

# Chronic Cerebrospinal Venous Insufficiency

A new paradigm and therapy for multiple sclerosis.

BY SALVATORE J.A. SCLAFANI, MD

**C**hronic cerebrospinal venous insufficiency (CCSVI) is a hemodynamic condition in which cerebrospinal venous drainage is altered and inhibited. Outflow obstructions of the internal jugular veins (IJVs), vertebral veins, and/or azygos vein (AZV) and their tributaries result in stasis or reflux of these outflow veins and redirection of flow through vicarious circuits. Cerebral blood flow and brain perfusion are retarded and may result in cerebral atrophy, venous microhemorrhage, and cerebral hypertension. Moreover, stasis may evolve into occlusions of these veins or the dural sinuses.<sup>1</sup>

The previously reported acute outflow obstructions of the dural sinuses and jugular veins have been due to hypercoagulable states, inflammation, iatrogenic trauma during prolonged catheterization, and compression by neck neoplasms and adenopathy.<sup>2-5</sup> These occlusions and stenoses cause acute manifestations of cerebral venous outflow obstruction. Mental confusion, severe headaches, weakness and lethargy, acute visual disturbances, and facial and glottic edema are clinically obvious and quite severe. Treatment of the obstructions, by angioplasty, angioplasty and stenting, or thrombolysis and stenting, results in prompt and satisfactory amelioration of these symptoms. It has also been shown that acute jugular incompetence can result in transient global amnesia.<sup>6</sup> The fact that venous insufficiency can cause acute neurological disturbances was convincingly demonstrated in a case report about a patient with a patent arm dialysis arteriovenous shunt who developed increasing headaches, gait disturbance, and cognitive dysfunction that significantly improved after ligation of that shunt.<sup>7</sup>

The majority of patients with CCSVI appear to have multiple sclerosis (MS), and the majority of patients with MS have CCSVI. MS is an inflammatory demyelinating disorder of the brain and spine with protean neurological manifestations. It is the most common



Figure 1. Preprocedural MR venogram shows a venous plethora of collateral veins throughout the neck. Arrows point to perceived stenoses of the distal lower cervical portion of the IJV.

neurological disorder of young adults. It is quite possible that some of the protean manifestations of MS, including fatigue and lethargy, headaches, and cognitive dysfunction, may actually represent symptoms of CCSVI itself.<sup>8</sup>

CCSVI is more insidious in its onset than acute venous insufficiency. In fact, the association of CCSVI with MS has been largely ignored despite Charcot's original description of the relationship of the cerebral veins and inflammatory lesions that are the hallmark of MS.<sup>9</sup>

Zamboni proposes that CCSVI has a role in the pathogenesis of MS. He suggests that resistance to cerebrospinal venous outflow causes vicarious redistribution through small collateral veins that cannot handle high flow.<sup>10</sup> He also suggests that tight endothelial junctions widen to allow diapedesis of red blood cells, T cells, and other immune cells into the brain, resulting in inflammation and hemosiderosis that is reminiscent of what is seen with venous insufficiency of the lower extremities. This is supported by iron deposition as seen on susceptibility-weighted magnetic resonance imaging (SW-MRI), which reveals that the inflammatory MS plaques always surround a central venous structure. MRI shows that the central vein and surrounding plaque have abnormal quantities of iron. Pathologically, the basement membranes of these deep veins are thickened, and hemosiderin deposits are present in the wall of and adjacent to the deep cortical veins. T cells and macrophages violating the blood-brain barrier provide a working explanation for the autoimmune cascade that result in demyelination and the neurological manifestations associated with MS.

## DIAGNOSIS

### Ultrasound

One could argue that the diagnosis of MS is sufficient to justify catheter venography to identify venous abnormalities worthy of angioplasty. However, Zamboni used ultrasound imaging to noninvasively screen patients who might have CCSVI, and this algorithm persists as the route of detection. His protocol includes transcranial and extracranial Doppler to detect deranged hemodynamics and B-mode ultrasound to detect stenoses and changes in cross-sectional diameters in the supine and the upright positions. He states that two of five characteristics lead to a diagnosis of CCSVI. The five characteristics are (1) reflux within the IJVs or vertebral veins, (2) reflux within any of the deep cerebral veins, (3) no flow in the IJV on activation of the thoracic pump upon inspiration, (4) failure of the IJV to increase in diameter in the supine position compared to the erect position, and (5) any B-mode abnormality such as septum, stenosis, abnormal valve, etc.



**Figure 2.** Bilateral IJV venography shows opacification of the vertebral plexus and drainage through the vertebral veins (arrows). Both IJVs had focal stenoses at the confluences of the IJV with the subclavian vein. Angioplasty improved but did not eliminate the stenoses.

### MR Venography and Computed Tomographic Venography

Others have used cross-sectional venography to evaluate venous stenosis (Figure 1). The majority of sites use MR venography, but occasionally, computed tomographic venography is also used. To evaluate the dural sinuses and the veins of the neck, two-dimensional and two-dimensional contrast-enhanced imaging is used. These cross-sectional studies show a variety of findings that include venous narrowing and collateral vessels throughout the neck. Occasionally, narrowing or occlusions of the dural sinuses are noted, but for the majority of times, findings are restricted to the neck. However, there is poor correlation between the anatomical findings on MR venography and subsequent catheter venography. Many areas of narrowing on MR venography are not constant and are not reproduced during catheter-based studies.

### Hemodynamics of Cerebral Venous Drainage Explain False-Positive Findings on MR Venography

To explain this enigma, one must understand the hemodynamics of cerebral venous outflow. The brain has two methods of venous drainage: blood drains

## COMMENTARY

# The Relationship Between CCSVI and MS

BY MICHAEL D. DAKE, MD, AND BARRY T. KATZEN, MD

In this article, Dr. Salvatore Sclafani presents an introduction to chronic cerebrospinal venous insufficiency (CCSVI) and the current understanding of its association with multiple sclerosis (MS). Much of the initial evidence supporting this possible relationship has been reported by Dr. Paolo Zamboni and colleagues. Using duplex ultrasonography and transcranial Doppler studies, they have documented the frequent association of abnormal venous hemodynamics with MS. In one study of 109 MS patients and 177 age- and gender-matched controls, subjects underwent a blinded transcranial and extracranial color Doppler sonographic assessment (TCCS-ECD) of five parameters related to venous outflow hemodynamics. These five criteria are detailed by Dr. Sclafani in his review. In controls, only 2.7% of the measurements were abnormal, whereas in MS patients, 47% of measurements were anomalous.<sup>1</sup>

In a study comparing duplex ultrasound with contrast venography, 40% to 70% of MS patients had evidence of flow disturbances and/or venous stenosis by TCCS-ECD. Of these patients, 86% and 91% had obstructive disease of the azygos or internal jugular veins, respectively, as assessed by traditional catheter venography.<sup>2</sup>

Some of the symptoms of MS mimic those observed in patients with superior vena cava syndrome. Relief of superior vena cava obstruction with venous angioplasty and stent placement, if required, provides swift and dramatic resolution of the symptoms of impaired cognition and fatigue.<sup>3</sup> Thus, it is not surprising that patients with CCSVI associated with MS also report rapid relief of these nonlocalizing symptoms.

It is well-recognized, however, that many symptoms of MS fluctuate and are largely subjective. It is possible that in the initial nonrandomized patient series reported to date, the improvement in symptoms could reflect a strong placebo effect. Nonetheless, the biological plausibility linking cerebral venous congestion to inflammation that is the hallmark of MS requires serious consideration. Whether the relief of the venous obstruction will have an impact on the course of the neurological disease remains to be seen.

Although the initial observations relating CCSVI and MS are interesting and potentially paradigm-shifting, they now need rigorous testing. As Dr. Sclafani correctly points out, there are life-threatening adverse effects that may complicate endovascular management of CCSVI. A randomized clinical trial is needed to assess the risks and benefits of endovascular treatment of this condition. There are many physicians and

others who have endovascular skills who are promoting and developing centers for treating these patients without regard for the lack of scientific data to support therapy. Patients with this disease have frequently suffered for long periods of time, often without great relief of symptoms and are often desperate for any alternative that may offer hope.

We remain very concerned about the possibility of misleading these individuals or exposing them to additional risk, outside of scientific efforts to get a better understanding of this potentially exciting therapy. Given the concerns of the neurology community, it would be unfortunate if the attempts to advance this field suffer the consequences of premature promotion of a procedure that could mislead patients, payors, and regulators.

Accordingly, we propose a global initiative to meticulously document the prevalence of venous anomalies in MS, by comparison to age- and gender-matched healthy individuals, as well as those with neurological disease not due to MS. In part, recent grants from the National MS Society awarded to seven investigative groups to study CCSVI will help initiate this effort in the United States and Canada. These observations may provide a basis for a clinical trial in MS to assess the long-term safety and efficacy of endovascular procedures in restoring normal venous hemodynamics, in relieving the nonlocalizing symptoms secondary to venous obstruction, and in slowing or halting the inflammatory and demyelinating processes. In parallel, the development of animal models will advance our understanding of how CCSVI may influence or even initiate the pathophysiology of MS.

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anteriorly through the internal jugular system in the supine position and posteriorly through the vertebral system when erect. In the normal, upright patient, the jugular vein collapses (narrows) because there is not enough blood flow through it to maintain distension. In the supine position, the normal IJVs distend because the supine position favors jugular flow. The same issues apply when there is increased resistance to jugular flow. The alternate vertebral venous outflow system shunts blood away from the jugular veins. Because pressure is normally low and only marginally rises with obstruction, distension of the obstructed system does not occur.

As a result, many of the narrowings seen in CCSVI are caused by compression of a collapsed system by external forces rather than due to stenoses. This may lead to unnecessary angioplasty. The common areas of questionably physiological stenosis seen on MR venography are located at the skull base, adjacent to the carotid bulb, or where strap muscles exert compression.

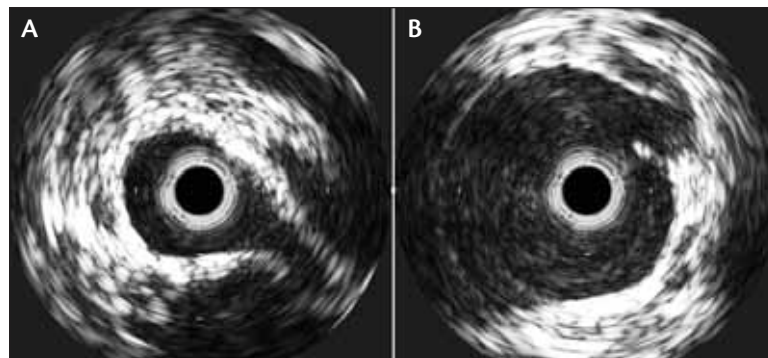
## VENOGRAPHY AND VENOGRAPHIC OBSERVATIONS

Venography remains the gold standard for evaluating the anatomy of the veins draining cerebrospinal blood flow. It should be emphasized that a reliable assessment of the azygos system can only be done by using catheter venography.

### Technique

The venographic evaluation is begun by placing a headhunter catheter in the left femoral vein with the purpose of excluding May-Thurner syndrome. The catheter is subsequently placed in the left ascending lumbar vein to assess the lumbar veins for hypoplasia and other abnormalities. The left renal vein is then catheterized to look for abnormalities of the renal vein tributaries. The purpose of these three studies is to look for causes of increased blood flow into lumbar veins that might be compromised by azygos stenosis.

The catheter is then placed in succession into the AZV and both IJVs. The catheter is positioned in the AZV at the junction with the hemiazygos vein. Contrast venography is done twice: first at 3 mL/s for a total volume of 10 mL to look for reflux, followed by a second, fuller injection at 8 to 10 mL/s for a total volume of 20 to 30 mL to delineate all the anatomy. The AZV and its



**Figure 3.** IVUS in resting state at the level of the stenosis of the central cervical IJV (A) shows narrowing of the IJV, which is collapsed around the catheter. The thoracic pump was activated, and flow into the IJV improved (B). IVUS shows distension; therefore, angioplasty was not performed.

tributaries are imaged to include the chest and abdomen. Some physicians measure pressures, but I have not found this to be helpful. Any stenosis is treated, as will be described later.

The catheter is then withdrawn from the AZV and advanced sequentially into each IJV. Catheterization of the IJV may be challenging because funneled narrowing of stenotic valve leaflets occurs near the origin of the vessel. Occasionally, an incomplete duplication is present posterior to the main ostium. This may make catheterization confusing and difficult. Two contrast injections are performed: one with a slow injection of 3 mL/s for a total volume of 10 mL and one with a fuller injection of 8 to 10 mL/s for a total volume of 20 mL. Film rates of 3 to 6 frames per second are necessary to get sufficient detail of the valves and to detect ostial narrowing that may become obscured as contrast enters the brachiocephalic veins and overlaps the confluents where stenosis is often located. Any stenoses or other outflow obstructions are treated at this time. Diluted contrast abnormalities (50:50 mixture of saline) is helpful in the IJV evaluation because valve abnormalities and some webs may be obscured by very dense contrast media.

### Venographic Findings

First, there are numerous collateral veins when outflow obstructions are present (Figure 2). These veins may be wildly abnormal and include hypoplasias and early divisions that reconnect to a larger conduit. The vertebral veins may be enlarged and can be confusing in their appearance. The pathology of this disease is a truncal malformation of the veins that is probably genetically determined; it is not an inflammatory or postphlebotic stenosis. Much of the resistance to blood flow is related to abnormal valve development. Fused, reversed, thick-



ened, and other abnormally located and developed valves cause resistance to flow. Atresias, hypoplasias, duplications, webs, septums, and kinks also occur. Most of these abnormalities are located centrally near the confluents. Challenges occur when more peripheral narrowings are present, which may be physiological.

### **INTRAVASCULAR ULTRASOUND**

Diagnosis by venography can also be subtle. I have found that intravascular ultrasound (IVUS) is very helpful in identifying some of these abnormalities, as well as in differentiating the narrowed veins caused by inadequate volume from the narrowed veins resulting from stenosis (Figure 3). IVUS enables a real-time assessment of the distensibility of collapsed veins. Simple maneuvers, such as slow sustained inspiration by activating the thoracic pump, allow improved distension of the vein and confirms that the narrowing is not fixed. Further, IVUS allows detection of improper or incomplete valve movement. Finally, incomplete duplications of the jugular vein may not be detected without IVUS.

### **TREATMENT OPTIONS**

Treatment of these abnormalities is still in development, and the ideal methodologies for treatment have not yet been established. Essentially, only one team has published an outcomes study.<sup>1</sup> Results were encouraging but showed limitations. Angioplasty with high-pressure balloons of diameters 4 mm greater than nominal diameters in 2- to 4-cm lengths is performed with venographic control. Inflations to maximum pressures for 30 to 60 seconds were used several times. Some of these obstructions are very resistant, and Cutting balloons (Boston Scientific Corporation, Natick, MA) are used with increasing frequency. Dr. Sinan Tariq, the leader of the Kuwaiti national trial, has been using valvulotomy devices with some success (personal communication, April 2010). Stenting is performed by some investigators for resistant narrowings. However, no reports have been published about their outcomes. I have not used stents in any cases yet.

### **AFTERCARE AND FOLLOW-UP**

The procedure is performed under local anesthesia in an ambulatory setting. Most patients are kept in the hospital for 1 or 2 hours and then discharged. Most physicians treat patients with clopidogrel or short-term anticoagulation with heparins, enoxaparin, or fondaparinux. Clinical and imaging follow-up varies among investigators. Assessment tools are predominantly clinical and include an expanded disability status score (EDSS), which is a neurological assessment of

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eight areas of the central nervous system, along with certain measures of disability and restriction in daily life. These scores are added up to give a rating on the EDSS, which ranges from 0 (normal) to 10 (death due to MS). From step 4 onward, the ability to walk becomes the key factor in determining the EDSS score.

## OUTCOMES

It must be emphasized that only one team has published any clinical results, and although promising, they were not overwhelming. Zamboni's group described an open-label experience of patients with MS who were allowed to stay on disease-modifying drugs for their MS. The results were encouraging, with statistically significant improvements in cognition and motor function and reduced exacerbation rates, and MRI confirmed diminished new brain lesion development. The patients who have shown the most positive results are those in the relapsing-remitting phase of the disease. Patients with primary progressive MS, for whom there is no proven treatment, had the least positive effects.

However, the dilatations are not always durable, with approximately half of the patients developing restenosis between 8 to 14 months. It is interesting that all patients who suffered from an exacerbation of symptoms had a restenosis and that no patients who had durable angioplasty experienced restenosis.

Overall, the procedure is well-tolerated, and patients do not require sedation. The complications reported in Zamboni's trial were minimal. I have had one early thrombosis that did not respond to thrombolytics and one case of atrial fibrillation that I thought might have been a response to treatment that modified autonomic neural transmission, but resolved within 12 hours. Those interventionists who have used stents have not yet reported outcomes in the literature.

Dr. Zamboni cautions against stents because they are not designed for placement at the confluents of the jugular vein with the subclavian vein where the jugular vein widens. Improved flow is shown to significantly increase the diameter of these veins. He worried about migration in his article, and indeed, one of the early patients treated with stenting by another interventionist is reported in the lay press to have required open heart surgery for stent retrieval.

## CAVEATS

CCSVI has not been well-accepted by the neurological community. Many leaders strongly oppose this treatment on the grounds that no randomized prospective trials have taken place, and they describe

the procedure as dangerous and invasive. Patients who are not enamored by current treatments find this mechanical solution alluring. They have become activists and are seeking physicians with catheter skills to begin these treatments. The fact that clinical improvements occur cannot be disputed. Although the placebo effect cannot be ignored, some of the anecdotal positive results have been impressive. Even before leaving the procedure room, patients describe improved cognition and a return of sensation and reduction in neuralgia within minutes. One patient, who was confined to a wheelchair because of spasticity, ataxia, and weakness, returned the next morning after a quick run up the stairs to show his ability to stand on one leg without difficulties.

However, these improvements may not persist, and exacerbation may occur within weeks of the procedure. Is this caused by recurrent stenosis or increased reflux? Nonetheless, the improvements warrant further investigation and well thought-out trials. The diagnosis is not always obvious. The current experience is about discovering who, what, and how to treat. Safety studies are needed to develop more information and experience. Additional work and publication of results are also necessary before there is advocacy of the widespread application of venoplasty for CCSVI. ■

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