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Review

Chronic Cerebrospinal Venous Insufficiency in Multiple Sclerosis: A Failed Concept

Nathan Kugler[1], Parag J. Patel[2], and Cheong Jun Lee[1]

[1]Division of Vascular Surgery, Medical College of Wisconsin, Milwaukee, WI,
[2]Division of Interventional Radiology, Medical College of Wisconsin, Milwaukee, WI, USA

In 2009 Paolo Zamboni et al. implicated that chronic cerebral venous congestion lead to the development of multiple sclerosis. In this review, we examined the role of chronic cerbrospinal venous insufficiency in multiple sclerosis and the proposed therapy entailing venous angioplasty and stenting of extracranial veins with available evidence to date.

Key Words: Chronic cerebrospinal venous insufficiency, Multiple sclerosis, Liberation procedure

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Corresponding author: Cheong Jun Lee
Division of Vascular Surgery, Medical College of Wisconsin, 9200 West Wisconsin Ave, Milwaukee, WI 53226, USA
Tel: 1-414-805-9160
Fax: 1-414-805-9170
E-mail: cjlee@mcw.edu
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INTRODUCTION

Multiple sclerosis (MS) is a T-cell mediated autoimmune disorder characterized by inflammatory demyelination in the central nervous system (CNS) [1]. In 1863, pathologist George Eduard von Rindfleisch reported that demyelinating plaques in MS tend to occur in a perivenular distribution and subsequent histological studies have revealed evidence of venous damage in the form of thrombosis, fibrin cuff deposition, and hemosiderin deposition [2]. These lesions, however are not isolated to MS, but are also found in other neurodegenerative disorders including the aging brain, Alzheimer's disease, and Parkinson's disease [3]. Based on this historical observation, Zamboni et al. [4] in 2009 conceptualized that venous congestion of the CNS plays a central role in the pathogenesis of MS. Deemed chronic cerebral venous insufficiency (CCSVI), the theory is characterized by the presence of combined stenosis of the principal pathways of extracranial venous networks; namely the internal jugular veins (IJV), the vertebral veins, and the azygous vein (AZV). The resultant venous insufficiency is implicated to cause chronic inflammation leading to the development of MS.

DISCUSSION

In his report in 2009, Zamboni et al. [4] found aberrant venous flow by color duplex studies in 65 individuals with MS and none in 235 control patients. He described five duplex ultrasound (DU) standards for detecting reflux or stenosis in the extracranial venous system. Having two of the five criteria is believed to support having CCSVI. Zamboni et al. [5] has previously reported a 100% sensitivity and specificity for the application of the criteria in the diagnosis of MS. To date, no study has been able to reproduce these findings. Yet, with the concomitant report of his open-label study on venous angioplasty of affected extracranial veins which showed significant clinical improvement in patient with MS, a media frenzy ensued.

Significant criticisms have been made regarding the DU criteria supporting the causative relationship between CCSVI and MS. For one, extracranial venous hemodynamics

naturally fluctuate, rendering DU assessments unreliable [6]. Secondly, only Zamboni's sonographers have been able to show consistent presence of CCSVI despite attempts to train other sonographers to interpret studies using his criteria. Zamboni partly blamed this discrepancy on the fact that others did not use the high quality equipment manufactured by SoNos, a high resolution ultrasound machine made by the very company he has financial stakes in, raising serious ethical concerns.

Recently, Comi et al. [7] published the results of their "Italian multicenter observational study of the prevalence of CCSVI in multiple sclerosis" (CoSMo study) which attempted to validate the presence of CCSVI in MS using Zamboni's DU criteria. The study involved 35 centers across Italy and included 1,874 patients; 1,165 patients with MS, 226 with other neurodegenerative disorders, and 376 healthy controls. The ultrasonographers were blinded, rigorously trained, and a consensus had to be obtained for DU diagnosis of CCSVI among 3 central sonographers. The CoSMo group found that in MS patients, the presence of CCSVI was 3.26%. In patients with other neurodegenerative disorders, the presence of CCSVI was 3.1% and in healthy controls 2.1%. Given the low frequency combined with the presence of CCSVI in all cohorts analyzed, the authors concluded that CCSVI was not associated with MS [7].

By combining other imaging modalities, investigators world-wide further sought after the relationship between CCSVI and MS. In a case-controlled study done in Canada, magnetic resonance (MR) venography in conjunction with DU was used to identify MS patients in individuals in whom the Zamboni criteria were met [8]. In the study, 100 MS patients were compared to age matched controls. All cases and controls underwent ultrasound imaging of the veins of the neck plus the deep cerebral veins, and MR imaging of the neck veins and brain. Among 199 patients total, there was one MS subject who fulfilled the minimum two ultrasound criteria for CCSVI. With MR venography, no significant differences were found in either the intra- or extra-cranial venous flow velocity or venous architecture between MS patients and controls [8]. Another case-controlled study by Traboulsee et al. [9] assessed patients for CCSVI using catheter venography in addition to DU. Patients with MS, their unaffected siblings, and unrelated healthy controls were assessed. Surprisingly, CCSVI based off of Zamboni DU criteria was more prevalent, but not specific to MS. Duplex detection of CCSVI was seen in 44% of MS patients, in 33% of the unaffected siblings, and in 45% of unrelated non MS affected controls demonstrating that extracranial venous narrowing greater than 50% is commonly seen with DU and not specific to MS patients. What was more compelling was the fact that only 1 of 65 (2%) of patients with MS had >50% narrowing based on catheter venography while 2% of unaffected siblings and 3% of unrelated controls had significant extracranial venous stenosis. This study further exemplified the observation that extracranial venous stenosis is a rare event and non-specific to MS.

Treatment of CCSVI primarily involves alleviating extracranial venous lesions with percutaneous transluminal angioplasty deemed the "liberation" procedure. In conjunction with his concept of CCSVI in 2009, Zamboni et al. [10] published the results of an open-label, unblinded trial of venous angioplasty of IJVs and AZVs in 65 patients with MS. Zamboni and the investigators involved in that report claimed significant clinical improvement was seen in subjects with relapsing-remitting MS. They reported a technical success >90%, while a dismal restenosis rate of 27%-44% was reported in the 18 months of follow up. Despite high restenosis rates, freedom from relapse of disease changed from 27% to 50% with reduction in the number of active MS lesions on MR from 50% to 12%. Furthermore, a significantly improved quality of life and function at 1 year was touted based on Multiple Sclerosis Functional Composite scores [10]. No complications were reported to have occurred in Zamboni's unblinded clinical trial.

Potential benefits of the "liberation" procedure rapidly took fire in print, social media, and other public media outlets and raised hopes in many people with MS. Many MS interest groups began feverishly advocating the procedure and in response Europe, the US, and Canada committed millions of dollars for research to validate the concept of CCSVI and the seemingly effective procedure. Although low procedural complication rates are touted with venous angioplasty, fatal brainstem hemorrhage, dissection and thrombosis of the target vein, intracardiac stent migration, and arrhythmias have been reported [11,12]. Despite the risks, MS patients have flocked to interventionalists offering the liberation procedure as a source of hope.

Aside from non-blinded case series, no level 1 data exists to support the effectiveness of the liberation procedure. The only class 1 evidence to date evaluating the treatment of CCSVI effectively undermines and contests the concept in the PREMiSe study (prospective randomized trial of venous angioplasty in MS) [13]. Siddiqui et al. [13] enrolled 19 patients who underwent randomization after having met CCSVI criteria; 10 underwent sham procedures while 9 underwent venous angioplasty. Primary endpoints measured included venous outflow restoration >75% at 1 month, new lesion activity, and relapse rate over 6 months. Secondary endpoints included changes in disability, brain volume, cognitive tests, and quality of life. The study was

double-blinded; subjects were blinded to the treatment and investigators evaluating response to treatment were also blinded to the treatment that the subject received. In the study, contrary to Zamboni's findings, there was a higher trend in new lesions (17 vs. 3, P=0.066) and relapse activity (4 vs. 1, P=0.289) in patients that were treated with venous angioplasty. No differences in other clinical endpoints were detected in patients who underwent venous angioplasty versus sham procedures. Interestingly, improvements occurred in some subjective outcome measures such as fatigue and quality of life among the patients that received the sham procedure. This particular observation supports the conclusion that positive response of patients in the prior open-label trials likely represents a placebo effect. PREMiSe concluded that venous angioplasty was not effective in treating MS patients with CCSVI, rather may exacerbate underlying disease activity in the short term [13]. While the PREMiSe study was small, it demonstrated that the concept of CCSVI and the proposed treatment does not hold well within the confines of a blinded, randomized control study.

Since, its conception, more reports refuting Zamboni's claim of CCSVI have been written compared to those that support the theory. Tsivgoulis et al. [14], in their recent report, revealed that there may be serious conflicts of interest in the publications that support the CCSVI concept. Their meta-analysis reviewing 19 case-controlled studies evaluating CCSVI in MS demonstrated significant heterogeneity within the literature. The authors ultimately found no causative relationship between CCSVI to MS [14]. When the publications were sorted by the investigators' involvement in the liberation procedure, the greatest factor contributing to a positive association of CCSVI in MS was indeed this serious conflict of interest [14]. Only 1 of 13 studies by investigators not involved in the liberation procedure found correlation between CCSVI in MS while 5 of 6 studies by investigators involved in the liberation procedure found that CCSVI is strongly associated. Reports such as this bring to light, significant, and potentially unethical motives that have influenced the evolution of the CCSVI theory.

CONCLUSION

There is now substantial evidence to say that CCSVI is a failed concept. A thorough cross examination of the literature reveals that the genesis of the CCSVI theory may have been a means to validate a misguided procedure. Given the lack of scientific validity which is significantly tainted by conflicting interests, the debate regarding CCSVI should be put to rest and extracranial venous angioplasty should be abolished as a treatment in patients with MS.

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