

# Chronic Cerebrospinal Venous Insufficiency In Multiple Sclerosis (CCSVI-MS) , Between The Phantom Hope Of Miraculous Endovascular Treatment And The Truth Of The Need For More Radical Treatment.

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## Abstract

Like breakthrough news of natural catastrophe, a radically different concept regarding the pathogenesis of multiple sclerosis (MS) has been proposed omitting the previous decades of research work in that field . 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 /and contribute to MS. Consequently, 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 (Zamboni 2006; Zamboni, Menegatti et al. 2007). Since this breakthrough news a fierce pandemic has struck worldwide where these endovascular 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, this procedure 'liberation procedure' as it has been labeled by some ; sparked a firestorm of interest in the medical and neurological communities, in both directions , to perform and not to perform. Each team has their rationale which is passionate at best, ranging from the myth that venous intervention is a miracle cure that must not be withheld from patients, to the feeling that the procedure is ineffective, unwarranted and dangerous at worst. The various views commonly see that those with differing beliefs are not acting in the best interest of the patients. As MS is a tuft practice of neurology, and neurointerventionalists interested in interventional treatment of neurological disorders are the neurology `s delivery man for neurointerventional procedures, we will attempt to analyze the available data and provide accordingly recommendations about whether or not endovascular treatment represents a reasonable option at this point of time for MS patients . To imagine the magnitude of a natural catastrophe, you should firstly bypass the denial phase to start counting the losses. So we will examine the source of the CCSVI theory and discuss the current data calling for or refuting its existence.

## INTRODUCTION

Like breakthrough news of natural catastrophe, a radically different concept regarding the pathogenesis of multiple sclerosis (MS) has been proposed omitting the previous decades of research work in that field . 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 /and contribute to MS. Consequently, 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 (Zamboni 2006; Zamboni, Menegatti et al. 2007).

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## **BRIEF REVIEW OF MULTIPLE SCLEROSIS**

MS is a nightmare for both patient and practicing neurologist. It is an 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, where prevalence of MS differs widely worldwide. In Caucasians, MS occurs in about 40 to 100 a person in 100,000, whereas in most East Asians and South Asians it is less than 10 in 100,000, and among Africans it is even fewer.([http://www.ninds.nih.gov/disorders/multiple\\_sclerosis/detail\\_multiple\\_sclerosis.htm](http://www.ninds.nih.gov/disorders/multiple_sclerosis/detail_multiple_sclerosis.htm)) Such big differences seem to suggest that different genetic backgrounds among races strongly affect MS susceptibility.

In temperate zones, a south-to-north gradient of MS prevalence has been shown repeatedly. This tendency is seen in high prevalence areas such as the United States, Europe, and Australia, as well as in low prevalence areas such as Japan.

The peak age at onset is 20-40 years. It affects females more than males and is more common among Caucasians. MS can present with just about any neurological symptom in any part of the nervous system, cranial nerves , visual , motor , coordination, sensory , autonomic, and myelopathic on different occasions with progressive disability.<sup>1</sup> Diagnosis is based on clinico-radiological 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.(Compston and Coles 2008)

The most prevalent hypothesis regarding the pathophysiological basis for MS is that it is an autoimmune inflammatory disease triggered by Environmental factors and genetic predisposition ; the former related to latitude, shortage of sunlight, low temperatures, or even certain infectious pathogens more frequent in northern areas are suspected. For example, less ultraviolet light during the winter in northern areas causes lower vitamin D3 production. Vitamin D possesses an immunoregulatory function and suppresses the development of experimental autoimmune encephalomyelitis in laboratory animals.(Compston and Coles 2008) Thus, the lower production of vitamin D might partly explain the south-to-north gradient of MS risk.

On the other hand, the genetic predisposition leading to myelin and axonal destruction in the brain and spinal cord by the immune system; the hypothesis that got consolidation from studies in Canada that revealed that MS risk was 300 times higher in twins, and the concordance rate of MS in monozygotic twins is significantly higher than in dizygotic twins(about 30% versus 5%), indicating the importance of genetic background.

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. (Compston and Coles 2008) These agents are not only costly but are associated with a wide spectrum of side effects ranging from mild to severe, which may represent the opening door for entering the new long awaited hope for cure.

## **The Relationship between CCSVI and MS**

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.(Zamboni 2006) He raised the possibility that chronic 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. Much of the initial evidence supporting this possible relationship has been based on the view adopted by Dr. Paolo Zamboni and

colleagues(Zamboni, Menegatti et al. 2007). They have documented the frequent association of abnormal venous hemodynamics with MS where they found CCSVI in all MS patients and in none of the controls , with a holistic sensitivity, specificity, positive predictive value and negative predictive value of 100% for all tests . Where they Used duplex ultrasonography and transcranial Doppler studies, and based 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(Zamboni, Galeotti et al. 2009; Zamboni, Menegatti et al. 2009).

They concluded that there was CCSVI in MS patients.(Zamboni, Galeotti et al. 2009; Zamboni, Menegatti et al. 2009; Zamboni, Menegatti et al. 2009) going further, he postulated that 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.(Zamboni 2006; Compston and Coles 2008)

In a second paper, Zamboni et al announced that catheter venography in patients who met CCSVI Doppler criteria showed stenosis in the azygos vein in 86% and one or both IJV were affected in 91%. In this study, the venographer was not blinded to the patients' diagnosis. (Zamboni, Galeotti et al. 2009; Zamboni, Galeotti et al. 2009) The study proposed four venographic patterns: (A) large IJV with one IJV or proximal azygos vein stenosis; (B) both IJV and proximal azygos vein stenosis; (C) both IJV and normal azygos system; and (D) multilevel azygos stenosis with or without IJV involvement. So consequently they postulated that these occlusions and stenoses cause acute manifestations of cerebral venous outflow obstruction in the form of mental confusion, severe headaches, weakness and lethargy, acute visual disturbances, and facial and glottic edema.

Giving more space for his "big idea" to grow hugely more , in 2009, Zamboni et al adopted treatment of the obstructions, by angioplasty, angioplasty and stenting, or thrombolysis and stenting, they reported their results on the endovascular treatment of 65 MS patients with CCSVI.(Zamboni, Menegatti et al. 2009) No isolated venous lesion was found,

and the distribution of venographic patterns was 30%, 38%, 14% and 18% of types A to D, respectively.(Zamboni, Menegatti et al. 2009) They performed percutaneous transluminal angioplasty (PTA) on all but one azygos lesion that did not respond to PTA alone and required stent placement.

### **EXTRAPOLATING RATIONALE FOR ENDOVASCULAR INTERVENTION!**

They extrapolated more evidence from some previous observations like the observation that acute jugular incompetence can result in transient global amnesia.(Schreiber, Doepp et al. 2005) Secondly 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.(Hartmann, Mast et al. 2001)

### **TO BE KEPT IN MIND WHEN READING IN BETWEEN LINES**

Pretreatment pressures beyond the stenosis were not significantly different from normal venous pressure and there was no significant change in pressure after angioplasty. Mean follow-up using extracranial Doppler was 18 months, with an overall restenosis rate of 47%; more common in the jugular than azygos veins. Clinical outcome at 18 months was reported as showing relapse free of 50% versus 27% preoperatively (Zamboni, Galeotti et al. 2009). It is important to note that the interpretation of the clinical results of this uncontrolled study is confounded since patients were continued on 'immunomodulating' therapy after endovascular therapy.

These medical therapies have been shown to significantly reduce relapse rates as well as the accumulation of MRI detectable enhancing lesions(Compston and Coles 2008) Finally, there was no improvement in patients with primary progressive or secondary progressive MS.(Zamboni, Menegatti et al. 2009)

### **CCSVI CONCEPT AND ITS RELATION TO MS , DECEIVING RELATIONSHIP AT WORST OR COMORBID RELATIONSHIP AT BEST OF CHANCES (NO THERAPEUTIC INDICATOR NOR RESPONSE BENCHMARK)**

This concept should be carefully interpreted in relation to MS pathology, whether it is causal or comorbid relationship

, this should be kept in mind specially in the light of the following facts .

### **A-ANATOMICAL PHYSIOLOGICAL ENIGMA**

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

anteriorly through the internal jugular system in the supine position and posteriorly through the vertebral system when erect. Normally, in the upright position, 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 (IJV drainer) which represent 70% of cases.

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 (non-IJV drainer) which represent 30% of cases. Because pressure is normally low and only marginally rises with obstruction, distension of the obstructed system does not occur. (Rowe 1946; Andeweg 1991; Yu, Rives et al. 2009)

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.(Rowe 1946)

### **B- SELECTING NON LOCALIZING MS MANIFESTATION FOR EVALUATING THERAPEUTIC RESPONSE**

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.(Philips, Bagley et al. 1999) Thus, it is not surprising that patients with CCSVI associated with MS also report rapid relief of this non-localizing 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. This is why we suggest to investigate this diagnostic

constellation of manifestations in frame of relating the CCSVI to chronic fatigue syndrome which is highly comorbid with MS patients.

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.(Zamboni 2006) On the other hand, 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.

### **C- IN THE ABSENCE OF RCTS, PRACTICING ENDOVASCULAR VENOUS INTERVENTIONS FOR MS PATIENTS IS LIKE RATIONALIZING PARAPSYCHOLOGY PRACTICE TO REPLACE MEDICINE**

It can only be hoped that the future will not judge us as irresponsible when we choose not to evaluate established procedures in the same way, on the (in my opinion undefensible) grounds that it is 'unethical'.

There are many physicians and others who have endovascular skills who are promoting and developing centers for serving these patients without regard for the lack of scientific evidence to support such practice. 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. Consequently, we should 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, sponsors, and regulators. So, 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 is more warranted.

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.(NIH Jun 11, 2010)

These observations may provide a basis for clinical trial in MS to assess the long-term safety and efficacy of endovascular procedures in restoring normal venous hemodynamics, in relieving the non localizing 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.

### **CHALLENGES TO THE ZAMBONI THESIS CREDIBILITY (WHAT IS AGAINST CCSVI ROLE IN MS)**

Although the Zamboni papers have been quite supportive of CCSVI, there is a growing number of papers that raise serious questions about its validity. In early 2010, Khan et al described a number of independently accepted characteristics of venous disease and MS that contradict the CCSVI theory:(Khan, Filippi et al. 2010)

1. Similar to other autoimmune diseases, MS is more common in young women while chronic venous insufficiency syndromes are not.
2. There are well known strong epidemiological associations between MS and environmental factors and genetic factors as above mentioned that are not mirrored by chronic venous insufficiency.
3. Central veno-occlusive disease can lead to syndromes of idiopathic intracranial hypertension, ischemic and hemorrhagic infarcts and edema, none of which is typically seen in MS patients.
4. Vascular abnormalities related to chronically diminished venous flow would be expected to increase over time, yet after the age of 50 years the incidence of MS is quite low.
5. There is no other model of decreased venous drainage and an organ specific immune response.
6. Transient global ischemia is known to occur with jugular insufficiency but this entity is not seen in MS.
7. Radical neck dissections remove all jugular veins

but they have never been seen to cause MS.

The above cited challenges to the Zamboni thesis are based on largely theoretical considerations. In an attempt to replicate the Doppler findings of Zamboni, Doepp et al studied 56 MS patients and 20 controls using similar CCSVI criteria.(Doepp, Paul et al. 2010) They found no patients in either the MS or control groups who had the two or more criteria required for a diagnosis of CCSVI. They concluded, based on these results as well as their extensive longitudinal experience with cranial venous Doppler ultrasound, that there is typically tremendous reserve capacity of the extrajugular pathways for cerebral venous drainage and that it is highly unlikely that IVJ stenosis would cause central venous congestion. Furthermore, they went on to discourage interventional procedures for CCSVI outside of the context of appropriately designed clinical research studies.(Doepp, Schreiber et al. 2004; Stanbrook and Hebert 2010) Additionally, Sundstrom et al looked at MRI of 21 patients with relapsing remitting MS and 20 healthy controls, and found no differences in internal jugular venous outflow between the two groups.(Sundstrom, Wahlin et al. 2010) Finally, preliminary data from Zivadinov et al, from the MS research group at the State University of New York in Buffalo, presented findings in the first 500 participants studied with venous Doppler looking at the prevalence of CCSVI in MS patients and controls. Using the requirement that 2 CCSVI Doppler criteria be met, CCSVI was found in 62.5% of MS patients, 25.9% of healthy controls and 45% of other neurological disorders.(Hojnacki, Zamboni et al. 2010; Zamboni, Menegatti et al. 2010; Zivadinov, Schirda et al. 2010) At least preliminarily, these results are different from the 100% sensitivity and specificity found by Zamboni and colleagues.(Zamboni, Galeotti et al. 2009)

### **SUMMARY**

There is little debate as to the potential ravages of MS and the sincere need to improve outcomes in patients suffering from this horrible disease. As such, when seemingly miraculous cures are proffered, it is our responsibility as Neuroscience communities to rationally review its benefit . There are few data supporting the validity of CCSVI. The lack of data could be counterbalanced by the great hope for the miracle of an endovascular treatment for such terrible disease. The topic has caused widespread attention and debate in the media, medical literature and the internet.(Hojnacki, Zamboni et al. 2010; Zivadinov, Schirda et al. 2010)

As of late October 2010, a Google search on ‘liberation procedure’ yielded about 3,650,000 results and approximately 189,000 for ‘CCSVI’. Sponsored links appear for treatment in many places around earth e.g. Costa Rica, India ,Mexico, Poland, Egypt and many other locations. The prospect of opening an open label, non-study related MS endovascular CCSVI practice can be very seductive from both physician and patient sides. 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. Some might argue that “the procedure is safe, if there is any possibility of ameliorating some of the symptoms of MS patients the procedure should not withheld from 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 . 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 forgoing, and in an attempt to help resolve the CCSVI conundrum, it would seem that the fundamental questions are:

1. Is that a cause relationship , if any or just comorbidity 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? To what extent should we consider the risk/benefit ratio
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 relationship actually exists. At the current time, the evidence supporting Zamboni’s concept of an association between CCSVI and MS are limited by Zamboni’s initial findings himself. 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.(Doepp, Paul et al. 2010; Sundstrom, Wahlin et al. 2010) Moreover, the early results of Zivadinov et al are also not very compelling.<sup>10</sup> 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. Evidence-Based Medicine (EBM) has become a popular approach to medical decision making and is increasingly part of undergraduate and postgraduate medical education. Consequently, few if any tests in medicine have 100% sensitivity and 100% specificity.(Hawkins 2005) Fortunately, the US and Canadian MS societies have undertaken seven studies to investigate the CCSVI-MS association.(NIH Jun 11, 2010) 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 noninvasive 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.

### **HOW WE COULD MEDICALLY INVEST CCSVI**

Until we have clear evidence regarding such phenomenon and its association with MS and its treatment safety and efficacy, I prefer its discussion as an observational phenomenon not a pathophysiological one. Consequently, 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.

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