Multiple sclerosis and chronic cerebrospinal venous insufficiency: a critical review

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Abstract: Chronic cerebrospinal venous insufficiency (CCSVI) was recently proposed as a contributing factor in the pathology of multiple sclerosis. This concept has gained remarkable attention, partly because endovascular neurointervention has been suggested as a treatment strategy. This review summarizes available evidence and provides a critical analysis of the published data. Currently, there is inconclusive evidence to support CCSVI as an etiological factor in patients with multiple sclerosis. Endovascular procedures should not be undertaken outside of controlled clinical trials.

Keywords: chronic cerebrospinal venous insufficiency, multiple sclerosis

The origin of the hypothesis

Chronic cerebrospinal venous insufficiency (CCSVI) as a potential etiopathogenic entity in multiple sclerosis (MS) has recently been suggested and gained significant attention.

Over the past few years, Zamboni and colleagues were the first to propose and explore this novel and controversial idea [Zamboni *et al.* 2009b,c,d]. The theory of CCSVI suggests that MS may be causally related to an inflammatory or immune reaction to iron that accumulates in the central nervous system (CNS) secondary to insufficiency of cervical and cerebral venous blood vessels [Zamboni, 2006]. The same investigators detected venous insufficiency by ultrasound and transcranial Doppler. These patterns of venous insufficiency in cranial and cervical blood vessels were seen in patients with MS and absent in control cohorts.

In 2010, Zivadinov and colleagues studied 16 patients with relapsing–remitting MS (RRMS) and eight matched, healthy controls by 3 T scanner using susceptibility-weighted imaging sequence [Zivadinov *et al.* 2010]. According to the authors, all 16 patients with MS fulfilled the diagnosis of CCSVI compared with none of the healthy controls. In patients with MS higher iron concentrations were found in the thalamus, globus pallidus, and hippocampus. Iron concentration measures were related to longer disease duration and increased disability, and increased MRI lesion burden and brain atrophy. Similar

results were reported by Haacke and colleagues in the same year [Haacke *et al.* 2010].

Subsequent studies

As mentioned above, the proposal of CCSVI as an etiological factor or disease modifier in MS is controversial. Subsequent to the initial observations, other investigators conducted their own studies to determine the existence and prevalence of CCSVI in patients with MS and control cohorts.

One positive study by Al-Omari and Rousan showed that in 25 patients with MS there was evidence of CCSVI in 84%, whereas none of the 25 controls displayed evidence of cerebral or cervical venous abnormalities [Al-Omari and Rousan, 2010]. There was no blinding of the investigators in this study.

All other published studies, however, could not reproduce the findings published by Zamboni and coworkers [Doepp *et al.* 2010; Krogias *et al.* 2010; Sundstrom *et al.* 2010; Wattjes *et al.* 2010; Yamout *et al.* 2010]. Doepp and colleagues found no evidence of CCSVI in patients with MS using Doppler criteria [Doepp *et al.* 2010]. Using magnetic resonance venography (MRV) and flow-quantification study, Wattjes and colleagues found no evidence of venous back flow in patients with MS, and no difference between patients with MS and controls in terms of outflow abnormalities [Wattjes *et al.* 2010]. Lastly, in a case–control study, Sundström and colleagues found no differences in internal jugular venous outflow,

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aqueductal cerebrospinal fluid flow, or the presence of internal jugular blood reflux in patients with MS [Sundstrom *et al.* 2010]. In their cohort, Krogias and colleagues found that only 20% of patients had the required neurosonological features of CCSVI. Yamout and colleagues performed selective extracranial venography on 42 patients with MS. Extracranial venous stenosis was seen in seven of 29 patients with early MS and 12 of 13 patients with late MS. Only three of 42 patients (all in the late MS group) demonstrated two vessel stenoses.

Worthington and colleagues conducted a cerebrospinal (CSF) study that showed normal ferritin levels in the CSF of patients with MS [Worthington *et al.* 2010]. The findings argue against the CCSVI-related CNS iron accumulation in MS.

The most recent negative data were published in 2011 [Baracchini *et al.* 2011; Mayer *et al.* 2011; Zivadinov *et al.* 2011].

Mayer and colleagues found no evidence of CCSVI in 20 patients with MS and only healthy controls fulfilled the criteria for CCSVI [Mayer *et al.* 2011].

Zivadinov and colleagues investigated the differences in the extracranial venous system in patients with MS and healthy controls by using MRV [Zivadinov *et al.* 2011]. Fifty-seven patients, 41 with RRMS and 16 with secondary progressive MS (SPMS), and 21 healthy controls were imaged with 3-T MRV. No significant differences in morphological features of flow in the internal jugular veins and vertebral veins were found between patients with MS and healthy controls in any of the examined MRV parameters.

Baracchini and colleagues studied the occurrence of CCSVI in clinically isolated syndromes (CISs). A total of 50 patients presenting with a CIS and evidence of dissemination in space of the inflammatory lesions underwent a comprehensive diagnostic workup, including extracranial and transcranial venous echo-color Doppler sonography. Patients who showed evidence of CCSVI were further evaluated by selective venography. A total of 50 healthy controls that matched the patients with CIS, 60 patients with transient global amnesia (TGA), and 60 healthy controls that matched the patients with TGA made up the control groups. The control groups also

underwent extracranial and transcranial venous echo-color Doppler sonography. Interestingly, transcranial venous echo-color Doppler was normal in all patients with CIS. One or more abnormal extracranial venous echo-color Doppler findings were observed in 26 of 50 (52.0%) of the patients with CIS, 35 of 110 (31.8%) of the controls and 41 of 60 (68.3%) of the patients with TGA. The eight (16%) patients with CIS who fulfilled the diagnosis of CCSVI were further evaluated for selective venography. Selective venography was completed in seven of these patients and did not disclose any venous anomalies or abnormalities.

Critical analysis

The controversy surrounding the theory of CCSVI in relation to MS has persisted, at least in part due to the fact that published results by Zamboni and colleagues were not reproducible by other investigators. While it has been argued that this is due to differences in methodologies, this argument is not convincing. Any strong biological signal should be visible by different detection assays, and it should be independent of the examiner.

Different methods can be applied to test whether the minimal conditions exist that establish a causal relationship between two items. One method is the Hill Criteria, originally presented by the British medical statistician Austin Bradford Hill, which established a causal link between cigarette smoking and lung cancer [Doll and Hill, 1950]. Subcriteria include strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy [Hill, 1965]. While Hill himself emphasized that 'None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required *sine qua non*' [Hill, 1965], they offer a strong degree of certainty that causal inference between two objects exists.

The biological plausibility of chronic cerebrospinal venous insufficiency in multiple sclerosis

When using the Hill criteria as a checklist to support or dispute an association between CCSVI and MS, none of the subcriteria are satisfyingly fulfilled. One critical subcriterion within the Hill criteria and any formal assessment of causal association is that of biological plausibility. A tissue diagnosis is still considered the gold standard to

confirm a clinical or paraclinical observation. Currently, there is no histopathological evidence of CCSVI in patients with MS. On biopsy and autopsy material from patients with MS there is generally no evidence of tissue edema or hemorrhagic infarctions, which are characteristics of severe venous insufficiency [Schaller and Graf, 2004]. Furthermore, it is unclear how a fixed anatomical deficit would cause the tremendous histopathological variations that have been described [Lucchinetti *et al.* 2000; Lucchinetti *et al.*, 1996]. Interestingly, CCSVI is reproducibly associated with TGA [Sakai *et al.* 2010; Chung *et al.* 2009, 2007, 2006; Schreiber *et al.* 2005; Sander *et al.* 2000], which has no known association with MS.

Clinically, a fixed anatomical defect would be inconsistent with the relapsing remitting nature of RRMS, or the female preponderance of RRMS [Alonso and Hernan, 2008], a trend that has been increasing with time. Very importantly, two very common anatomical targets in MS, namely the optic nerve and the spinal cord, are hard to explain by the CCSVI hypothesis. MS of the spinal cord cannot be explained based on CCSVI because of the extremely complex venous drainage in the spinal cord that is explained in the major anatomy textbooks. Optic neuritis, an extremely common finding in MS, is not associated with venous stasis.

Epidemiological data also appear to conflict with the concept of CCSVI. A decrease in disease activity during the second and third trimester of pregnancy [Confavreux *et al.* 1998] is inconsistent with CCSVI as increased intraabdominal and intrathoracic pressures reduce blood flow to the right heart. The geographical variations in MS prevalence [Rosati, 2001; Kurtzke, 1975] cannot be explained by the CCSVI theory. The beneficial response to immunomodulatory therapeutic agents with diverse modes of actions is also difficult to reconcile with CCSVI. In addition, one would expect that if MS is caused by a mechanical vascular problem, the incidence of MS should increase with advancing age, which is not the case in MS [Alonso and Hernan, 2008].

CCSVI is also inconsistent with other factors that have recently been shown to play a pathogenetic role in MS, including vitamin D insufficiency [Soilu-Hanninen *et al.* 2008; Vukusic *et al.* 2004] and an exposure to Epstein–Barr virus [Nielsen *et al.* 2007].

Treatment data

In a prospective, open-label trial, Zamboni and colleagues demonstrated that endovascular intervention using percutaneous transluminal angioplasty was feasible and safe [Zamboni *et al.*, 2009a]. In addition, the authors reported favorable outcomes in patients with RRMS.

The authors evaluated 65 patients with MS (35 with RRMS, 20 with SPMS and 10 with primary progressive MS. According to the study, the Multiple Sclerosis Functional Composite (MSFC) at 1 year improved significantly in patients with RRMS.

The major confounding factor in the study was the medical treatment. All the patients were on disease-modifying treatment, which was an inclusion criterion. Thus, favorable outcomes observed in this study may have been related to disease-modifying treatment rather than the vascular intervention. Bias was another important issue in the study. The study did not have a control arm. Therefore, the improvement in MSFC may have been due to placebo effect. In addition, neurologists in this study were not blinded. It should also be noted that the percentage of annual relapse reduction that was found in this particular study (22%) was lower than the decrease found in placebo-treated patients in most randomized, placebo-controlled trials.

It should be noted that almost half of the internal jugular PTA cases restenosed on follow up, which is a major technical problem limiting the routine use of the procedure [Zamboni *et al.* 2009a]. While the procedure has been reported to be safe, there were severe complications related to the angioplasty and stenting. Two cases with severe adverse events have been reported in the scientific literature: a death due to intracranial bleeding related to anticoagulation; and intracardiac stent migration [Samson, 2010].

Conclusion

Based on conflicting published data, it is currently unclear whether CCSVI exists as a pathologic entity, or as an anatomic variant in patients with MS. It is even less substantiated that there is a causal association between CCSVI and MS.

Based on a review of the literature, it is our view that the concept of CCSVI is inconsistent with the epidemiology, pathology and many of the clinical features of MS. Pending further

investigations, no therapeutic interventions involving treatment of plausible CCSVI should be recommended for patients with MS outside of controlled clinical settings.

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Conflict of interest statement

None declared.

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