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Overview

Influence of chronic cerebrospinal venous insufficiency on demyelinating diseases

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Abstract

We analyzed all the arguments against chronic cerebrospinal venous insufficiency (CCSVI) as a medical entity, and its association with a disabling demyelinating disease, multiple sclerosis (MS). We revised all the findings suggesting a possible connection between these two entities. By comparing the results obtained by different study groups, we noted a great variability in prevalence of CCSVI in MS patients, ranging from 0 to 100%. Overall the reported prevalence is respectively 70% in MS vs. 10% in controls, and a recent meta-analysis assessed an over 13 times increased prevalence in MS. Postmortem studies show a higher prevalence of intraluminal defects in the main cerebral extracranial vein in MS patients respect to controls. Several pathophysiological studies demonstrate correlation between CCSVI and neglected vascular aspects of MS. Particularly, global hypo-perfusion of the brain, as well as reduced cerebral spinal fluid dynamics in MS was shown to be related to CCSVI. After careful review of all obtained data we can conclude that great variability in prevalence of CCSVI in MS patients can be a result of different methodologies used in vein assessment, training, application of unapproved diagnostic criteria, or different approach to the problem itself. By many studies it has been shown that CCSVI can be inserted in the list of multiple factors involved in pathogenesis of MS, as well as other neurodegenerative diseases.

Chronic cerebrospinal venous insufficiency (CCSVI) can be considered one of the multiple factors involved in the pathogenesis of demyelinating diseases, primarily multiple sclerosis (MS). It is a syndrome characterized by stenoses or obstructions of the internal jugular (IJ) and/or azygos (AZ) veins with disturbed flow and formation of collateral venous channels *(1, 2)*. Venous narrowing are primary obstructions, mainly related to segmental hypoplasia or, more frequently, to intraluminal defects like webs, fixed valve leaflets, membrane, inverted valve orientation, etc. *(3, 4, 5)*.

The basis and foundation of venous anomalies are not entirely clear yet. Venous lesions are described as truncular venous malformations, presenting as intraluminal defects or segmental hypoplasia *(6, 7, 8)*. Developmental arrest in advanced stages of vascular trunk formation during fetal life can result in such truncular venous malformations. Such lesions are: aplasia, hypoplasia or hyperplasia of the vessel, a defective vessel with obstruction from intraluminal lesions (e.g., vein web, spur, annulus, or septum) or dilatation (e.g., jugular vein ectasia/aneurysm).

TABLE 1

Prevalence of CCSVI in patients with MS and healthy controls.

Author (ref)	MS Patients		Controls
	CCSVI	Total	CCSVI
Zamboni et al, 2009 [1]	65(100%)	65	0(0%)
Zivadinov et al, 2011 [42]	162(56.1%)	289	374(22,7%)
Doepp et al, 2011 [34]	0(0%)	56	0(0%)
Mayer et al, 2011 [28]	0(0%)	20	1(5%)
Yamout et al, 2010 [70]	19(45%)	42	–
Baracchini et al, 2011 [30]	8(16%)	50	1(2%)
Al Omari et al, 2010 [5]	21(84%)	25	0(0%)
Simka et al, 2010 [27]	64(91%)	70	–
Bastianello et al, 2011[26]	610(86%)	710	–
*Marder et al, 2011 [29]	0(0%)	18	–
Centonce et al, 2011[71]	42(50%)	84	20(36%)
Zamboni et al, 2010 [72]	18(100%)	18	6(0%)
Zaharchuck et al, 2011[73]	21(54%)	39	–
Zivadinov et al, 2011[3]	10(100%)	10	–
Krogias et al, 2010 [74]	2(20%)	10	0(0%)

*18 controls with migraine or no neurological disease.

Radiological studies of healthy subjects did not demonstrate these types of lesions *(9–18)*, while CCSVI-like lesions were described associated to myelopathies *(19, 20)*.

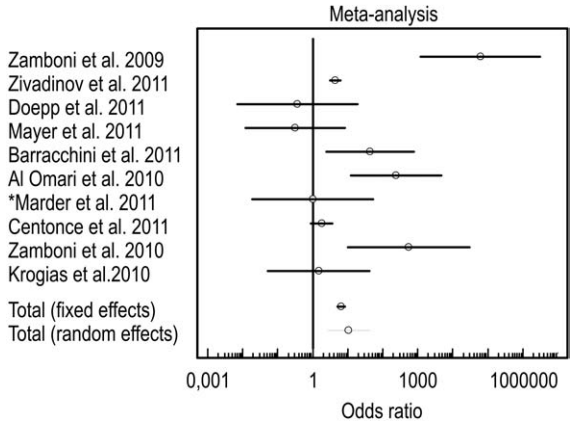
However, there are many publications pointing against the existence and the association of CCSVI in MS. Bagert *et al. (21)* state that investigations did not succeed in verifying the relationship between CCSVI and MS and they question the existence of CCSVI. Khan *et al. (22)* stated that endovascular procedures in MS were »research endeavors«, and that endovascular procedures should be discouraged. A Canadian group *(23)* concluded that »the performance of an interventional venous angioplasty … is not appropriate at this time«. Reekers *et al.*'s *(24)* randomized trials did not show a difference in the prevalence of venous stenosis between groups of patients with or without MS. But a recent meta-analysis done by Laupacis *et al. (25)* showed a positive association between CCSVI and MS, with an increased risk of more than 13 times.

The aim of this Motion is to analyze all the arguments against CCSVI as a medical entity and a subset of MS. In addition, we revise all the findings suggesting a possible connection between these two entities.

In the growing field of publications trying to demonstrate either positive or negative association of CCSVI with MS we will discuss the results of studies published so far. These studies show very variable results which we aim to comment. We observed grouping of results into two main groups; those with a CCSVI prevalence higher than 60%, from 60%–100% *(1–3, 5, 26–27)*, and those with absence of such lesions *(28, 29)*, or CCSVI prevalence under 60% *(30, 31)* (Table 1)(Figure 1). This variability could be the result of differences in technique, training, experience or criteria used *(32, 33)*.

Moreover, a recent meta-analysis done by Laupacis *et al. (25)* showed a positive association between CCSVI and MS. A systematic review and meta-analysis of all reports from 2005 till June 2011 was performed, comparing the frequency of CCSVI and MS. Their findings proved a significant association between CCSVI and MS even after exclusion of the first study by Zamboni, the meta-analysis was repeated after inclusion of Doepp's study, in which none of the patients or controls had CCSVI, which also showed similar results. Despite this, a strong association between CCSVI and MS was concluded (OR 3.5, 95% 0.8–15.8).

But, are the studies in opposition really so opposite? Doepp and al. reported no CCSVI in MS patients *(34)*, but their results did show a significant reduction of venous outflow in MS patients when their position changed from supine to upright, which points towards a disturbed venous outflow[4]. Doepp *et al. (34)* demonstrate a much larger change in blood flow volume in normals compared to MS patients when the subjects go from a supine to upright position. They find a change of 128 ml/min and 56 ml/min for the right and left sides respectively for MS patients. But they found a much larger change of 266 ml/min and 105 ml/min for their normal subjects. This result actually suggests the presence of CCSVI proven with a different protocol. The causes of reduced outflow changing posture to upright can be from intraluminal septum, membrane, immobile valve affecting the hydrostatic pressure gradient. The presence of such blockages in the extracranial and extravertebral cerebral veins have been proven by using catheter venography *(1, 35–38)*. More interestingly, Diaconu *et al.* communicated at ECTRIMS (European Committee for Treatment and Research in Multiple Sclerosis) the results of a post-mortem study clearly showing a highest prevalence of jugular septimentation with possible hemodynamic con-



*18 control subjects with migraine or no neurological disease.

Figure 1. *Meta-analysis of CCSVI prevalence in different studies.*

sequences in MS patients respect to controls *(39)*. This result is confirmed by another autoptic study *(40)*. Baracchini *et al.* reported 16% of CCSVI in MS patients at disease onset, compared to 2% of CCSVI in healthy controls *(30)*. This finding suggests that CCSVI represents a nine times higher risk factor for disease onset, showing increased susceptibility to MS in CCSVI subjects *(41)*. Zivadinov et al. recently reported CCSVI more likely to be a secondary phenomenon to MS *(42)*. Their results showed that CCSVI was found in 50% of pediatric MS cases as well as in 38% of CIS cases, thus making the conclusion rash *(43)*.

A well-established explanation for this great variability is the amount of training and experience investigators have in echo-colour Doppler imaging. Studies show *(32, 42)* that inter-operator variability decreases post-training (from k=0.47 to k=0.80) while intra-operator reproducibility in trained operators was k=0.75. Apart from this, ultrasound imaging still remains an operator-dependent investigation.

Despite all, in more than 2000 investigated subjects, the prevalence of CCSVI was 70% in MS patients compared to prevalence of 10% in healthy controls. Studies claiming to be in opposition to CCSVI still show different elements of abnormality of venous outflow in MS patients compared to their healthy controls.

A positive connection between CCSVI and MS is suggested by studies which tend to prove the presence of cerebral hypoperfusion in MS patients. MR studies in MS patients show a decrease in cerebral perfusion, affecting widespread areas including normal-appearing white matter (NAWM) *(44)*.

A factor promoting development of ischemic brain lesions in individuals with MS is globally decreased cerebral perfusion. A decrease in cerebral blood flow in both gray and white matter was shown by SPECT (single--photon emission computed tomography) and PET (positron emission-computed tomography) studies. A study using dynamic susceptibility contrast-enhanced MRI (DSC-MRI) showed significantly decreased cerebral blood flow (CBF) and prolonged mean transit time throughout the NAWM of the brain in MS patients, compared to controls *(45)*. A study of regional pattern of perfusion in NAWM reported a substantially decreased cerebral blood flow (CBF) and cerebral blood volume (CBV) in all NAWM regions in MS patients regardless of disease form *(46)*. Several reports claim hypoperfusion in the cerebral cortex and subcortical gray matter of patients with MS *(47–50)*. This was proven by Varga *et al. (51)* using DSC-MRI to assess CBF in cerebral NAWM, thalamus, and putamen in MS patients and controls. CBF was decreased in NAWM of patients with CIS and RRMS, but not in healthy controls, suggesting a CBF decrease of NAWM in early stages of disease. The hypoperfusion is believed to start in NAWM and it progresses into the gray matter. So definitely, hypoperfusion is part of MS.

Several mechanisms try to explain cerebral hypoperfusion *(52, 53)*. However, among the theories trying to explain diffuse and global hypoperfusion of brain parenchyma, CCSVI is the only finding explaining why CBF is reduced at any point of the microcirculatory network, in consequence of the disturbed outflow in the main venous outflow route *(44)*. This is confirmed by a study showing a robust correlation between the number of extracranial venous flow abnormalities detected by ultrasound and the severity of reduced CBF measured in the brain microcirculation *(54)*. In contrast, the other theories trying to explain global brain hypoperfusion fail to clarify why the flow is reduced either in NAWM and in NAGM (normal-appearing gray matter). Moreover, reduced CBF means stasis, highly characteristic of chronic venous disease. Stasis contributes to explain red blood cell extravasation with consequent iron-laden macrophages and perivenous iron depositions.

Due to perivenular pattern of focal MS lesions, CCSVI causes the stretching of endothelial tight junctions, causing diapedesis and degradation of erythrocytes, which results in iron deposition surrounding the veins in brain parenchyma *(55)*. Advanced MRI studies have shown higher iron concentrations in the thalamus and basal ganglia of MS patients, in a deposition pattern associated with venous drainage roots *(56)*. The high iron concentrations in MS lesions might be caused by iron release from the proteins to which it binds as a result of oligodendrocyte destruction occurring during inflammation and consequential lesion formation.

Cerebrospinal fluid dynamics and venous hemodynamics

The cerebrospinal fluid (CSF) if formed in lateral ventricles and mainly flows through brain's ventricular system, over and around cerebral hemisheres, and is absorbed by arachnoid villi into the superior sagittal sinus. Normal circulation of the CSF desires an optimal balance between ultrafiltration of CSF and its clearance from CSF spaces into the venous system at the level of dural sinuses, which depands mainly on efficient venous drainage *(57, 58)*. A blinded MR pilot study demonstrated venous outflow disturbance in MS patients *(59)*. Subjects with CCSVI showed higher frequency of venous reflux, blocked flow, B-mode abnormalities, and reduced IJV compliance which led to increased VHISS *(54)* (Venous Hemodynamic Insufficiency Severity Score) and lower net cerebrospinal fluid CSF flow. The study showed that impaired CSF dynamics may be a factor contributing to the increased volumes in 3rd and lateral ventricles, which was frequently observed in MS patients. Authors demonstrated that CCSVI has a significant impact on brain pathophysiology, especially on intracranial fluid balance.

We cannot deny that CSF flow, and symptoms of MS show a relationship to CCSVI, so we present several symptoms of MS, studied by scientists who have proven a vascular background to the problem.

Optic neuritis: A study of retinal blood vessels and their integrity *(60)* showed that more than half of patients with optic neuritis, who had vascular abnormalities, developed MS, in comparison to those without vascular abnormalities.

Transverse myelitis: It is considered also related to MS. It occurs more often in occupations linked to Valsalva maneuver causing many pressure changers, and occurring in everyday life, depending on professional physical demands *(61)*.

Idiopathic intracranial hypertension (IIH): MS patients are found to have IIH, a 3D MR venography (MRV) study showed 90% of MS patients to have sinovenous stenosis *(62)*. It is not clear whether these stenoses are caused by the hypertension, or it is the other way around *(63, 64)*. What is the link between IIH and MS? Is one causing the other, or is IIH coincidentally found in individuals with MS? Russian literature seems to commonly accept the association of raised intracranial pressure in the setting of MS exacerbations *(65)*.

Hydrocephalus: CSF has an important role in regulation of cerebral volume, by responding to incoming arterial flow and outgoing venous flow. Considering that about 70% of cerebral blood is venous blood, it is not surprising that veins play an important role in system compliance *(66)*. There is evidence of venous compression in patients with communicating hydrocephalus. This finding could relate to loss of visibility of medullary veins in more severe cases (as seen by susceptibility weighted imaging) *(67)*. Recently, venous insufficiency has been linked to hydrocephalus *(68)*. References show an association of hydrocephalus with intracranial venous occlusion, jugular venous obstruction, superior vena cava hypertension and superior vena cava occlusion. Also, it has been shown that hydrocephalus caused by jugular stenosis is reversible *(69)*.

We analyzed all the arguments against CCSVI as a medical entity, and it's association with MS. We revised all the findings suggesting a possible connection between these two entities. After careful review of all obtained data we can conclude that great variability in prevalence of the syndrome in MS patients can be a result of different methodologies used in vein assessment, training, application of unapproved diagnostic criteria, or different approach to the problem itself. However, all obtained data point towards a need for further investigation of this syndrome in MS as well as other demyelinating and neurodegenerative diseases.

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