Diagnosis and Treatment of Chronic Cerebrospinal Venous Insufficiency in Multiple Sclerosis

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the identification and subsequent treatment of chronic cerebrospinal venous insufficiency (CCSVI) in patients with multiple sclerosis (MS) to be **investigational.***

Background/Overview

CCSVI may be associated with 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."

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 (CCSVI) have also been considered. The core foundation of this vascular theory is that venous drainage from the brain is abnormal 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. Balloon dilatation, with or without stenting, has been proposed as a means to treat the outflow problems, thereby alleviating CCSVI and 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 duration > 0.8s) 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 > 0.5s). 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 (< 0.3cm), 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 Δ-).

Centers for Medicare and Medicaid Services (CMS)
No national coverage determination (NCD) was identified. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Diagnosis of Chronic Cerebrospinal Venous Insufficiency and Association with Multiple Sclerosis
Interest in the role of CCSVI in MS followed reports from a European vascular surgeon, Zamboni. Zamboni et al. 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. Using 5 ultrasound criteria (previously described), Zamboni defined the condition of CCSVI. In initial research reports, Zamboni et al reported both sensitivity and specificity of 100% in separating MS patients from controls when applying these criteria.

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 and meta-analyses.

Systematic Reviews
In 2014 a meta-analysis on the association between CCSVI and MS was published by Tsivgoulis et al. Included in the meta-analysis were 19 studies with a total of 1250 MS patients and 899 healthy controls. CCSVI was associated with MS in the pooled analysis with an odds ratio (OR) of 8.35 (95% confidence interval [CI], 3.44 to 20.31; p<0.001). Heterogeneity across studies was considerable with a reported I^2 of 80.1%. In additional sensitivity analyses, the OR associating CCSVI and MS decreased. In the most conservative sensitivity analysis, which excluded 8 studies (studies by Zamboni or associated groups and studies conducted in Italy or by advocates of endovascular procedures for CCSVI), MS was not associated with CCSVI with an OR of 1.35 (95% CI, 0.62 to 2.93; p=0.453). Additionally, heterogeneity was not found with a reported I^2 of 0%.

Zwischenberger et al in 2013 reported on a meta-analysis of the association between MS and CCSVI diagnosed by ultrasound. Included in the meta-analysis were 13 studies with a total of 1141 MS patients and 738 healthy controls. Initial analysis demonstrated CCSVI was associated with MS with an OR of 2.57 (p<0.001), but heterogeneity was significant with a reported I^2 of 82.7% (p<0.001). In a subsequent analysis of 9 studies with 4 outliers (studies with disproportionately high ORs) removed, the OR decreased, but still

associated CCSVI with MS with an OR of 1885 (p<0.001) and heterogeneity decreased with an I^2 of 18 (p=0.279).

A systematic review of the association between CCSVI and MS was published in 2011 by Laupacis et al. 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% CI, 2.6 to 71.4). There was a large amount of heterogeneity in this measure as well, with a reported I^2 of 89%. Several sensitivity analyses were performed, with marked variability of the OR 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 that included a smaller number of studies (n=4) came to similar conclusions. The rate of CCSVI in MS patients ranged from 7% to 100%, and the rate in non-MS patients ranged from 2% to 36%. There was a significant association between CCSVI but with a high degree of heterogeneity (I^2=96%) and an OR for association that had extreme variability, from approximately 2 to more than 26,000.

Clinical Studies

The largest study performed to date is a U.S. study by Zivadinov et al that used ultrasound to evaluate CCSVI in 499 subjects. 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 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 (ie, 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 1 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 from the original study 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, 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. 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 to 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. 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 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 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 et al evaluated 56 patients with MS and 20 controls and found that none met the criteria for CCSVI using ultrasound.

Section Summary
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% to 100%. Many of these studies report higher rates of CCSVI in MS patients, but others do not. Systematic reviews and meta-analyses have reported that the combined OR 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
In 2014, Siddiqui et al published results from a prospective, double-blind, sham-controlled randomized controlled trials (RCT) of venous angioplasty in MS patients with CCSVI. This trial enrolled 9 patients in intervention group and 10 in the sham-controlled group. All patients met the criteria for diagnosis of CCSVI. The primary end points of the trial included safety at 24 hours and 30 days postangioplasty; greater than 75% restoration of venous outflow at 30 days; the presence of new MS lesions; and relapse rate over 6 months. Secondary end points included changes in disability scores, brain volume, cognitive test scores, and QOL measures. All patients tolerated the procedures well; no operative or postoperative complications were identified. One patient in the angioplasty group experienced an episode of symptomatic bradycardia. No significant differences were observed in venous outflow characteristics between the treated and control groups, nor were any significant improvements observed in clinical disease scores among treated patients compared with controls. The results of this RCT are limited by the small number of patients. However, the failure to show a beneficial effect of venous angioplasty on MS activity supports a lack of efficacy for this treatment.

Some experts have suggested that the results show clinical equipoise no longer exists with regard to venous angioplasty and CCSVI and that further clinical study of the former would be unethical. The authors of a 2015 comprehensive literature review of venous angioplasty as treatment of CCSVI in MS concur with the editorial. They indicate that this procedure has no proven efficacy, may exacerbate underlying disease activity, and state that the treatment should no longer be offered, even in clinical trials.

In a 2012 Cochrane review, Van Zuuren et al found no RCTs
on the treatment of CCSVI in MS patients. While there are ongoing clinical trials, the reviewers concluded the efficacy or safety of percutaneous transluminal angioplasty (PTA) 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. MSIS scores significantly improved at each evaluation after angioplasty on both the physical and psychologic 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. 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 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 RCT is warranted.

Zamboni et al also reported a smaller series of 8 patients with ultrasound criteria for CCSVI undergoing immediate venoplasty compared with 7 patients undergoing delayed venoplasty. There were improvements on the EDSS 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 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 1 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 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. 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 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 1 patient (0.4%). Intraprocedural arrhythmias occurred in 1.3%, and 1 patient was diagnosed with a stress-induced cardiomyopathy following the procedure.

An FDA alert was issued in May 2012 concerning the potential for adverse events following endovascular interventions for MS. Reports of adverse events obtained by 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 because of the potential for harms.

Section Summary
A prospective, double-blind, sham-controlled RCT of venous angioplasty in MS patients (N=20) with CCSVI published in 2014 showed no significant differences in venous outflow characteristics between the treated and control groups, nor any significant improvements in clinical disease scores among treated patients compared with controls. The results of this RCT are limited by the small number of patients.

The efficacy of venoplasty for CCSVI has been evaluated only in small case series and 1 very small trial of immediate versus delayed treatment. These studies report improvements in symptoms and disease-specific QOL 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. RCTs are needed to adequately assess efficacy, especially when subjective patient-reported outcomes are used as the primary end point.

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. 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 and Unpublished Clinical Trials
One large, unpublished phase 3 trial that might influence this policy is listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT01371760	Randomized Multi-centered Study for Evaluating the Efficacy and Safety of Angioplastic Surgery of the Extracranial Veins in the Treatment of Multiple Sclerosis	679	Aug 2014

NCT: national clinical trial.

Summary
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% to100%. Some studies report higher rates of CCSVI in patients with MS compared with 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. Some currently available studies report improvement in patient-reported symptoms following treatment, but this evidence is not sufficient to establish efficacy. . A prospective, double-blind, sham-controlled RCT of venous angioplasty in MS patients (N=20) with CCSVI published in 2014 showed no significant differences in venous outflow characteristics between the treated and control groups, nor any significant improvements in clinical disease scores among treated patients compared with controls. The results of this RCT are limited by the small number of patients. However, the failure to show a beneficial effect of venous angioplasty on blood flow or symptoms supports a lack of efficacy for this treatment.

Adverse events occur at a low overall rate, but serious adverse events can occur, and FDA issued an alert in 2012 concerning the potential for serious adverse events with treatment of CCSVI.

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Policy History

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Code Type	Code
CPT	37238, 37239, 37248, 37249
HCPCS	No codes
ICD-10 Diagnosis	G35

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B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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