Chronic Cerebrospinal Venous Insufficiency in Multiple Sclerosis—A Medical, Sociological, and Media Controversy

Aaron Miller, MD, FAAN

Medical Director, Corinne Goldsmith Dickinson Center for Multiple Sclerosis and Professor of Neurology, Mount Sinai School of Medicine

Abstract

In 2009, Zamboni et al. coined the term "chronic cerebrospinal venous insufficiency" (CCSVI). On the basis of transcranial and extra-cranial color-coded Doppler ultrasonography, they operationally defined CCSVI as occurring when at least two out of five "abnormalities" were present. They claimed to find CCSVI in 100 % of 109 individuals with multiple sclerosis (MS) and in none of 177 healthy controls. Zamboni's group subsequently reported an uncontrolled treatment trial of cerebral venoplasty, which was termed the "liberation procedure", and claimed that the procedure benefited people with MS. The Zamboni reports were received with considerable skepticism, regarding both their biological plausibility and the claims of 100 % sensitivity, specificity, positive predictive value, and negative predictive value. No investigators have subsequently been able to replicate the Zamboni observations. Although some additional reports have indicated finding venous abnormalities in more MS patients than in other groups, most have either found no association of CCSVI with MS, or else have found substantial numbers of controls, either healthy or with other neurologic disease, to have the abnormalities. The original Zamboni reports were widely publicized in the mainstream media, especially in Canada, and sparked a raging controversy in the social media. Patients clamored for trials of cerebral venoplasty and others demanded its availability or traveled around the globe to undergo the procedure. The Canadian Institutes of Health Research have now solicited proposals for a Phase I/II clinical trial. At this point, additional scientific studies, including many funded by the National Multiple Sclerosis Society and the Multiple Sclerosis Society of Canada, are moving toward completion and will hopefully allow a proper judgment of the validity of the concept of CCSVI in relationship to MS. In the meantime, it is important that physicians remain respectful of patients' views, but that they are not reticent about expressing their own professional opinions based on available evidence, while emphasizing the importance of proper scientific research.

Keywords

Chronic cerebrospinal venous insufficiency, liberation procedure, cerebral venoplasty, multiple sclerosis, social media, Canadian Institutes of Health Research, National Multiple Sclerosis Society, Multiple Sclerosis Society of Canada

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Correspondence: Aaron Miller, MD, FAAN, Mount Sinai School of Medicine, 5 East 98th Street, 1st Floor, New York, NY 10029. E: aaron.miller@mssm.edu

Beginning with the publication of a paper by Paolo Zamboni in 2009[1] that claimed an association between a number of cerebral venous 'abnormalities' and multiple sclerosis (MS), the international MS community has been embroiled in a debate, unprecedented in scope and controversy. The original Zamboni paper defined 'chronic cerebrospinal venous insufficiency' (CCSVI) as the presence of two or more of five criteria they described as abnormalities of the venous system draining the brain and spinal cord based exclusively on examination by transcranial and extracranial color-coded Doppler examination.

The initial Zamboni study evaluated 109 MS patients and 177 healthy controls and the investigators reported the occurrence of CCSVI in every MS patient and in none of the controls. In other words, the authors claimed that the presence of CCSVI was 100 % sensitive, 100 % specific, and had 100 % positive predictive value and 100 % negative predictive value for MS. This paper was followed later in 2009 by a report by the Zamboni group of an uncontrolled treatment trial of cerebral venoplasty in 65 patients with MS.[2] The authors observed that patients receiving the intervention, which was termed 'liberation procedure', were significantly more likely to be relapse-free post-operatively than pre-operatively and to have fewer gadolinium enhanced lesions post-operatively. In addition the authors noted that, based on the multiple sclerosis functional composite (MSFC) score, the cohort improved at one year. The findings of the Zamboni group were subsequently catapulted to international attention by a series of reports in the mainstream media, especially in Canada. Understandably excited by the undeniable appeal of the prospect of obtaining dramatic improvement or even a 'cure' of their MS, patients around the world began to seek the procedure and

to demand it where it was not readily available, again particularly in Canada. The controversy and dialogue spread rapidly through the social media, with numerous reports of subjective symptomatic improvement by individuals with MS who had undergone the procedure.

Skepticism in the Scientific Community

The initial Zamboni reports were met with considerable skepticism by most of the MS scientific and professional community. Like any scientific observation, the validity of the CCSVI association with MS required confirmation. Soon after the initial publications, MS experts, as well as others, began to point out numerous flaws in the Zamboni methodology, as well as citing evidence that questioned the biologic plausibility of the CCSVI hypothesis. This initial incredulity was undoubtedly heightened by the claims of 100 % correspondence between CCSVI and MS, as rarely, if ever, do biologic phenomena occur in an all-or-none fashion. The critiques have noted that the normal human venous anatomy is highly variable and not well-defined and that the venous drainage of the brain is highly flexible and redundant, as well as posture-dependent. No previous descriptions of CCSVI have appeared; blockage of internal jugular veins (IJVs) has never before been associated with MS; and head and neck surgeons not uncommonly tie off either or both IJVs without deleterious effect. Furthermore, MS patients have neither clinical nor radiologic findings consistent with increased venous pressure.

From a methodologic perspective, critics have emphasized that the technician in the Zamboni study was unblinded and that the ultrasound procedure is very operator-dependent. In the treatment study, which was conducted at a single center, no control group with sham procedure was included and the study was non-randomized. Zamboni et al. themselves noted no benefit in patients with progressive disease and observed a 47 % restenosis rate in treated IJVs.

No Replication of Zamboni Results

What about attempts to replicate the Zamboni observations and to investigate the possibility of venous abnormalities in MS patients through methodologies other than ultrasound alone? To date, no published series has even approached the Zamboni results in terms of sensitivity or specificity. In the largest series reported to date, including 499 subjects (289 with MS), Zivadinov et al found evidence for CCSVI in 56.1 % of MS patients and only 38.1 % of subjects with clinically isolated syndrome, compared to an occurrence in 22.7 % of healthy control subjects and 42.5 % of those with other neurologic diseases.[3] Additional small ultrasound series by Doepp et al.,[4] Sundström et al.,[5] and Wattjes et al.[6] failed to find any support for the Zamboni hypothesis. In a subsequent study using magnetic resonance venography Doepp et al., also failed to substantiate CCSVI.[7] Nonetheless, a recent meta-analysis by Laupacis et al.[8] found that the published data did suggest the possibility of an association between CCSVI and MS. However, the authors emphasized that no definitive conclusions could be drawn because the cited studies were too heterogenous in their inclusion criteria and methodology and they lacked adequate blinding. Subsequent to the publication of the meta-analysis, among numerous additional presentations at the large international meeting of the European Committee for Treatment and Research in Multiple Sclerosis/Americas Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS/ACTRIMS) in Amsterdam in October 2011, nearly all failed to provide support for venous insufficiency in MS.

The skepticism of the scientific community about CCSVI, juxtaposed to the relentless clamor of the MS patient community for trials of CCSVI (or even to make the procedure generally available), has created an inevitable tension and a conundrum for funding agencies. In 2010, the National Multiple Sclerosis Society, along with the Multiple Sclerosis Society of Canada, reached the conclusion that the CCSVI hypothesis required further investigation, and committed $2.4 million to fund seven North American studies aimed at replicating the Zamboni findings, as well as exploring other ways to elucidate the status of the venous system in people with MS, and also to look at people at early stages of MS (or even children) who would be expected to be affected if CCSVI plays a causative role in MS. In addition, the Italian MS Society also funded a large ultrasound study, whose preliminary results presented in Amsterdam in October 2011 failed to substantiate the Zamboni claims.

Canadian Institutes of Health Research Announcement of Phase I/II Trials

Despite the reservations of much of the MS professional community, yet facing continuing political pressure, the Canadian Institutes of Health Research (CIHR) announced on November 25, 2011 that it would issue a request for proposals (RFP) for a Phase I/II clinical trial of cerebral venoplasty in MS.[9] The announcement was made despite an earlier statement by Alain Beaudet, President of the CIHR in August 2010, following a meeting of a multidisciplinary scientific working group on CCSVI, that noted: "In the absence of clear and convincing evidence for CCSVI, the performance of an interventional venoplasty trial with its attendant risk to MS patients is not appropriate at this time. It is unlikely that a proposal… would pass a peer review panel because evidence that CCSVI exists is currently lacking. Similarly there are serious ethical issues associated with doing such a trial given the lack of convincing evidence for CCSVI." It is difficult to understand from a purely scientific perspective the justification for undertaking a therapeutic trial at this time in view of the fact that the preponderance of evidence that has emerged since the August 2010 statement has been negative. The CIHR can muster some support for its position, from the Laupacis meta-analysis,[8] requested by the Institute, which found "a markedly higher prevalence of CCSVI in MS patients compared to HC [healthy controls] that was statistically significant, even when a 'conservative' analysis was conducted", albeit noting that "the results do not allow definitive conclusions to be reached." The announcement of the RFP, undoubtedly influenced by intense patient and political pressure in Canada, is tempered by its final statement emphasizing that any such proposed trial will have to pass scrutiny of institutional review boards whose approval seems far from certain at this time.

Significance of Canadian Institutes of Health Research Announcement in Public Domain

One thing is certain, however. That is the clear recognition that CCSVI has been a medical/sociologic phenomenon of immense magnitude in the MS patient and professional community. A variety of factors coalesced to create the "perfect storm". A patient population with a (potentially) serious illness existed and those affected, already often

distrusting the pharmaceutical industry, were naturally attracted to the possibility of a quick (and simple) fix rather than the long-term use of unpleasant (and often ineffective) drugs. The concept of CCSVI had been published in a respected peer-reviewed paper and followed by a report of "successful" therapy, which was given the politically-charged name "liberation procedure". Furthermore, the paper's principal author's own wife has MS. The fires were fanned by the promulgation of the story by the mainstream media in print, television, and the Internet. The ease and rapidity of unfiltered communication through social media threw oil on the fire. Finally, the unavailability of the venoplasty procedure in some venues, as well as perceived initial insensitivity of MS Societies, fostered continued protest and demands.

As the CCSVI controversy continues, hopefully to be resolved with the time-tested methods of appropriate scientific investigation, how should physicians respond to patient inquiries and sometimes to their demands to undergo venoplasty? Physicians should always be respectful of patient's views, but should not be reluctant to offer their professional opinion based on a thoughtful consideration of available evidence. This can dovetail with a discussion that emphasizes the importance of proper scientific research. The physician must always respect patient autonomy, avoid acting judgmentally, and emphasize that he or she will always be available to offer the patient continued care and support.

However the CCSVI story plays out, as it inevitably will, scientists, physicians, and patients should seek to benefit from what it teaches us. These lessons include recognizing the importance of empathy for those affected by serious illness, understanding the enormous power and speed of the social media, and comprehending the delicate balance between patient desire and the need for scientific rigor that will enable the utilization of relatively scarce financial resources in a way that maximizes patient safety while providing the best opportunity to understand and ultimately treat human disease. ■

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