Chronic Cerebrospinal Venous Insufficiency and Multiple Sclerosis

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A chronic state of impaired venous drainage from the central nervous system, termed chronic cerebrospinal venous insufficiency (CCSVI), is claimed to be a pathologic phenomenon exclusively seen in multiple sclerosis (MS). This has invigorated the causal debate of MS and generated immense interest in the patient and scientific communities. A potential shift in the treatment paradigm of MS involving endovascular balloon angioplasty or venous stent placement has been proposed as well as conducted in small patient series. In some cases, it may have resulted in serious injury. In this Point of View, we discuss the recent investigations that led to the description of CCSVI as well as the conceptual and technical shortcomings that challenge the potential relationship of this phenomenon to MS. The need for conducting carefully designed and rigorously controlled studies to investigate CCVSI has been recognized by the scientific bodies engaged in MS research. Several scientific endeavors examining the presence of CCSVI in MS are being undertaken. At present, invasive and potentially dangerous endovascular procedures as therapy for patients with MS should be discouraged until such studies have been completed, analyzed, and debated in the scientific arena.

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Recently, the topic of chronic cerebrospinal venous insufficiency (CCSVI) and its potential relationship to multiple sclerosis (MS) has generated tremendous interest in the news media, spilling over to the patient and scientific communities. Described as a state of chronic impaired venous drainage from the central nervous system (CNS), the emergence of CCSVI with respect to MS is based on the work done by Zamboni and colleagues.[1] This was followed by a small open-label study conducted to study the effect of endovascular angioplasty in MS patients with CCSVI.[2] Prompted by this series of events, this Point of View will review available information on CCSVI, its potential relationship to MS pathology, and what further research needs to be undertaken while keeping patient safety foremost.

Transcranial color-coded Doppler sonography (TCCS) is a technique that superimposes a color-coded image of blood flow of intracranial vessels on a gray scale image to evaluate intracranial veins. By combining TCCS and extracranial color-Doppler sonography (ECD), Zamboni and colleagues studied 109 MS patients and 177 matched controls.[3] Based on venous flow parameters established in their laboratory, they found 288 normal and 257 anomalous TCCS-ECD parameters in MS patients. In contrast, 861 normal and 24 anomalous parameters were seen in control subjects. The authors focused in particular on 5 anomalous parameters of cerebral venous drainage: (1) reflux in the internal jugular (IJV) and vertebral veins (VV), (2) reflux in the deep cerebral veins, (3) high-resolution B-mode evidence of IJV stenosis, (4) flow

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not detectable by Doppler in the IJV and/or the VV, and (5) reverted postural control of the main cerebral venous outflow pathways. They claimed that these parameters were not seen in normal subjects, although others have reported IJV valve insufficiency in 29 to 38% of healthy volunteers under pressure-controlled maneuvers.[4,5] In the study by Zamboni and colleagues,[1] the presence of at least two of these anomalous parameters in a single subject was defined as abnormal. They reported that only MS patients and not controls met the criteria for abnormal extracranial cerebral venous outflow. This observation perfectly overlapped with the diagnosis of MS, with a reported 100% sensitivity, 100% specificity, 100% positive predictive value, and 100% negative predictive value. These findings could reflect spectrum bias, which occurs when a diagnostic test is assessed under sampling conditions that are not clinically representative.[6] Moreover, it is difficult to determine flow in the deep cerebral veins using ultrasound because the angle of insonation is $>60°$. There is also the potential of interference arising from the pulsation signal of the posterior communicating artery located adjacent to the draining jugular sinuses. In a separate study by Zamboni and colleagues, 65 MS patients and 235 controls underwent TCCS-ECD.[1] Whereas the technician and the interpreting physician were blinded to the diagnosis, it is not clear whether the performing sonographer was blinded to the diagnosis. The authors report that they were able to separate 100% of MS patients from controls. All 65 MS patients, as part of a nonblinded substudy, underwent selective catheterization of the IJV and azygous veins (AV).[1] They found that IJV and AV were stenosed in 91% and 86% of the patients, respectively. More recently, percutaneous transluminal angioplasty was performed in these 65 MS patients, who were then followed for up to 18 months.[2] During this period, it was determined that some of the clinical outcomes were improved, mostly in the relapsing-remitting MS cohort (35/65). However, the small sample size, lack of controls, unblinded neurologic evaluations, significant restenoses of 47% of IJV, and inconsistent magnetic resonance imaging (MRI) protocols limit the interpretation of their data. Due to high restenosis rate, they suggested that a "logical alternative would be stent insertion."[2] Furthermore, all patients remained on their disease-modifying therapies, making any interpretation of "efficacy" even more tenuous. In a separate publication, the same investigators imply that CCSVI causes venous reflux leading to iron buildup in the brain, which may be a primary event in the MS disease pathology, triggering subsequent inflammatory injury to the CNS.[7] The potential role of increased iron deposition and iron-mediated injury to the CNS is not exclusive to MS and is well-documented in many neurological disorders, particularly neurodegenerative diseases.[8,9] Yet CCSVI was never observed in the "other neurologic disease" controls studied by Zamboni and colleagues, which included Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.[1]

The results reported by Zamboni and colleagues have raised many questions regarding the cause of MS, and how it may be treated based on the theory of CCSVI. This necessitates carefully conducted and dispassionate research exploring the possibility that CCSVI might indeed contribute to the pathogenesis of MS. The intracranial venous return has not been routinely investigated by TCCS in the normal population. The work done by Zamboni and colleagues,[1] although innovative, is limited by the lack of discussion of TCCS technique and the absence of a reference standard, such as MRI, for intracranial vascular evaluation. The vessels evaluated by Zamboni and colleagues included the extracerebral veins (VV and IJV) and at least one of the deep cerebral veins (basal vein of Rosenthal, great vein of Galen, or internal cerebral veins). This approach introduces variation into the results, because ideally, all 3 deep cerebral veins should have been examined. In a prior study by the same investigators, they noted that the main parameters of TCCS investigation of the intracranial veins are the flow parameters, such as flow direction, flow velocity, and resistive index.[10] However, these parameters do not appear to have been evaluated in their CCSVI study in MS patients.[1] Lack of MRI for examining the intracranial vessels and lesion distribution did not allow the evaluation of the plaques' topography with the refluxing veins. These limitations necessitate a more cautious interpretation of their findings. It also makes the robustness of this approach to investigate intracranial venous return unclear.

Several well-known features of MS, including the autoimmune nature of the disease involving complex T- and B-cell–mediated responses,[11] challenge CCSVI as the etiology of MS or as contributing to the disease pathophysiology. Is the presence of cranial venous outflow stenosis and formation of substitute venous circulation circles, largely a phenomenon observed in women, as nearly two-thirds of the MS patients are women?[12] Interestingly, most other systemic autoimmune diseases also show greater prevalence in women than men, although stagnant venous outflow may not be germane to the known pathology of those diseases such as lupus and rheumatoid arthritis.[13] Being a vascular phenomenon, it would be logical to expect a chronically stagnant venous flow from the CNS only to get worse and more prevalent over time. Yet

the incidence of MS becomes rare at age 50 years and older.[14]

Several genetic susceptibility factors for MS have been identified, including major histocompatibility complex (MHC) and non-MHC loci.[15] The presence of HLA-DR2 increases the risk of developing MS and other autoimmune disorders, primarily through association with T-cell–mediated responses.[16,17] However, there are no data to suggest how these allelic expressions may alter cerebrospinal venous flow, if that is hypothesized to be the underlying pathology leading to the development of MS. It is also well known that genetic predisposition alone cannot explain the significant differences in risk among people of common ancestry who migrate to areas of high or low MS prevalence.[18] The geographic distribution of MS and the resultant change in risk among migrant populations provide strong evidence in support of environmental risk factors for developing MS.[19,20] Data related to sunlight exposure in association with low vitamin D level and immune response to Epstein-Barr virus infection are associated with a higher risk of developing MS in the pediatric clinically isolated syndrome (CIS) population, challenging the hypothesis that MS is more likely to be a consequence of venous stasis.[21,22] Several lines of evidence suggest that MS pathogenesis includes an environmental trigger that first primes the immune system and then initiates an immune response to unknown CNS antigens, including myelin antigens.[23,24] However, currently there is no precedence for reduced venous drainage and induction of an organ-specific immune response. Other histopathologic studies have shown early loss of oligodendrocytes in active MS lesions and the absence of lymphocytes in the perivascular spaces as key features of MS pathology.[25] The contribution of CCSVI to this observation is also unclear.

Venous occlusion secondary to flow disturbances is characterized by hemorrhagic and ischemic infarctions, and edema associated with increased intracranial pressure.[26] These features are not typically seen in the brain or spinal cord of MS patients. Furthermore, the widespread primary demyelination, characteristic for both white and gray matter lesions in MS patients,[27] is not present in conditions of acute or chronic venous brain disease. However, more subtle chronic alterations of venous blood flow could theoretically augment tissue injury in MS. A disturbance of venous outflow may increase pressure within the venous drainage pathways. This is likely to facilitate the exit of inflammatory cells from the venous circulation to gain entry into the CNS, and amplify perivenous inflammation. However, it was recently shown that in the late stages of MS, inflammation may die out and decline to levels seen in age-matched controls.[28] This would not be the case if impaired venous drainage was the primary pathology in MS, because it would be expected to increase with time and age. In CCSVI, the retinal and ophthalmic venous systems that ultimately drain into the internal jugular veins are likely to have impaired venous drainage. Whereas optic neuritis is a common clinical occurrence in MS, venous stasis retinopathy is not. The latter represents the earliest stages of chronic ocular ischemia, characterized by a variety of retinal hemorrhages.[29] In contrast, retinal nerve fiber layer atrophy is a well-recognized feature of MS.[30] It would not be logical to disassociate one form of retinal injury from the other, if all are a result of impaired ocular venous drainage.

Also suggested by Zamboni et al,[1] chronic inefficient venous drainage from the azygous vein accounts for the clinical manifestations of spinal cord involvement in MS, that is, recurrent episodes of transverse myelitis and progressive myelopathy. Histopathologic studies show both axonal loss and demyelination in the spinal cord in MS,[31,32] but not the typical features expected from raised intraluminal venous pressure.[26] Furthermore, the venous drainage of the spinal cord is complex and comprised of at least 4 distinct intercommunicating systems: (1) intrinsic small capillary veins, (2) extrinsic veins (including pial, collector, and radicular veins), (3) internal vertebral venous plexus, and (4) external vertebral venous plexus.[33] These venous systems communicate with occipital, basilar, vertebral, intercostal, lumbar, and lateral sacral veins.[34] The intramedullary veins drain the spinal cord parenchyma and also participate in extensive transmedullary anastomoses.[35] The lumbar veins also communicate with the inferior vena cava. Cadaver studies have shown that venous reflux through the radicular veins appears to be a physiologic phenomenon, with a regulatory mechanism protecting the spinal cord from high venous pressure.[34] The complex venous drainage system of the spinal cord inherent with extensive protective communicating systems makes chronic venous insufficiency of the azygous vein unlikely to be responsible for the clinical and histopathologic features of spinal cord involvement in MS.

Increased cerebral venous pressure occurs in central venous thrombosis, idiopathic intracranial hypertension, pulmonary hypertension, and chronic obstructive pulmonary disease,[36–38] yet none of these disorders is associated with MS or poses a risk of developing MS. Interestingly, transient global amnesia is well known to occur in association with jugular venous insufficiency,[39,40] but is not a feature of MS. Radical neck dissection is a standard surgical procedure in the management of head and neck can-

cer, which besides extensive malignant and nonmalignant tissue removal, removes all jugular veins and associated lymph nodes en bloc.[41] MS and related inflammatory demyelinating disorders of the CNS have never been reported as complications of radical neck dissection in over a century since the original description of this procedure in 1906.[42] Brain MRI scan obtained several weeks after bilateral internal and external jugular venous ligation did not reveal any lesions or parenchymal abnormalities,[43] and brain MRI scans in the long-term follow-up of patients who have previously undergone radical neck dissection have not shown any pathology suggestive of MS (personal observations, I.Z.). The cerebrospinal venous architecture is a highly complex and evolved system of venous blood flow with numerous variations, collaterals, and even the possibility of a watershed zone separating the periventricular venous drainage from the deep white matter venous flow.[44,45] This raises further questions regarding the results of the study by Zamboni et al,[1] who claim the ability to completely (100%) distinguish MS patients from controls with TCCS-ECD criteria established in their laboratory.

These and many other arguments that challenge the theory of CCSVI proposed by Zamboni and colleagues should lead to a constructive scientific debate. There is also the possibility that the development of venous flow abnormalities may be secondary to other disease processes in MS. This could be partly addressed by examining patients for the presence of CCSVI in the earliest stages of the disease, that is, CIS or children with MS. The role of the autonomic nervous system and the technical variations in the application of transcranial Doppler (TCD) studies as it may apply to MS have to be carefully considered.[46–48] Future TCD studies should involve multiple sites, to overcome the well-known limitations of single site studies, especially in the application and acceptance of abnormal parameters of cerebrospinal venous flow, because there is no published consensus on standardized criteria for normal venous return using ECD-TCCS. Studies employing magnetic resonance venography (MRV) to examine venous stenosis in MS will have to examine both caliber and hemodynamic flow abnormalities, as well as determine the significance of these potential findings. In contrast to studies examining carotid artery stenosis and its clinical significance,[49,50] there are no such data for IJV or AV. Meticulously conducted MRV studies from multiple centers may be needed to provide insight into CCSVI and its potential relationship with MS. The inclusion of a carefully selected control population in these studies cannot be overemphasized. Correlation of CCSVI with the well-established clinical, immunologic, histopathologic, and imaging features of MS needs to be investigated.

It is critical not to compromise patient safety during the conduct of these research endeavors. Anecdotal reports have indicated that endovascular procedures including placement of stents in the IJV have been carried out in MS patients as a clinical treatment procedure, and in some cases have led to serious injury. Potentially fatal outcomes including migration of the venous stent into the heart and perforation of the ascending aorta are uncommon but known complications of venous stent insertions.[51,52] Any invasive endovascular procedures including angioplasty and venous stent placement should be discouraged until there is conclusive evidence to justify their indication in MS.

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