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

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Abstract

In 2009, Zamboni et al. coined the term "chronic cerebrospinal venous insufficiency" (CCSVI). On the basis of transcranial and extra-cranial colour-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 neurological disease, to have the abnormalities. The original Zamboni reports were widely publicised in the mainstream media, especially in Canada and sparked a raging controversy in the social media. Patients clamoured for trials of cerebral venoplasty and others demanded its availability or travelled 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 relation 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 emphasising 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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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 colour-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 biological 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 biological 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 radiological findings consistent with increased venous pressure.

From a methodological perspective, critics have emphasised 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 centre, no control group with sham procedure was included and the study was non-randomised. 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 neurological 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 emphasised 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 clamour 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 US$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 emphasising 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/sociological 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 emphasises the importance of proper scientific research. The physician must always respect patient autonomy, avoid acting judgmentally and emphasise 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 recognising 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 rigour that will enable the utilisation of relatively scarce financial resources in a way that maximises patient safety while providing the best opportunity to understand and ultimately treat human disease. ■

1. Zamboni P, Galeotti R, Menegatti E, et al., Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis, *J Neurol Neurosurg Psych*, 2009;80:392–9.
2. Zamboni P, Galeotti R, Menegatti E, et al., A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency, *J Vasc Surg*, 2009;50:1348–58.
3. Zivadinov R, Marr K, Cutter G, et al., Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS, *Neurology*, 2011;77(21):e124–6.
4. Doepp F, Paul F, Valdueza JM, et al., No cerebrocervical venous congestion in patients with multiple sclerosis, *Ann Neurol*, 2010;68:173–83.
5. Sundström P, Wåhlin A, Ambarki K, et al., Venous and cerebrospinal fluid flow in multiple sclerosis: A case-control study, *Ann Neurol*, 2010;68:255–9.
6. Wattjes MP, van Oosten BW, de Graaf WL, et al., No association of abnormal cranial venous drainage with multiple sclerosis: a magnetic resonance venography and flow-quantification study, *J Neurol Neurosurg Psych*, 2011;82:429–35.
7. Doepp F, Wurfel JT, Pfueller CF, et al., Venous drainage in multiple sclerosis: A combined MRI and ultrasound study, *Neurology*, 2011;77(19):1745–51.
8. Laupacis A, Lillie E, Straus, et al., Association between chronic cerebrospinal venous insufficiency: a meta-analysis, *CMAJ*, 2011;183(16):e1203–12.
9. Canadian Institutes of Health Research, The Government of Canada launches a request for research proposals for clinical trial on Chronic Cerebrospinal Venous Insufficiency and MS. Available at www.cihr.ca/e/44561.html (accessed November 27, 2011).

Moving Towards the Pan-European Unification of MS Nurses

emsp
european multiple sclerosis platform aisbl

Nurses play a critical role in MS patient care; however, outcomes of the Multiple Sclerosis-Nurse Empowering EDucation (MS-NEED): European Survey show disparities in nursing standards across Europe. To avoid inequalities in patient care, it is important to recognise nursing in MS as a speciality within Europe, to standardise and benchmark training, and to share best practice.

First and Only European CME Accredited MS Nurse Training Curriculum – Coming Soon!

Objectives:

- **Increase** MS Nurses' competency in patient and family advocacy and brokerage, health education, symptom and treatment management, and develop leadership skills for the advancement of patient care
- **Engage** all MS Nurses – but with an initial focus on those starting their career in MS Nursing and who may not have access to vocational training

Content Overview – Key Modules:

1. Understanding MS
2. Clinical Presentation
3. Diagnosing MS
4. Treating MS
5. Caring and Supporting MS Patients

Next Steps:

- Pilot testing taking place in Malta (May 2012) and Spain (June 2012)
- Launch in English / Spanish: Q4 2012 (NB: Additional language launches scheduled)

Setting the Standard - MS Nurse White Paper

OBJECTIVES

- **Drive awareness** and understanding of the MS Nurse role in Europe to improve patient access to care and optimise their quality of life
- **Articulate** the benefits of the MS nurse role to stakeholders to conserve and protect their posts

CONTENT OVERVIEW

- Why is MS Nursing necessary? What is an MS Nurse?
- What are the advantages of MS nursing for nurses, people with MS, their families and neurologists?
- Current challenges faced by MS Nurses
- MS Nursing in Europe
- The potential of MS Nursing

NEXT STEPS

- Co-ordination of review and feedback on White Paper by key nurse advocates across Europe
- Secure endorsement from key professional medical bodies across Europe

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In cooperation with:

RIMS rehabilitation in multiple sclerosis european network of ms centres

IOMSN International Organization of Multiple Sclerosis Nurses

Multiple Sclerosis-Nurse Empowering EDucation (MS-NEED): European Survey is led by the European MS Platform (EMSP) in cooperation with the International Organization of MS Nurses (IOMSN) and Rehabilitation in MS (RIMS).