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Letter to the Editor

Chronic Cerebrospinal Venous Insufficiency: A Failed Concept

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Dear Editor:

I appreciate the response and interest to our recent article regarding chronic cerebrospinal venous insufficiency (CCSVI) in multiple sclerosis (MS) a failed concept. Rasman has eloquently pointed out a number of important points of discussion surrounding the controversy behind the concept of CCSVI. The main point being the high degree of variability behind the diagnostic ultrasound (DU) criteria that define CCSVI and the inability of other investigators to replicate the data initially published by Zamboni et al. [1]. Zamboni et al. [1] reported that diagnosis of chronic cerebrospinal venous insufficiency required fulfillment of at least 2 of 5 ultrasound criteria: Reflux (71% vs. 0%), B-mode evidence of internal jugular vein stenosis (37% vs. 0%), absent flow detectable by doppler ultrasonography in the internal jugular or vertebral veins (52% vs. 3%) and reversed postural flow in the internal jugular vein (55% vs. 11%). When these criteria were applied in the evaluation of 109 patients with multiple sclerosis and 177 controls, each patient was deemed to meet at least 2 criteria, whereas none of the control participants did so. The sensitivity, specificity, and positive and negative predictive values for the proposed criteria were each 100%. To date, not one single published report has been remotely close in being able to reproduce these findings. The basic premise of defining a scientific concept is reproducibility of an observed finding. It is entirely surprising that the across numerous medical subspecialties, a set of observed criteria reported to have 100% sensitivity lacks a corroborating study. Only Zamboni and his associates are able to replicate CCSVI in MS patients. Numerous prominent groups across the globe, to a larger scale, have found no evidence of CCSVI in MS patients as defined by Zamboni's DU criteria and standards when sonographers and clinicians were double and triple blinded [2-12].

I believe there are two critical issues that cause the variability. The diagnostic criteria proposed for chronic cerebrospinal venous insufficiency are overly inclusive and nonspecific. As such up to 25% of normal individuals in certain studies met criteria for CCSVI [13]. More importantly, the reported Zamboni criteria has inherent pathophysiologic implausibility when used to define a causal relationship between CCSVI and MS. To break down individually, let's examine the technical and physiologic concerns regarding the criteria for reflux. For one, Barreto et al. [10] did not obtain spectral Doppler measurements of duration for reflux, a fundamental technique to determine presence of venous insufficiency. Furthermore, the 0.88-second threshold used to identify reflux in the internal jugular vein was not based on validated methodology. In normal venous physiology, retrograde flow in the internal jugular vein is observed in the valve near the confluence with the subclavian vein. In the study by Costello et al. [4], there was no evidence of large-volume reflux which approached the intracranial veins, rather non pathologic reflux of blood was limited to the level of the thyroid cartilage. Reflux in the internal jugular vein is non pathologic, and is frequently detected in up to 50% of normal individuals and in 40% of patients with MS.

The second criteria, venous 'stenosis' as defined by Zamboni et al. [1] was reported as a 50% reduction in the cross-sectional area of the internal jugular vein or a value

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less than or equal to 0.3 cm^2. In normal anatomy, the internal jugular vein is not a uniform structure. Its diameter continually changes from its origin and distally through its course intracranially. It may naturally narrow or widen at branching points. The diameter varies greatly with posture and central venous pressure (patient's volume status). As with any vein, it is highly compressible. Defining internal jugular vein stenosis as a 50% reduction in diameter in a highly fluctuating, and compressible environment is extremely difficult and cannot be standardized. The measurements would be entirely arbitrary. The report from which the 0.3 cm^2 cross sectional area is derived from indicated that up to 25% of normal individuals have diameters less than 0.4 cm^2, and measurements less than or equal to 0.3 cm^2 were observed without associated pathology [14]. Speaking from experience of having placed hundreds of central lines and vena caval filters under ultrasound guidance, and having observed significant variations in the compressibility of the vein under differing physiologic conditions such as congestive heart failure, hepatic compromise, renal failure, and volume depletion, the notion of defining internal jugular vein stenosis would be subjective without practical means for validation.

Detecting absence of flow in the internal jugular veins or the vertebral veins as a criteria also raises serious technical concerns. Zamboni et al. [1] reported that flow in the veins were examined by placing the probe longitudinally and transversely. Others have raised concerns about these methods which lends itself to criticisms regarding the Zamboni sonographers' ultrasound techniques and understanding of doppler physics [4]. Any time a structure is interrogated at perpendicular angles and approach 90°, the cosign dependent doppler signal will diminish toward zero. Evaluation of a vessel in transverse planes lends itself to false-positive impression absent flow.

Lastly let us examine the reversal of postural flow criteria. As alluded to before there is significant, naturally occurring variations in central venous flow, dependent upon an individual's volume status and cardiac status amongst other pathologic conditions such as hepatic insufficiency and renal disease. Zamboni's belief that a posture dependent flow variation in the jugular vein is a signifier of insufficiency and subsequent pathology is again an arbitrary conclusion. The observed variations in venous physiology can be recapitulated in normal individuals by adjusting their volume status.

In all, CCSVI in MS is a concept based on criterion without means for validation. It is why corroborative studies are not able to reproduce the same sensitivity for the association of CCSVI in MS patients. Randomized trials to better define the concept of CCSVI in MS maybe a good idea, but how does one propose to conceive a standardized reporting scheme of anatomic, structural, and flow variations of a normally dynamic environment that is naturally subject to arbitrary observations of pathophysiology? Although Rasman proposes that the three meta-analysis show association of CCSVI with MS [15-17], one should carefully examine these reports. Most importantly, one should be concerned to not assume association as being equivalent to causality. The Zwischenberger et al.'s [17] study that Rasman's cited purposefully excluded 3 studies that showed no correlation of CCSVI in MS and 4 studies were arbitrarily excluded to 'improve homogeneity' of the reporting. I raise serious concern about the methodology of this report and its inherent bias. Even so, the authors themselves conclude 'there was no evidence that CCSVI has a causative role in MS'. Similarly, Laupacis et al. [15] raised questions regarding the available studies they chose to analyze and concluded, 'poor reporting of the success of blinding and marked heterogeneity among the studies included in our review precluded definitive conclusions.' What can be concluded is that bias exists in the reports showing positive correlation between CCSVI in MS. The updated analysis by Tsivgoulis and associates that Rasman mentions never demonstrated correlation, but heterogeneity. What was shown is that correlation between CCSVI and MS is only demonstrated when reports published by investigators who are proponents of the endovascular treatment for CCSVI were selected and analyzed, a serious ethical bias that cannot be overlooked.

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