Chronic Cerebrospinal Venous Insufficiency in Multiple Sclerosis Patients

There is speculation that CCSVI may contribute to the symptoms experienced by MS patients, but what do the data tell us so far?

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Multiple sclerosis (MS) is a chronic disease of the central nervous system characterized by inflammation and demyelination.[1] It is estimated that MS is diagnosed in more than 10,000 patients every year in the United States alone.[2] MS can lead to a wide range of neurologic symptoms including fatigue, headaches, decreased cognition, optic nerve dysfunction, diplopia, decreased balance, extremity weakness, and bladder and bowel dysfunction. The etiology of MS is unknown, although most point to an autoimmune basis at present.[3] Many patients with MS receive disease-modifying drugs to prevent relapse and slow disease progression.

Chronic cerebrospinal venous insufficiency (CCSVI) is a recent theory put forth to explain the pathogenesis of MS and its associated symptoms.[4] The early work of Charcot and Putnam laid the groundwork for this theory by suggesting the possibility that a relationship existed between the venous drainage from the central nervous system and the lesions associated with MS.[5,6] The CCSVI theory states that extracranial venous outflow obstruction (Figure 1A) can lead to venous hypertension and dilatation, which can result in chronic venous reflux,[7] prolonged circulatory transit time,[8] lower net flow of cerebrospinal fluid,[9] and blood brain barrier disruption.[10] The latter can potentially cause an infiltration of immune cells (which can cause an autoimmune reaction) and/or red blood cells (which can cause perivenous iron deposition and inflammation) into the central nervous system, both of which may contribute to the development or progression of MS.[11]

Zamboni et al have described success with treating this condition with angioplasty of the internal jugular (IJ)

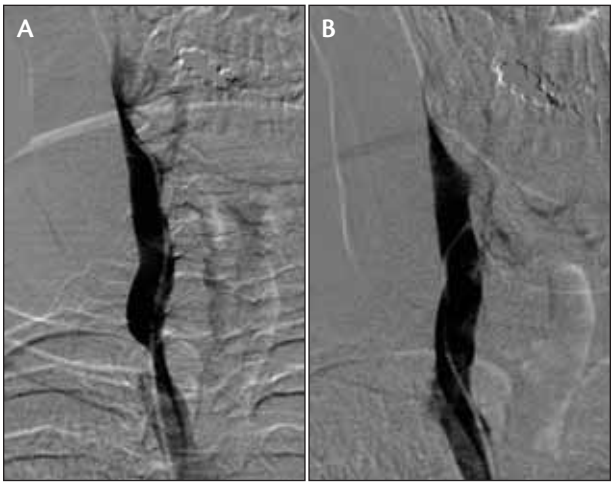

Figure 1. Right anterior oblique view of selective venograms before (A) and after (B) treatment of a severe stenosis of the proximal right IJ vein with angioplasty.

(Figure 1B) and azygous veins.[12] Given the significant motivation on the part of patients suffering from MS to actively seek out treatment options that may address both symptoms and the underlying etiology of this condition, it is not surprising that so much attention has been paid to CCSVI. The purpose of this article is to review the data that are currently available regarding CCSVI and the potential role it may play in the care of patients with MS.

DIAGNOSING CCSVI

The diagnosis of CCSVI using noninvasive imaging has been one of the challenges associated with this condition. The ultrasound technique described by Zamboni et

al has been the most commonly used imaging modality for this purpose.[13] This technique involves the evaluation of five different parameters to assess venous flow: reflux in the IJ or vertebral veins, reflux within the deep cerebral veins, evidence of a stenosis within the IJ vein on grayscale images, undetectable flow in the IJ veins, and the absence of the normal decrease in cross-sectional area of the IJ vein when moving from a supine to an upright position.

In a study of 109 MS patients and 177 controls, Zamboni et al found that 47% of measurements were abnormal in the MS patients and only 2.7% were abnormal in the control population. When at least two criteria were used to define a positive examination, the positive and negative predictive values were 100%. Other authors have found an increased prevalence of CCSVI in MS as well, although not to the same extent as Zamboni et al.[14-16] This, however, has not been a consistent finding among investigators. For example, Doepp et al found no differences in venous flow between MS patients and healthy controls.[17]

Although this has led some researchers to conclude that CCSVI is not a true pathologic entity, it has led others to recognize that not every patient with MS has an ultrasound examination consistent with CCSVI. It has been suggested that ultrasound may not be the most effective way to diagnose CCSVI, particularly when specialized training appears to be necessary to optimize the diagnostic accuracy and reproducibility of this technique.[18]

Magnetic resonance imaging is the standard imaging modality used to both diagnose and follow patients with MS.[19] It effectively shows the lesions associated with MS and is a prominent part of the McDonald criteria used to diagnose MS.[20] Magnetic resonance venography has been used to detect evidence of venous insufficiency in this population.[21] It is believed to be a useful modality for this purpose because it can visualize the actual extracranial venous stenoses while also assessing brain perfusion and iron content within the brain. However, it too has been found to be an inconsistent way to diagnose CCSVI in this patient population.[22,23]

Most interventionists consider selective venography to be the gold standard for diagnosing CCSVI. Bartolomei et al studied 65 patients and found that all patients had multiple and significant extracranial venous stenoses involving the IJ and/or azygous veins.[24] Interestingly, four patterns of extracranial disease were found in these patients: type A (stenosis of the proximal azygous vein with a stenosis of one IJ vein), type B (stenosis of the azygous vein and both IJ veins), type C (stenosis of both IJ veins and a normal azygous vein), and type D (stenosis of the azygous vein with normal IJ veins). These patterns were shown to correlate with the type of MS and the presenting symptoms at the time of MS onset.

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At the first meeting of the International Society for Neurovascular Disease held in March 2011 in Bologna, Italy, Denislic reported the results of a study evaluating 65 MS patients with venography and compared the findings with the Expanded Disability Status Scale (EDSS), which is an overall measure of neurologic impairment ranging from 0 (normal neurologic examination) to 10 (death due to MS).[25,26] They found that patients with an EDSS score > 6 had significantly more treatable lesions on venography than patients with a lower EDSS score, indicating that the severity of venous disease increases with the severity of the patient's neurologic condition.

TREATMENT AND RESULTS

Once diagnosed, it is of course important to know whether or not treatment of this condition leads to a significant change in the clinical condition of the patient. In the initial pilot study Zamboni et al performed venography on 65 MS patients with CCSVI diagnosed on ultrasound.[12] Patients with a stenosis > 50% in severity were treated with angioplasty using 10- to 12-mm balloons in the IJ veins and 8- to 10-mm balloons in the azygous vein. The relapsing-remitting patients in this group had sustained clinical improvement based on the Multiple Sclerosis Functional Composite; only limited improvement was seen in patients with primary and secondary progressive MS.

The Multiple Sclerosis Functional Composite tests upper extremity dexterity with a timed 9-hole peg test, leg/walking function with a timed 25-foot walk, and cognitive function with a Paced Auditory Serial Addition Test.[27] In addition, all of the relapsing-remitting patients with continued venous patency at 18 months were relapse free, leading some to conclude that angioplasty may affect disease progression. Unfortunately, the primary patency rate at 18 months was 53% in the IJ vein, but it was 96% in the azygous vein.

TABLE 1. REPORTED COMPLICATIONS AFTER ENDOVASCULAR TREATMENT OF CCSVI

	Mandato et al[32]	Ludyga et al[31]
Minor Complications		
Contrast reaction	2.7% (7/257)	Not reported
Transient headache (< 30 days)	8.2% (21/257)	Not reported
Persistent headache (> 30 days)	0.4% (1/257)	Not reported
Transient neck pain (< 30 days)	15.2% (39/257)	Not reported
Orbital pain	0.4% (1/257)	Not reported
Difficulty removing balloon	0% (0/257)	1.2% (4/344)
Puncture site bleeding/hematoma	0.8% (2/257)	1.2% (4/344)
Symptomatic restenosis requiring retreatment (< 30 days)	1.6% (4/257)	Not reported
Transient cardiac arrhythmias	1.2% (3/257)	0.6% (2/344)
Minor gastrointestinal bleeding	0% (0/257)	0.3% (1/344)
Major Complications		
Postprocedural venous thrombosis (< 30 days)	1.2% (3/257)	0.6% (2/344)
Stress-induced cardiomyopathy	0.4% (1/257)	Not reported
Surgical removal of angioplasty balloon	0% (0/257)	0.3% (1/344)

Since this initial study, other reports have emerged about the outcomes after angioplasty in this patient population. Malagoni et al studied 35 MS patients with significant fatigue and found sustained improvement in fatigue and a greater ability to perform daily activities after angioplasty.[28] At the International Society for Neurovascular Disease meeting, Zarebinski reported on the results from a study of 420 MS patients treated with angioplasty and found significant improvement in fatigue but no significant improvement in EDSS score or the MS Impact Scale-29.[29] Mehta also reported the results from a study of 150 patients with MS. They found significant improvements in quality of life and fatigue after angioplasty.[30] In addition, they reported a technical success rate of 77% (defined as < 20% residual stenosis) and a reintervention rate of 9%.

In the original study by Zamboni et al, the reported complication rate was extremely low, with only six patients reporting a self-limited postprocedure headache.[12] Since that time, two other studies have specifically reported the complications associated with venous angioplasty and stent placement to treat CCSVI. Ludyga et al retrospectively reviewed 344 procedures performed in 331 patients and Mandato et al retrospectively reviewed 257 procedures in 240 patients.[31,32] The complications reported in these papers are outlined in Table 1. Severe complications that have been reported include cardiac arrhythmias,

stress-induced cardiomyopathy, adverse drug events (including an intracerebral hemorrhage secondary to anticoagulation), and intracardiac stent migration in the setting of stent placement.[31-33]

SUMMARY

At the present time, anecdotal reports continue to surface about the positive changes reported by patients after endovascular treatment of stenoses within the IJ and azygous veins. However, one can in no way state that enough research has been done to conclude that CCSVI is a true pathologic entity occurring with an increased frequency in MS patients, that this entity is responsible for the symptoms and disease progression seen with MS, and that treatment significantly improves the quality of life in these patients. As a result, additional research is going to be critically important moving forward.

This sentiment was echoed in the recent report from the Research Consensus Panel convened by the Society of Interventional Radiology Foundation, which supported the need for additional well-designed studies in areas including basic science work to better understand the relationship between venous stenoses, hypertension, and CCSVI; single-center studies to define appropriate patients to treat and develop standardized procedural technique; and multicenter, prospective, randomized trials to demonstrate efficacy.[34] Ongoing studies include registries in Europe and the United States as well as several prospective single-arm and randomized, blinded studies. Ultimately, these studies will help grow our understanding of CCSVI and help determine what role treatment of this entity can and should play in the care of patients with MS. ■

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