

# Chronic cerebrospinal venous insufficiency in Multiple Sclerosis: A note for caution

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## Introduction

Multiple Sclerosis (MS) is generally considered to be a chronic immune-mediated inflammatory disorder of the central nervous system, influenced by environmental and genetic factors. An association between impaired venous drainage from brain and spinal cord, termed chronic cerebrospinal venous insufficiency (CCSVI), and risk of MS has recently been proposed by Zamboni and colleagues from Italy.<sup>[1]</sup> The same group also studied the effect of percutaneous venoplasty on MS patients in an open-label, single-group pre-post trial.<sup>[2]</sup> These events led to a worldwide media hype as well as a tremendous interest generated among patients and the scientific community. We herein review this concept and present our point of view on this so-called "liberation therapy."

## Background and biological rationale

A recent hypothesis<sup>[3]</sup> states that the cascade of autoimmune damage in MS could be triggered by narrowing of veins and restricted flow, especially in the internal jugular veins (IJV) and azygous vein (AV). Resistance of outflow from the venous system leads to backpressure and congestion. The resulting venous reflux or venous hypertension then results in erythrocyte diapedesis and iron deposition within the brain, resulting in oxidative tissue damage, T-cell activation and inflammatory central nervous system damage.

The involvement of cerebral venous system in MS had been proposed long ago based on observations that MS plaques are generally centered around small veins or venules<sup>[4]</sup> and extend outwards along branch veins, termed as "Dawson's fingers."<sup>[5]</sup> Adams<sup>[6]</sup> studied evidence of cerebral vein involvement in

patients with MS. Forty-one percent of his cases showed some evidence of chronic inflammatory vein damage causing increased permeability and hemorrhage. He proposed that venous wall damage is an important aspect of MS plaque pathology. However, it is unclear whether this is the cause or an intermediate step in the pathogenesis of MS resulting from another cause. It may be worth noting that Adams found hemosiderin deposition in only 30% of his cases.<sup>[6]</sup> Walton and colleagues<sup>[7]</sup> detected iron deposition in only two of the 13 postmortem specimens of MS patients.

One method to indirectly assess iron accumulation in brain parenchyma is estimation of cerebrospinal fluid (CSF) ferritin, as presence of iron in brain stimulates intrathecal ferritin (iron storage protein) synthesis.<sup>[8]</sup> Worthington and colleagues<sup>[9]</sup> found comparable CSF ferritin levels in relapsing remitting or primary progressive MS patients and in the controls. There was no change in CSF ferritin level in MS patients over 3-year follow-up, challenging the very novel proposal of progressive iron accumulation in the pathogenesis of CCSVI.

If the venous hypertension theory is correct, then incidence of MS should be high in conditions with increased venous pressure. Venous hypertension is present in cerebral venous obstruction or internal jugular valve incompetence in pulmonary hypertension and chronic obstructive pulmonary disease,<sup>[10]</sup> but the medical literature is silent on their association with MS. No parenchymal lesions or abnormalities have been seen after bilateral jugular vein ligation or removal during radical neck dissection in head and neck malignancy.<sup>[11]</sup>

## CCSVI and MS: Association studies

Zamboni *et al.*<sup>[1]</sup> evaluated 65 patients of MS and 235 controls with transcranial color-coded Doppler sonography and extracranial color Doppler sonography (TCCS-ECD) based on self-designed criteria [Table 1].

They found 185 positive and 145 negative parameters in the MS group, in contrast to the control group with 33 positive and 1,142 negative parameters. All 65 MS patients fulfilled at least two parameters, but the same was not observed in any of the control subjects. This observation perfectly matched with

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the diagnosis of MS, with a reported sensitivity, specificity, positive predictive value and negative predictive value of 100%. All 65 MS patients underwent percutaneous venography, and were found to have IJV and AV stenosis in 91% and 86% patients, respectively. In a separate study<sup>[12]</sup> by the same group in 109 MS and 177 matched controls, 257 anomalous and 288 normal TCCS-ECD parameters were observed in MS patients, in contrast to 24 anomalous and 861 normal parameters in controls. Again, all MS patients and none from the control group fulfilled CCSVI criteria. These studies have however been criticised for their methodology as there was complete lack of discussion on the TCCS-ECD technique and absence of a reference standard (such as MR venogram) to diagnose venous impairment. Both studies were performed at a center with an unblinded assessment of both sonographic and angiographic findings.

Other groups across the world have also independently investigated this hypothesis in case-control studies [Table 2]. Doepp and colleagues<sup>[13]</sup> performed extended TCCS-ECD studies (including CCSVI criteria) in 56 MS patients and 20 controls. They found 10 abnormal and 570 normal TCCS-ECD parameters in MS patients along with four abnormal and 96 normal parameters in control subjects. None of the patient or controls fulfilled >1 CCSVI criteria. Another study<sup>[14]</sup> evaluated 20 MS patients and 20 age- and gender-matched controls by MR venography along with flow quantification. Neuroradiologists were blinded to clinical data and structural brain imaging. They found that 10 MS patients and eight healthy controls had anomalous venous drainage, but none from either group had venous backflow on flow quantification study. The author concluded that these findings reflect anatomical variants of venous drainage rather than clinically relevant venous flow

**Table 1: Criteria for CCSVI: At least 2 out of 5 required for diagnosis**

Reflux in the IJVs and/or VVs in sitting and supine posture
Reflux in the deep cerebral veins
High-resolution B-mode evidence of IJV stenoses
Flow not Doppler detectable in the IJVs and/or VVs
Reverted postural control of the main cerebral venous outflow pathways

obstruction. Krogias and colleagues<sup>[15]</sup> studied this hypothesis in 10 MS patients and seven controls by TCCS-ECD. Only two MS patients and none from the control group fulfilled the CCSVI criteria. Recently, phase contrast magnetic resonance imaging (PC-MRI) and additional contrast-enhanced MRI were used to assess venous flow in 21 MS patients and 20 healthy controls.<sup>[16]</sup> Although all aspects of CCSVI criteria were not studied, the authors did not find any significant difference in venous abnormality between the two groups. Likewise, few other recent studies have also observed a lack of association between CCSVI and MS.<sup>[17-20]</sup>

In a recent publication, Zivadinov and colleagues<sup>[21]</sup> assessed 499 subjects, consisting of 283 MS patients, 163 healthy controls, 26 with other neurological diseases and 21 subjects having clinically isolated syndrome using transcranial and extracranial venous Doppler evaluation. They found CCSVI prevalence in 56.1%, 22.7%, 42.3% and 38.1% subjects, respectively. However, no causation could be established.

Results of the above studies show a striking contrast among them. In a case-control study, the control group is meant to represent the prevalence of exposure in the general population. The prevalence of CCSVI in the control group has ranged from 0%<sup>[13,14,17,18]</sup> to 36%<sup>[20]</sup> and, among cases, from 0%<sup>[13,14,17]</sup> to 100%.<sup>[1,12]</sup> The striking heterogeneity calls for an explanation and more studies before accepting that there exists an association between MS and CCSVI.

#### CCSVI and MS: Therapeutic interventional study

The first therapeutic interventional study was a prospective, open-label trial done by Zamboni and colleagues.<sup>[2]</sup> They performed percutaneous transluminal venoplasty in 65 MS patients and followed them up for a period of 18 months. Investigators concluded that CCSVI endovascular treatment significantly improved outcome in the Relapsing Remitting MS group (35/65) as relapse-free patients changed from 27% to 50% postoperatively and MR gadolinium-enhancing lesion from 50% to 12%. This study had several short-comings, such as small sample size, absence of a control group, nonblinded assessment and all patients continued to be on disease-

**Table 2: Association studies of MS with venous abnormality**

	Study center	Technique used	MS patient group patients fulfilling CCSVI criteria/total	Control group controls fulfilling CCSVI criteria/total	Association of CCSVI and MS
Zamboni <i>et al.</i> <sup>[1]</sup>	Italy	TCCSECD	65/65	0/235	Strong
Zamboni <i>et al.</i> <sup>[12]</sup>	Italy	TCCS-ECD	109/109	0/177	Strong
Doepp <i>et al.</i> <sup>[13]</sup>	Germany	TCCS-ECD	0/56	0/20	No
Wattjes <i>et al.</i> <sup>[14]</sup>	Netherland	MRV and flow quantification	0/20*	0/20*	No
Krogias <i>et al.</i> <sup>[15]</sup>	Germany	TCCS-ECD	2/10	0/7	No
Sunderstrom <i>et al.</i> <sup>[16]</sup>	Sweden	PC-MRI and MRV	5/21*	5/20*	No
Mayer <i>et al.</i> <sup>[17]</sup>	Germany	TCCS-ECD	0/20	1/20	No
Barachhini <i>et al.</i> <sup>[18]</sup>	Italy	TCCS-ECD	4/60	0/60	No
Tsivgoulis <i>et al.</i> <sup>[19]</sup>	Greece	TCCS-ECD	1/42*	1/43*	No
Centonze <i>et al.</i> <sup>[20]</sup>	Italy	TCCS-ECD	42/84	20/56	No
Zivadinov <i>et al.</i> <sup>[21]</sup>	USA	TCCS-ECD	162/289	37/163	Moderate

TCCS-ECD = Transcranial color-coded Doppler sonography and extracranial color Doppler sonography; MRV = Magnetic resonance venogram; PC-MRI = Phase contrast magnetic resonance imaging; \*Venous reflux seen

modifying therapy during the follow-up period. There was a high rate of restenosis of IJV (47%) during the follow-up period, which casts doubt about the effectiveness of the intervention.

In another pre-post open-label trial by Kostecki *et al.*,<sup>[22]</sup> 36 patients with confirmed MS and CCSVI underwent endovascular treatment by the means of the uni- or bilateral jugular vein angioplasty with optional stent placement. Six months after the procedure, re-stenosis in postpercutaneous transluminal venoplasty jugular veins was found in 33% of the cases. Among 17 patients who underwent stent implantation into the jugular vein, re-stenosis or partial in-stent thrombosis was identified in 55% of the cases. At the 6-month follow-up appointment, there was no significant improvement in the Expanded Disability Status Scale.

Pre-post study designs, as in the above study, has often shown benefits with intervention but later proved to be ineffective or even harmful as randomized controlled studies (RCT) in many cases. In a pre-post study by Knox and colleagues,<sup>[23]</sup> authors presented clinical evidence supporting safety and efficacy of human growth hormone in promoting respiratory independence in intensive care unit (ICU) patients who had failed the standard weaning protocol. When the same was studied in two multicenter RCTs, it was found that patients in the growth hormone group had prolonged duration of ventilator use, ICU or hospital stay as well as increased mortality compared with the placebo group.<sup>[24]</sup> In another example, researchers claimed a dramatic improvement in symptomatology of virtually all 110 patients undergoing extra cranial-intra cranial (EC-IC) arterial bypass procedure for cerebrovascular disease.<sup>[25]</sup> The RCT of 1,337 patients however found an increase in fatal and nonfatal stroke among the group undergoing surgery versus those receiving medical care.<sup>[26]</sup>

#### Safety profile of endovascular treatment for CCSVI

Percutaneous angioplasty procedures in patients diagnosed as having CCSVI were well tolerated (visual analogue scale for pain  $3.4 \pm 0.3$ ), with no major complications.<sup>[2]</sup> However, a report from the Stanford University raised serious concerns on safety issues as one of the patients developed fatal intracerebral hemorrhage following post-stenting anticoagulant administration. In another report, a jugular vein stent placed in an MS patient dislodged in the right ventricle, requiring emergency open heart surgery.<sup>[27]</sup> In a recently published report<sup>[28]</sup> from Calgary, Canada, five MS patients who underwent endovascular CCSVI procedures (outside Canada) developed complications including IJV stent thrombosis, cerebral sino-venous thrombosis, stent migration, cranial nerve injury and injury associated with venous catheterization. As increasing numbers of MS patients are seeking such procedures, these five cases represent the beginning of a wave of complications for which standardized care guidelines do not exist.

#### Our point of view

The rationale of iron deposition and MS causation is still hypothetical, and the association of CCSVI and MS is yet to be proven. Even investigators of this concept have suggested that "the results of this pilot study warrant a subsequent randomized control study." In many countries like the United

States of America and Canada, the CCSVI concept is considered within the domains of research. The intense media hype as well as promotion of this concept as a therapy by investigators and centers performing the procedure across the world has resulted in a phenomenon of "vascular tourism" in some countries around the globe. The advertisements on the internet calling this a "liberation therapy" have further provided a boost to medical tourism. Several CCSVI groups on social networking sites like Facebook have patients appearing as leading advocates. We feel that more studies are required to establish the association, and venoplasty with or without stenting needs to be studied within the purview of research. At present, there is a need for properly designed studies to prove the association of CCSVI and MS, which should be followed by controlled therapeutic trials to establish its efficacy.

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