Chronic cerebrospinal venous insufficiency and the doubtful promise of an endovascular treatment for multiple sclerosis

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INTRODUCTION

Recently, a radically different concept regarding the pathogenesis of multiple sclerosis (MS) has been proposed. Termed chronic cerebrospinal venous insufficiency (CCSVI), it suggests that macro occlusive abnormalities of the extracranial venous drainage pathways of the brain and spinal cord can cause or contribute to MS. As a consequence of this theory, it has been suggested that angioplasty and possibly stenting of the internal jugular and/or azygos veins can improve the signs and symptoms of MS. These interventions have been performed sporadically across the globe in an open label fashion and never in the context of a well designed, controlled, randomized and blinded clinical trial. Despite this, the procedure has been labeled by some as ‘liberation procedure’ and caused a firestorm of interest in the medical and MS communities, both for and against its utilization. The arguments on all sides are passionate, ranging from the belief that venous intervention is a miracle cure that must not be withheld from patients, to the feeling that the procedure is ineffective and unwarranted at best and dangerous at worst. The various camps commonly protest that those with differing views are not acting in the best interest of their patients.

BRIEF REVIEW OF MULTIPLE SCLEROSIS

MS is a fearful and unpredictable disease that brings an enormous physical, emotional and financial burden on patients, family, relatives, friends and society in general. It is the most common cause of physical disability, with estimated 250 000–350 000 individual diagnosed with MS in the USA. The peak age at onset is 20–40 years. It affects women more so than men and is more common among Caucasians. MS can present with any part of the nervous system, sensory, motor, cranial nerves, visual, autonomic, coordination and myelopathic on different occasions with cumulative disability. Diagnosis is based on clinical and imaging criteria (McDonald criteria) to establish the dissemination in place (different CNS sites) and time (at least 30 days between clinical relapses and 90 days for new MRI lesion without clinical relapse). The clinical course of MS is most commonly relapsing remitting, with return to baseline after each relapse, followed by secondary progressive starting as relapsing remitting, then primary progressive MS. The most prevalent hypothesis regarding the pathophysiological basis for MS is that it is an autoimmune inflammatory disease triggered by environmental factors (toxic and infectious triggers) with genetic predisposition leading to myelin and axonal destruction in the brain and spinal cord by the immune system. To date, MS management has been limited to the indefinite administration of disease modifying medications and immune modulating agents which may reduce the number and severity of relapses. These agents are not only costly but are associated with a wide spectrum of side effects ranging from mild to severe.

THE CCSVI THEORY AND SUPPORTIVE DATA

In 2006, Zamboni, an Italian vascular surgeon, in an article titled ‘The big idea: iron-dependent inflammation in venous disease and proposed parallels in multiple sclerosis’ suggested that there were similarities between chronic venous disease of the extremities and MS. He raised the possibility that venous reflux or obstruction in cerebral and spinal veins might have a relationship to MS.

Several years later, Zamboni et al reported on blinded transcranial and extracranial color Doppler sonographic findings in patients with MS and matched healthy controls and those with other neurological disorders. They focused on five findings: (1) reflux in the internal jugular vein (IJV) or vertebral veins >0.88 s; (2) reflux propagated in at least one out of the three deep cerebral veins >0.55 s; (3) high resolution B mode evidence of proximal IJV stenosis; (4) flow not Doppler detectable in the IJV or vertebral veins despite deep inspirations; and (5) negative difference of the cross sectional area of the IJV comparing the value obtained in the supine versus the sitting position. The authors concluded that detection of two or more of these findings constitutes the diagnosis of CCSVI. They found CCSVI in all MS patients and in none of the controls. The sensitivity, specificity, positive predictive value and negative predictive value of the test were all 100%. They concluded that there was CCSVI in MS patients.

In a second paper, Zamboni et al published that catheter venography in patients who met CCSVI Doppler criteria showed stenosis in the azygos vein 86% of the time and one or both IJV were affected in 91%. In this study, the venographer was not blinded to the patients’ diagnosis. The study proposed four venographic patterns: (A) large IJV with one IJV or proximal azygos vein stenosis; (B) both...
Enhancing lesions. Finally, there was no medical therapies have been shown to improve outcomes in patients suffering from this terrible disease. As such, when seemingly miraculous cures are proffered, we believe that it is our responsibility as neurointerventionalists to rationally review its use.

There are few data to support the validity of CCSVI. The lack of data seems counterbalanced by the great hope for the miracle of an endovascular treatment for MS. The topic has caused widespread attention and debate in the media, medical literature and the internet. As of late August 2010, a Google search on ‘liberation procedure’ yielded about 2,650,000 results and approximately 181,000 for ‘CCSVI’. Sponsored links appear for treatment in Mexico, Poland, Costa Rica, India and other locations. At least one toll free telephone number akin to ‘1-800-I Treat MS’ has been created.

The prospect of opening an open label, non-study related MS endovascular CCSVI practice can be very seductive. For physicians, the barriers to entry are small since most interventionalists are technically able to perform these procedures and the required devices are readily available. At the same time, there are many patients who are desperate for a procedure which might improve their condition despite the lack of evidence to support its benefits and almost regardless of its potential risks. Indeed, some might argue that because the procedure is safe, if there is any possibility of ameliorating some of the symptoms of MS patients the procedure should be offered to them. However, no invasive procedure is completely safe. In fact, there are increasing reports of complications related to PTA or stenting for CCSVI, including intracranial hemorrhage, stent migration into the heart and jugular vein thrombosis.

The moniker, ‘liberation procedure’, is a marketer’s dream and by itself suggests unrealistic but compelling expectations. Many patients are willing to pay cash, sometimes tens of thousands of dollars, for a single procedure. Many patients rave about their procedures, yet outside of a well controlled trial, it is hard to disprove the placebo effect and prove the true clinical benefits.

In view of the foregoing, and in an attempt to help resolve the CCSVI conundrum, it would seem that the fundamental questions are:

1. Is there a cause and effect relationship between CCSVI and MS, and in which direction does this work?
2. If CCSVI does cause or worsen MS, should this be treated with endovascular therapies?
3. If endovascular treatment is contemplated, which therapy should be offered?
and under what technical and clinical circumstances should they be applied? There is paramount need for credible scientific evidence that will allow us to address these questions. Firstly, we should encourage trials using non-invasive studies to test if CCSVI—MS actually exists. At the current time, the corroboration evidence supporting Zamboni’s initial findings of an association between CCSVI and MS are limited. In fact, the majority of additional evidence—including the work of Doepp et al and Sundstrom et al, cited in this review—actually failed to replicate the findings of Zamboni and colleagues.7–9

Moreover, the early results of Zivadinov et al are also not very compelling.10 In addition, the initial claim by Zamboni et al that they had developed a perfect test for CCSVI—MS raises serious questions about the credibility of their evidence. As pointed out by Novella, few if any tests in medicine have 100% sensitivity and 100% specificity.20

Fortunately, the US and Canadian MS societies have undertaken seven studies to investigate the CCSVI—MS association.14,15 The necessity of requiring an invasive diagnostic study such as catheter venography to evaluate the CCSVI—MS association is more difficult to reconcile at this point, particularly since the seminal findings of Zamboni et al which initiated this entire controversy were based on non-invasive Doppler ultrasound.

If the association between CCSVI and MS cannot be confirmed, then further studies evaluating CCSVI treatment are unnecessary. While it could be argued that even if the prevalence of venous ‘abnormalities’ is similar in patients with MS and controls, venous intervention in MS should still be studied since MS patients might be more susceptible to the detrimental effects of CCSVI than normal patients, this position seems tenuous at best.

If an association between CCSVI and MS can be established, then the next logical step would be to design multicenter randomized clinical trials to assess the benefits of endovascular interventions.

CONCLUSION

More evidence is needed to establish the association between CCSVI and MS. If more solid clinical evidence can confirm that the CCSVI—MS relationship is real, randomized clinical trials will be required to assess the benefits of endovascular interventions. If these trials establish a benefit for endovascular therapy, then at that point treatment can be made widely available. However, until these steps are taken, in our opinion, there is no role for the endovascular treatment of CCSVI in the MS patient outside of approved clinical trials.

Competing interests None.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 29 September 2010
Published Online First 23 October 2010

doi:10.1136/jnis.2010.003947

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*J NeuroIntervent Surg* 2010 2: 309-311 originally published online October 23, 2010
doi: 10.1136/jnis.2010.003947

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Corrections

There was an error in an article published in the December 2010 issue of the journal (Chronic cerebrospinal venous insufficiency and the doubtful promise of an endovascular treatment for multiple sclerosis. J NeuroIntervent Surg 2010;2:309–11. Published Online First: 23 October 2010. doi:10.1136/jnis.2010.003947). On page 310, second paragraph, fourth sentence should read: ‘Pretreatment pressures beyond the stenosis were not significantly different from normal venous pressure, however, a change in pressure was demonstrated after angioplasty’.


Several author names were omitted from an article published in the December 2010 issue of the journal (The POST trial: initial post-market experience of the Penumbra system: revascularization of large vessel occlusion in acute ischemic stroke in the United States and Europe. J NeuroIntervent Surg 2010;2:341–4. doi:10.1136/jnis.2010.002600). The correct author list is as follows:

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