Chronic Cerebrospinal Venous Insufficiency and Multiple Sclerosis

(65 characters)

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Abstract

A chronic state of impaired venous drainage from the central nervous system, termed as 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 a therapy for patients with MS should be discouraged until such studies have been completed, analyzed, and debated in the scientific arena.

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 these 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 the

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 five anomalous parameters of cerebral venous drainage: (i) reflux in

the internal jugular (IJV) and vertebral veins (VV), (ii) reflux in the deep cerebral

veins (DCV), (iii) high-resolution B-mode evidence of IJV stenosis, (iv) flow not

Doppler-detectable in the IJV and/or the VV, and (v) 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 internal jugular vein 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. highly unusual findings in clinical research. With such high level of diagnostic accuracy, These findings could reflect spectrum bias, which occurs when a diagnostic test is assessed under sampling conditions that are not unlikely to be clinically representative (6). Moreover, these findings are not easy to interpret because it is difficult to determine flow in the deep cerebral veins using ultrasound since the angle of insonation is greater than 60 degrees. 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, 65 MS patients and 235 controls underwent TCCS-ECD (1). While the technician and the interpreting physician were blinded to the diagnosis, it is not clear if the performing sonographer was blinded to the diagnosis. The authors claim report that they were able to separate 100% of MS patients from controls. also a difficult result to achieve. All 65 MS patients, as part of a non-

blinded sub-study, 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

(PTA) 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 re-stenoses of 47% IJV, and inconsistent MRI protocols

limit the interpretation of their data. Due to high re-stenosis 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 build up 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

in the brain and iron-mediated injury to the CNS is not exclusive to MS and is

well-documented in many neurological disorders, particularly neurodegenerative

diseases this phenomenon is not exclusive to MS (8,9). Yet, CCSVI was never

observed in the "other neurologic disease" controls studied by Zamboni and

colleagues that included Alzheimer's disease, Parkinson's disease, and

amyotrophic lateral sclerosis (1).

As a result of the great deal of media attention that has been given to CCSVI, the

causal debate of MS has been invigorated by the work of Zamboni and colleagues, who euphemistically refer to the endovascular treatment of the "blocked" veins in MS patients as the "Liberation" treatment. Consequently, thousands of patients have expressed an interest in volunteering for studies to examine if they have stenoses or blockages of the IJV and AV. Anecdotal reports suggest that some sites in the U.S. and Europe have undertaken endovascular procedures for MS patients including venous "stenting".

Despite the intriguing results and claims The results reported by Zamboni and colleagues, their data should be considered preliminary at best. There is no doubt that their work though preliminary, 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. many questions must also be addressed regarding CCSVI and MS with. The intracranial venous return has not been routinely investigated by TCCS in the normal population. The work done by Zamboni and colleagues (1), though 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, since ideally, all three 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), which also lacked figures of

TCCS images to document the results the authors described. Lack of MRI for

examining the intracranial vessels and lesion distribution did not allow the

evaluation of the plaques' topography with the refluxing veins. Collectively, 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 even 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 since 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). Since the peak age of incidence of MS is between 25

and 35 years (14), it is unclear why it would take two to three decades for a

9

stagnant venous drainage to lead to the development of MS. At the same time,

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).

Similarly, MS is rare in the tropics and subtropics (16), yet there is no published

report of chronic venous flow disorders based on similar geographic incidence

and prevalence.

Several genetic susceptibility factors for MS have been identified including MHC

and non-MHC loci (15). Also noteworthy is that first-degree relatives of MS

patients are 20 to 50 times more likely to develop MS than the general population

(18). 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 is no data to suggest how these allelic

expressions may alter cerebrospinal venous flow or what makes first-degree

relatives of MS patients more susceptible to venous blockages if that is

hypothesized to be the underlying pathology leading to the development of MS. It

is also well-known that genetic predisposition alone can not 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 population provide strong evidence in

support of "environmental" risk factors for developing MS (19,20). Data related to

sun light exposure in association with low vitamin D level and immune response

10

to EBV 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. Moreover, the presence of CSF

oligoclonal bands indicative of intrathecal humoral response, is not exclusive to

MS and may be seen in several other CNS disorders in which the pathology is

unlikely to be affected by abnormalities of the cerebrospinal venous circulation

(28). Other histopathologic studies have shown early loss of oligodendrocytes in

active MS lesions and the absence of lymphocytes in the perivascular spaces as

a key feature of MS pathology (25). The contribution of CCSVI to this observation

is also unclear.

The pathology of MS, characterized by the hallmark of inflammatory

demyelination, is different from that seen in conditions of Venous occlusion

secondary to flow disturbances The latter 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 grey matter lesions in MS patients (27) is not present in

11

conditions of acute or chronic venous brain disease. However, more subtle

chronic alterations of venous blood flow could theoretically augment tissue injury

in MS. Chronic perivenous inflammation in the brain may release inflammatory

mediators into the venous lumen and consequently, alter venous endothelium.

vessel walls in the drainage pathways. In such a case, A disturbance of venous

outflow may increase pressure within the venous drainage pathways. This is

likely to facilitate may which by itself may make it easier for the exit of

inflammatory cells to leave from the venous circulation in the small veins and

venules, 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 cause

of the problem-since it would be expected to imagine such a problem actually

increase with time and age. High-field susceptibility-weighted imaging at 3 Tesla

has shown reduced visibility of venous vasculature in the periventricular white

matter in MS patients compared to controls suggestive of a diffuse

hypometabolic process (32). However, in CCSVI, one would anticipate the

venous vasculature to be more prominent due to impaired venous drainage and

higher venous luminal pressure. In CCSVI, presumably, the retinal and

ophthalmic venous systems that ultimately drain into the internal jugular veins,

are likely to have impaired venous drainage due to CCSVI. While Equally

intriguing is extrapolating the argument of impaired venous drainage associated

with 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, However, while retinal nerve fiber layer (RNFL) atrophy is a well recognized feature of MS common occurrence in MS (30). venous stasis retinopathy that usually, is not a feature of MS. 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 i.e. 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 intra-luminal venous pressure (26). Furthermore, the venous drainage of the spinal cord is complex and comprised of at least four distinct intercommunicating systems: (i) intrinsic small capillary veins, (ii) extrinsic veins (including pial, collector, and radicular veins), (iii) internal vertebral venous plexus, and (iv) 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). Therefore,

Given 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 are

associated with MS or pose 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 cancer, which

besides extensive malignant and non-malignant tissue removal, removes all

jugular veins and associated lymph nodes en bloc (41). Multiple sclerosis or

related inflammatory demyelinating disorders of the CNS have never been

reported as a complication 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, IZ). The cerebrospinal venous architecture is a highly complex and

evolved system of venous blood flow with numerous variations, collaterals, and

14

even the possibility of a watershed zone separating the periventricular venous drainage from the deep white matter venous flow (44,45). This further raises questions regarding the results of the study by Zamboni et al. (1), claiming 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. and research to reproduce their preliminary findings. Association, if proven, should not be construed as causality. There is also the possibility that the development of venous flow abnormalities may be secondary to other diseases processes in MS. This could be partly addressed by examining patients for the presence of CCSVI in the earliest stages of the disease i.e. CIS or children with MS. The role of the autonomic nervous system and the technical variations in the application of 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 since there is no published consensus on standardized criteria for normal venous return using ECS-TCCD. Studies employing MR 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 is 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 carefully selected control population in these studies can not be overemphasized. Furthermore, attempts should be made to Correlation of CCSVI with the well-established clinical, immunologic, histopathologic, and imaging features of MS needs to be investigated.

It would be critical not to compromise patient safety to ensure that during the conduct of these research endeavors. patient safety never be compromised. Anecdotal reports have indicated that endovascular procedures including placement of stents in the internal jugular vein 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). Therefore, Any invasive endovascular procedures including angioplasty and venous stent placement should be discouraged until there is conclusive evidence to justify their indication in MS. Attempts should be made to study the plausibility of CCSVI in MS and to correlate it with the well-known clinical features of the disease along with seminal observations from the vast immunologic, histopathologic, and imaging studies conducted over the past several decades.

16

17

18

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