) MS, and all patients underwent percutaneous transluminal angioplasty (PTA). Mean follow-up was 18 months. In this study, outpatient endovascular treatment of CCSVI was noted to be feasible, with a minor complication rate. Postoperative venous pressure was significantly lower. The endovascular treatment was noted to improve MS clinical outcome measures, especially in the relapsing remitting group: the rate of relapse-free patients changed from 27% to 50% postoperatively (p<0.001). The Multiple Sclerosis Functional Composite at 1 year improved significantly in relapsing remitting patients (p<0.008) but not in primary progressive or secondary progressive. Physical quality of life (QOL) improved significantly in relapsing remitting (p<0.01) and in primary progressive patients (p<0.03), with a positive trend in secondary progressive (p<0.08). The authors concluded that PTA of venous strictures in patients with CCSVI is safe, and especially in patients with relapsing remitting disease, the clinical course was positively influenced by treatment. The authors also indicated these results were from a pilot study and that a subsequent randomized controlled study is warranted.

Zamboni et al. also reported a smaller series of 8 patients with ultrasound criteria for CCSVI undergoing immediate venoplasty compared to 7 patients undergoing delayed venoplasty. (14) There were improvements on the EDSS (expanded disability status scale) for both groups following treatment, but no difference between groups in the first 6 months comparing immediate versus delayed treatment subjects. The relapse rate during the initial 6 months was 0.12% in the treatment group versus 0.66% in the control group, but this difference did not meet statistical significance. There were also trends toward improvement for the immediate
treatment group on magnetic resonance imaging (MRI) scans, such as the number of T2 lesions, but these differences also did not reach statistical significance. No short-term adverse events were reported following the procedure, but the rate of restenosis at one year was 27% in treated patients.

Adverse events: The initial small case series of venoplasty reported few adverse events. However, a number of larger case series have now been published that report on complications following endovascular interventions for CCSVI.

Burton et al. (15) described 5 patients who had undergone venoplasty and presented with complications of the procedure. The complications were internal jugular vein stent thrombosis, cerebral sinovenous thrombosis, stent migration, cranial nerve injury, and injury associated with venous catheterization. There was not a denominator in these studies to determine the rate of these events.

Petrov et al. reported on the safety profile of 495 venoplasty procedures performed in 461 patients with MS, including 98 stent implantations. (16) There were no deaths, major bleeding events, or acute exacerbations of MS. The most common procedure-related complication was vein dissection, which occurred in 3.0% of cases. Other complications included cardiac arrhythmias (1.2%), groin hematoma (1.0%), vein rupture (0.4%), and acute stent thrombosis (1.6%). Mandato et al. (17) reported adverse events within 30 days of endovascular intervention for 240 patients with MS over an 8-month period. Neck pain occurred in 15.6% of patients, most commonly following stent implantation. Headache occurred in 8.2% of patients and was persistent past 30 days in one patient (0.4%). Intraprocedural arrhythmias occurred in 1.3%, and one patient was diagnosed with a stress-induced cardiomyopathy following the procedure.

An U.S. Food and Drug Administration (FDA) alert was issued in May 2012 concerning the potential for adverse events following endovascular interventions for MS. (18) Reports of adverse events obtained by the FDA included death, stroke, detachment and/or migration of stents, vein damage, thrombosis, cranial nerve damage, and abdominal bleeding. This alert included the caveat that clinical trials of this procedure require FDA approval and an investigational device exemption due to potential for harms.

Conclusions. The efficacy of venoplasty for CCSVI has been evaluated only in small case series and one very small trial of immediate versus delayed treatment. These studies report improvements in symptoms and disease-specific quality-of-life measures. However, this evidence is insufficient to determine the efficacy of venoplasty because of the small amount of literature and the lack of controlled studies. Randomized controlled trials (RCTs) are needed to adequately assess efficacy, especially when subjective patient-reported outcomes are used as the primary endpoint.

A few case series of several hundred patients have reported on adverse events. These studies establish that adverse events are uncommon following venoplasty, but serious adverse events do occur. The FDA issued an alert in May 2012, noting the existence of serious complications, including death, and the need for ongoing monitoring. It is not currently possible to estimate the rate of serious adverse events such as death or major bleeding with confidence.
Ongoing Clinical Trials
A review of online site ClinicalTrials.gov on April 18, 2013 identified 1 active Phase 3 study. The BRAVE-DREAMS (Brain Venous Drainage Exploited Against Multiple Sclerosis) study is a multicenter, randomized, parallel group, blinded, sham-controlled trial to compare percutaneous balloon angioplasty to sham catheter venography in 679 patients with relapsing-remitting MS or secondary progressive MS and CCSVI. (NCT01371760)

Summary
Chronic cerebrospinal venous insufficiency (CCSVI) may be associated with multiple sclerosis (MS), although this is controversial and an active area of research. Correction of CCSVI has been attempted via percutaneous venoplasty. The intent of this procedure is to relieve MS symptoms by improving venous drainage of the central nervous system. Correction of CCSVI by this method may be referred to as the “Liberation Procedure.”

The association of CCSVI with MS is uncertain. The rate of CCSVI in MS patients varies widely in the literature for unclear reasons, from 0-100%. Some studies report higher rates of CCSVI in patients with MS compared to non-MS patients, but others do not. If there is an association between MS and CCSVI, it is not known whether this is a causative factor for MS or a secondary result of the disease. It also appears that CCSVI can occur in other disorders, and is not specific for MS.

Treatment of CCSVI with endovascular interventions has been attempted, but controlled trials to determine efficacy are lacking. The currently available studies report improvement in patient-reported symptoms following treatment, but this evidence is not sufficient to establish efficacy. Adverse events occur at a low overall rate, but serious adverse events can occur, and the FDA issued an alert in 2012 concerning the potential for serious adverse events with treatment of CCSVI.

Practice Guidelines and Position Statements
The Cardiovascular and Interventional Radiological Society of Europe (CIRSE) commentary on the treatment of chronic cerebrospinal venous insufficiency notes that “Thus far, no trial data are available, and there is currently no randomized controlled trial (RCT) in progress. Therefore, the basis for this new treatment rests on anecdotal evidence and successful testimonies by patients on the Internet. CIRSE believes that this is not a sound basis on which to offer a new treatment, which could have possible procedure-related complications, to an often desperate patient population.” (19)

The Society for Interventional Radiology (SIR) (20) published a position statement on the association of CCSVI with MS and the efficacy of endovascular treatments. Their recommendations included the following statements:

- At present, SIR considers the published literature to be inconclusive on whether CCSVI is a clinically important factor in the development and/or progression of MS, and on whether balloon angioplasty and/or stent placement are clinically effective in patients with MS.
- SIR strongly supports the urgent performance of high-quality clinical research to determine the safety and efficacy of interventional MS therapies, and is actively working to promote and expedite the completion.
The U.K. National Institute for Health and Clinical Excellence (NICE) published a guidance document on the use of percutaneous venoplasty to treat CCSVI in patients with MS. (21) This document contained the following statements on the diagnosis and treatment of CCSVI:

- Current evidence on the efficacy of percutaneous venoplasty for chronic cerebrospinal venous insufficiency (CCSVI) for multiple sclerosis (MS) is inadequate in quality and quantity. Therefore, this procedure should only be used in the context of research.
- NICE encourages further research on percutaneous venoplasty for CCSVI for MS, in the form of robust controlled clinical trials. Studies should clearly define selection criteria and patient characteristics. They should also clearly define technical success which may include measurement of pressure gradients across treated vein segments before and after venoplasty. Outcomes should include clinical and quality of life measures.

The European Society of Neurosonology and Cerebral Hemodynamics (ESNCH) issued a statement on CCSVI and MS in 2012. (22) The ESNCH statement indicates the proposed criteria for the diagnosis of CCSVI is questionable due to methodological and technological errors, and lack of validation. The statement strongly discourages any interventional treatment for CCSVI in MS, such as transluminal angioplasty and/or stenting, due to lack of evidence and risk of serious complications.

**CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**CPT/HCPCS**

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**DIAGNOSES**

Experimental / investigational for all diagnoses related to this medical policy.

**REVISIONS**

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