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Chronic Cerebrospinal Venous Insufficiency and Multiple Sclerosis

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Chronic cerebrospinal venous insufficiency has recently been proposed to be etiologic to multiple sclerosis. Independent investigation into this theory during the past 2 years has not succeeded in verifying this relationship. A critical analysis of the scientific methods used in the original studies of chronic cerebrospinal venous insufficiency in multiple sclerosis reveals several methodological problems with regard to potential bias and confounding. The current evidence calls into question whether chronic cerebrospinal venous insufficiency in multiple sclerosis exists at all.

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During the past 2 years, there has been significant interest among both multiple sclerosis (MS) researchers and patients with MS in the theory that MS may be caused by abnormal venous drainage of the central nervous system and that correction of such venous abnormalities might be beneficial in MS. The idea that venous defects, termed *chronic cerebrospinal venous insufficiency* (CCSVI), are etiologic to MS was suggested by a series of investigations by Pablo Zamboni and colleagues published in 2009. Critical examination of the original articles by Zamboni et al reveals serious methodological problems that cast some doubt on the validity of their data and conclusions. Despite a lack of convincing evidence to support CCSVI in MS, invasive and potentially risky endovascular procedures are commonly being performed in patients with MS. Since the publication of the original articles by Zamboni et al, several independent investigators have attempted to replicate the findings, but so far none have succeeded despite an enormous dedication of research funds to the effort worldwide. The current evidence calls into question whether CCSVI exists at all, to say nothing of whether it might be etiologic to MS. Until and if the existence of CCSVI in MS is established by independent investigations, clinical trials of invasive treatments of CCSVI in MS are not appropriate in our opinion.

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ZAMBONI ET AL: CCSVI AND MS

In early 2009, Zamboni et al published the first of a series of investigations into the relationship between CCSVI and MS.[1] In this study, 109 patients with clinically definite MS and 177 control subjects underwent transcranial and extracranial color Doppler sonographic examinations. Five parameters of abnormal venous outflow were defined as being indicative of CCSVI and were measured in all subjects (**Table 1**). Subjects with MS were found to have abnormal venous parameters more frequently than control subjects. The presence of at least 2 of the 5 parameters was observed as being diagnostic of MS with 100% specificity, 100% sensitivity, and positive and negative predictive values for MS of 100%.[1] Zamboni et al went on to perform selective venography in 65 patients with MS as well as several control subjects. These investigators reported that patients with MS had multiple severe extracranial stenoses and that these abnormalities were not identified in control subjects.[2]

Table 1. Doppler Venous Hemodynamic Criteria for Chronic Cerebrospinal Venous Insufficiency in Multiple Sclerosis[a]

Criterion
Reflux in internal jugular veins and/or vertebral veins in sitting and supine posture
Reflux in deep cerebral veins
High-resolution B-mode evidence of internal jugular vein stenosis
Flow not Doppler detectable in internal jugular veins and/or vertebral veins
Reverted postural control of main cerebral venous outflow pathways

[a] Criteria are by Zamboni et al.[2]

METHODOLOGICAL ISSUES: BIAS AND CONFOUNDING

In these initial exploratory studies, there were several methodological problems in the design and implementation of the investigations that may have influenced the validity of the results. First, there is a question of potential observer bias in the ultrasonographic measurements. The authors reported that the ultrasound technicians and the interpreting physicians were blinded as to whether the subject had MS, but no description of the method of such blinding was provided in the articles. In fact, the principal interpreting physician of the Doppler studies was identified as "PZ" in the journal article,[2] suggesting that this interpreter was Pablo Zamboni himself, the principal investigator of the study. Again, this circumstance casts doubt on the objectivity of the measurements in the study and raises the possibility that observer bias may have influenced the observations.[2] Furthermore, the articles had no description of any methods used to limit intraobserver or interobserver bias, raising further doubt about the reliability of these measurements. Last, the control groups included subjects with other neurological disease, but none had other inflammatory neurological disease. The exclusion of such individuals in the control groups may have led to a selection bias within the study population such that the investigators failed to explore the possibility that CCSVI might be an epiphenomenon of central nervous system inflammation in general (CCSVI is the result of MS) rather than CCSVI being the cause of MS as suggested by the authors.

In spring 2009, Zamboni et al reported the results of a treatment trial using percutaneous transluminal angioplasty (PTA) on the stenotic veins in the 65 patients with MS who underwent venography.[3] They reported that PTA in patients with relapsing-remitting MS increased the rate of relapse-free patients from 27% preoperatively to 50% postoperatively ($P<.001$) and decreased the rate of gadolinium-enhancing lesions on magnetic resonance imaging (MRI) from 50% preoperatively to 12% postoperatively ($P<.001$).[3] Furthermore, the Multiple Sclerosis Functional Composite score, which assesses several clinical dimensions relevant to MS disease activity at 1 year, improved significantly in this patient cohort.[3]

As with the Doppler studies, there were several methodological factors in this treatment trial that may have influenced the observations. First, there is a question of confounding of the results by concomitant initiation of disease-modifying therapy (DMT) in MS in the study population just prior to the PTA intervention. One assumes (although it is not explicitly stated) that the 65 subjects with MS in the PTA study[3] are the same 65 subjects with MS who were in the Doppler study that was published just a few months earlier[2] because in both studies the 65 subjects are described as having identical forms of MS: 35 subjects with relapsing-remitting MS, 20 subjects with secondary progressive MS, and 10 subjects with primary progressive MS. In the article on the Doppler studies, the authors indicated that 33% of the subjects with MS were not receiving any DMT for MS[2] at the time of the measurements. In the PTA treatment trial, however, 100% of the 65 subjects with MS were receiving DMT. In fact, receiving DMT was an inclusion criterion for the PTA study.[3] This inclusion requirement suggests that a sizable number of subjects with MS who had not previously received DMT at the time of baseline data collection[2] were asked to start standard DMT to enroll in the PTA study.

The overall clinical improvement observed in this group of patients with MS who underwent PTA is potentially confounded by the coincident initiation of DMT in that the clinical improvement may have been the result of newly started DMT rather than the PTA procedure. In our opinion, this potential confounder is one of the most egregious methodological problems with the initial treatment trial by Zamboni et al.

Furthermore, in the PTA trial, there was no control group and therefore no blinding of neurologists. Without a control group, the placebo effect may also have contributed to the observed clinical improvement; without blinding of neurologists, observer bias may have skewed the observations away from the null hypothesis. Both of these factors are important examples of ways in which this investigation may have been biased such that the observations were an overestimation of the effect of cerebrospinal PTA in MS.

It also has to be assumed that only those patients who had substantial disease activity and who very likely had not responded favorably to pharmacological interventions were enrolled in this trial. It is well recognized that patients with unusually high disease activity at a given moment often behave differently in this regard when followed up during a period of time. Specifically, clinical and paraclinical markers of disease activity will diminish. This phenomenon is referred to as regression to the mean. Regression to the mean has to be taken into account in correctly interpreting long-term studies of cohorts treated without a placebo control group, including the trial by Zamboni et al, that use the baseline period as the control.[4]

The methods of MRI data collection in the PTA trial were also substandard. In the PTA treatment trial, the authors reported a significant decrease in the rate of gadolinium-enhancing lesions on MRI in subjects with MS after treatment with PTA.[3] However, there is virtually no description of the methods by which these MRI data were collected. For example, there is no mention of who interpreted the MRIs or when the baseline MRIs were performed. It is unclear whether baseline MRIs were per-

Table 2. Application of the Bradford Hill Criteria for Causality on the Relationship Between Chronic Cerebrospinal Venous Insufficiency and Multiple Sclerosis

Bradford Hill Criterion	Description of Criterion	Evidence in CCSVI and MS	Criterion Met?
Strength of association	The larger the association, the more likely that the relationship is causal	Highly variable among different investigators	No
Consistency	Consistent findings observed by different persons in different places with different samples	Published data so far reveal a lack of consistent findings among investigators	No
Specificity	Evidence that the disease (MS) is specifically the result of the exposure (CCSVI)	None	No
Temporality	The effect (MS) has to occur after the exposure (CCSVI)	None	No
Biological gradient	Greater exposure (CCSVI) should generally lead to greater incidence of the effect (MS)	None	No
Biological plausibility	A biologically plausible mechanism between cause (CCSVI) and effect (MS)	CCSVI does not explain the long-recognized immune system pathology in MS	No
Coherence	Coherence between epidemiological knowledge of disease (MS) and new association (CCSVI and MS)	CCSVI does not explain the long-observed epidemiological phenomena of female preponderance in MS, the latitudinal gradient of incidence of MS, or the increased risk of MS after mononucleosis	No
Experiment	Changing exposure (CCSVI) changes outcome (MS)	No randomized, placebo-controlled, double-blind trial has been done	No
Analogy	Examples of similar exposures (venous insufficiency) and outcomes in other biological systems	There is no evidence that other diseases that cause increased cerebral venous pressure are associated with MS	No

Abbreviations: CCSVI, chronic cerebrospinal venous insufficiency; MS, multiple sclerosis.

formed as part of the study at all or whether prior MRIs were used as a pretreatment baseline. The authors even concede that "MRI was not always performed with the same instrument, followed the same protocol, or was at the same intervals."[3] Again, this lack of transparency in the description of the methods used to collect and analyze MRI data raises doubt about the validity of the MRI outcomes in this study.

CCSVI RESEARCH BY OTHER INVESTIGATORS

Since the original articles on CCSVI in MS by Zamboni et al were published in 2009, there has been significant interest in CCSVI and its treatment within the MS community, among both patient advocacy groups and the scientific community alike. As a result, there has been a significant push to fund further research to replicate and confirm the observations by Zamboni et al. So far, however, the published results have proven to be quite variable in their findings, and no independent study has found that venous abnormalities in MS exist to the same extent as that reported by Zamboni et al.

In April 2010 at the annual meeting of the American Academy of Neurology, Zivadinov and colleagues[5] presented preliminary findings of a large epidemiological study aimed at defining the prevalence of CCSVI in MS. Subjects with MS, subjects with clinically isolated syndrome, subjects with other neurological diseases, and healthy control subjects were evaluated by Doppler using the 5 criteria for CCSVI as defined originally by Zamboni et al. At the time of that meeting, 499 subjects (289 with MS) had completed evaluation. The prevalence of CCSVI was reported to be 56.1% in subjects with MS, 38.1% in subjects with clinically isolated syndrome, 42.5% in subjects with other neurological diseases, and 22.7% in healthy control subjects.[5] These data have yet to be published. Although venous abnormalities were identified in some patients with MS, they were not identified to the same extent as that observed by Zamboni et al. Also, they were identified in a large proportion of healthy control subjects, which Zamboni et al did not observe.

The results of several other independent investigations into CCSVI and MS were published in 2010 and 2011,[6-8] and none of these studies supported the original findings by Zamboni et al. Doepp and colleagues[6] published the results of a Doppler study of patients with MS and control subjects. A total of 56 patients with MS and 20 control subjects without a neurological diagnosis underwent extracranial and transcranial color-coded sonography. Internal jugular vein stenosis was not detected in any case or control subject, and none of the investigated subjects fulfilled more than 1 criterion for CCSVI[6] as originally defined by Zamboni et al. Sundström et al[7] published the results of an investigation of 21 patients with relapsing-remitting MS and 20 control subjects. All subjects underwent phase-contrast MRI of the jugular veins to assess blood flow. No significant differences were observed between cases and controls.[7] Also, magnetic resonance angiography was performed in the patients with MS only, and of these 21 cases, only 3 were found to have internal jugular vein stenoses.[7] Wattjes et al[8] reported a magnetic resonance venographic study of 20 patients with MS and 20 age- and sex-matched control subjects. Venous anomalies (ie, stenoses or occlusion) were found in 10 patients with MS and 8 healthy control subjects. There was no reflux identified in any patient with MS or control subject. Wattjes and colleagues concluded that venous anomalies are frequently seen in both patients with MS and healthy control subjects and

Table 3. Evidence-Based Categories of Recommendation of Treatments[a]

Level	Description
A	Good scientific evidence suggests that the benefits of the clinical service substantially outweigh the potential risks; clinicians should discuss the service with eligible patients
B	At least fair scientific evidence suggests that the benefits of the clinical service outweigh the potential risks; clinicians should discuss the service with eligible patients
C	At least fair scientific evidence suggests that there are benefits provided by the clinical service, but the balance between benefits and risks is too close for making general recommendations; clinicians need not offer it unless there are individual considerations
D	At least fair scientific evidence suggests that the risks of the clinical service outweigh potential benefits; clinicians should not routinely offer the service to asymptomatic patients
1[b]	Scientific evidence is lacking, of poor quality, or conflicting, such that the risk vs benefit balance cannot be assessed; clinicians should help patients understand the uncertainty surrounding the clinical service

[a] According to US Preventive Services Task Force guidelines.[27]
[b] Invasive treatments for chronic cerebrospinal venous insufficiency in multiple sclerosis meet level 1 criteria for recommendation.

that such anomalies are simply anatomical variants and not pathological.[8] These 3 independent investigations into CCSVI and MS not only cast doubt on whether CCSVI is the cause of MS, they call into question whether CCSVI exists at all.

CCSVI IN MS: ANALYSIS OF CAUSAL RELATIONSHIP

Zamboni and colleagues have postulated that CCSVI is a critical causal factor in MS and that reversal of the venous stenoses of CCSVI through invasive interventions can improve clinical outcomes in patients with MS. In addition to the methodological problems of the articles by Zamboni and colleagues, there are other analyses of this theory that fail to support its likelihood.

In 1965, Austin Bradford Hill[9] published detailed criteria for assessing scientific evidence of causation in biological systems. These 9 criteria, the so-called Bradford Hill criteria, are accepted guidelines to be used in the analysis of cause-and-effect relationships in medical science. Full consideration of the relationship between CCSVI and MS using the Bradford Hill criteria (**Table 2**) suggests that there is very little validated scientific evidence to support the theory that CCSVI is the cause of MS, especially among the criteria of biological plausibility, coherence, and analogy.

Biological Plausibility

Singh and Zamboni[10] have argued that CCSVI is etiologic to MS and that the biological mechanism of disease hinges on iron overload. The theory holds that impaired cerebrospinal venous hemodynamics lead to increase venous pressure and result in erythrocyte extravasation at the perivenular level and disruption of the blood-brain barrier. This red blood cell extravasation results in iron deposition within the brain parenchyma, which, it is postulated, leads to the inflammation and tissue injury seen in MS.[10] What is not controversial is the fact that patients with MS appear to have increased iron deposition in the brain as measured by MRI, most sensitively by susceptibility-weighted imaging sequences.[11,12] Whether this observed increase in iron in the central nervous system is etiologic to MS or alternatively is the result of MS is a fundamental and yet unanswered question in the debate of CCSVI and MS. Worthington et al[13] reported that cerebrospinal fluid ferritin (iron storage protein) levels were not elevated in MS but were significantly elevated in other diseases in which iron overload is etiologic to disease, such as superficial siderosis. Thus far, evidence linking CCSVI to iron overload is lacking.[14]

Moreover, in the consideration of the postulated etiologic role of CCSVI in MS, it is worth remembering that the existing studies are but radiological assessments. No histopathological investigation into these venous abnormalities has thus far been published. It is essential that the Doppler and venographic findings of Zamboni and colleagues be further evaluated in the pathology laboratory and that they be confirmed to cause true outflow abnormalities in patients with MS before theories of the role of CCSVI in MS can be seriously considered.

Furthermore, a fixed anatomical defect as seen in CCSVI would be unlikely to cause the relapsing-remitting disease course that is so common in the early stages of MS, and it is unlikely to be causally related to the geographical variations in MS prevalence.[15,16] It is also challenging to explain a decrease in disease activity during the second and third trimester of pregnancy[17] with CCSVI, as the intra-abdominal and intrathoracic pressures are increased during that time and reduce blood flow to the right heart. As such, evidence supporting the biological plausibility of CCSVI as the cause of MS is lacking.

Finally, MS has long been considered to be a disease of the immune system, and the evidence that the disease responds to immunomodulatory or immunosuppressive drugs is incontrovertible. The theory of CCSVI, which essentially represents a structural venous abnormality, does not easily fit into the well-accepted understanding of MS as a disease of the immune system.

Coherence

For a biological relationship to be causally associated, there must be coherence between the epidemiologic knowledge of the disease and the new association. Long-established dogma in MS epidemiology includes a female preponderance among those affected, a latitudinal prevalence gradient, and a decreased relapse rate among pregnant women.[17,18] There is also emerging evidence that risk factors for the development of MS include a history of mononucleosis,[19-21] vitamin D deficiency,[22] and high

titers of antibody against Epstein-Barr virus.[23-25] However, none of the accepted epidemiologic knowledge about MS has any clear connection with disorders of the cerebral venous system. As such, there is a lack of coherence between existing knowledge of MS and the newly proposed theory of CCSVI as the cause of MS.

Analogy

The Bradford Hill criterion of analogy is satisfied when examples of exposures and outcomes similar to the relationship in question exist in other biological systems. In this case, other conditions resulting in increased cerebral venous pressures would have to be similarly associated with MS or other central nervous system inflammatory conditions. Many disorders result in increased cerebral venous pressure, including venous sinus thrombosis, idiopathic intracranial hypertension, chronic obstructive pulmonary disease, and others, yet none of these conditions have any association with MS.[26]

INVASIVE TREATMENTS OF CCSVI IN MS

Since the publication of the PTA treatment trial of CCSVI in MS by Zamboni et al, invasive procedures such as angioplasty and stenting of the cerebrospinal veins have been performed on eager patients with MS by interventional radiologists in the United States and Europe, despite the lack of convincing evidence for the efficacy of such procedures and despite known risks associated therein. Because these inpatient treatments are not approved by the US Food and Drug Administration, patients with MS usually resort to paying for them. It is our opinion that such procedures should not be offered to patients with MS, not only because their efficacy is unproven and the procedures carry risk but also because it is not yet clear that CCSVI in MS exists at all based on the independent investigations into this question published in 2010 and 2011.[6-8] Furthermore, a simple evidence-based analysis of such treatments according to the US Preventive Services Task Force guidelines suggests that there is only level 1 evidence on which to recommend PTA for CCSVI in MS (**Table 3**). The level 1 category states that "evidence is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined."[27]

CONCLUSIONS

It is fair to conclude that the strong relationship between CCSVI and MS reported by Zamboni et al has yet to be verified, despite several completed studies by independent investigators, and that the published studies aimed to replicate the findings by Zamboni et al have shown significant variability in their results. Many more studies are currently under way, especially in the United States where the National Multiple Sclerosis Society has dedicated $2.2 million in research funding toward investigation into CCSVI.

There have been several position papers published in 2010 and 2011, some of which written by internationally recognized MS researchers, in which authors have expressed doubt about CCSVI in MS and urged caution among the MS scientific community in consideration of the theory.[26,28,29] Khan et al[26] took the most severe position by suggesting that "invasive endovascular procedures should be discouraged until there is conclusive evidence to justify their indication in MS," including such procedures in "research endeavors." We agree with Khan et al and submit further that invasive research investigations into treatment of CCSVI are inappropriate until the question of whether CCSVI exists in MS is settled.

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