

Multiple Sclerosis and Chronic Cerebrospinal Venous Insufficiency

Information Sheet

What is Chronic Cerebrospinal Venous Insufficiency?

Chronic Cerebrospinal Venous Insufficiency (CCSVI) is a term coined by Dr. Paolo Zamboni to describe a reduced flow of blood in veins draining the brain and spinal cord. According to Dr. Zamboni, CCSVI is the result of an abnormal variation of extracranial venous anatomy, and is the cause of Multiple Sclerosis (MS).

Is CCSVI linked to Multiple Sclerosis?

There is currently no clear evidence of a link between CCSVI and MS.

In April 2009, Dr. Zamboni's group reported¹ that 100% of MS patients have internal jugular or azygos venous abnormalities, and 0% of normal healthy controls show CCSVI. This study suggested that CCSVI might be the underlying cause of MS.

Since then, several additional studies on this topic have been published and/or presented at international conferences. Conflicting results as to whether CCSVI exists and whether it is associated with MS have emerged from these studies.

Several recent studies have also demonstrated a wide variation in the patterns of venous drainage of the brain in both MS patients and people with no evidence of MS (controls), underlining the difficulty involved in concluding that a vein that is 'narrowed or blocked' will cause MS.

A synthesis review" on the CCSVI/MS issue was recently published in the Canadian Medical Association Journal by Dr. Laupacis and his collaborators. It suggests a statistically significant association between the CCSVI condition and MS. However, as the large variation in the results do not allow definitive conclusions to be drawn, the authors consider that more high-quality studies are needed to determine definitively whether CCSVI is more frequent in individuals with MS as compared to those without MS.

What is currently being done to research Zamboni's claim?

The MS Society of Canada and the National MS Society (USA) launched in 2010 an initiative to support seven studies that are currently looking at the question of whether CCSVI is linked to MS. These studies propose rigorous protocols (e.g., blinded experiments as opposed to the un-blinded pilot study of Dr. Zamboni) and resort to a variety of imaging techniques to provide solid evidence to answer this question.

To monitor the results from these studies, as well as from related studies from around the world on venous anatomy and MS, the Canadian Institutes of Health Research (CIHR) set up a Scientific Expert Working Group in July 2010. This group is made up of the principal investigators of the seven MS Society-sponsored studies, of the scientific leadership from CIHR and the US, Canadian and Italian MS Societies, and of a representative from the provinces and territories.

What is the treatment for CCSVI and is it safe?

In 2009, Dr Paolo Zamboni proposed a new surgical procedure to treat MS. This procedure consists in opening narrowed veins through the insertion of a balloon inside the vessels, a medical intervention referred to as venous angioplasty. In some procedures, a stent is also used to keep veins from closing up.

Angioplasty and stenting have been used in clinics in India, Costa-Rica, Bulgaria, Poland and elsewhere to treat CCSVI.

Arterial angioplasty and the insertion of stents into certain arteries are established medical procedures. However, venous angioplasty is rarely used because the incidence of re-stenosis is so high. The prevailing medical opinion is that while "balloon angioplasty" for veins may be relatively safe, it is difficult to justify the procedure as the veins eventually will re-stenose. In addition, there is a distinct possibility that the damage to the inner lining of a vein can increase the risk of thrombosis of that vein and **can** cause pulmonary embolus.

Venous stent placement usually requires the use of blood thinners, which can lead to complications, such as internal bleeding. Potentially fatal outcomes due to the migration of a venous stent into the heart have also been reported.

There are increasing reports of complications related to the CCSVI treatments offered abroad," and many national and international MS associations advise MS patients against these treatments.

Experts around the world recommend moving cautiously with a Phase I/II clinical trial on the safety and efficacy of the procedure proposed by Dr. Zamboni. For instance, a recent systematic literature review conducted by Dr. Laupacis and his collaborators on the CCSVI issue concluded that "serious medium to long-term complications after endovascular therapy have been reported, such as stent migration, serious hemorrhage, pulmonary embolism, thrombosis of the internal jugular vein requiring thrombectomy, and death. More studies of long-term follow-up after endovascular therapy are needed"

In January 2012, a scientific committee, who reviewed the clinical trial proposal submitted by Dr. Zamboni to the Italian MS Society, concluded that "a randomized, sham-controlled clinical trial in a large number of subjects would be premature until stronger evidence of a causative association of CCSVI to MS, or stronger evidence of a treatment effect of venoplasty (...) are available". This expert committee noted that venoplasty is an invasive procedure with non-negligible risks of adverse events. The committee unanimously agreed that in light of safety concerns, there is a need for high-quality clinical trials to establish safety and obtain preliminary evidence of efficacy in a relatively small number of patients.

What is currently being done in Canada to evaluate the safety and efficacy of the procedure proposed by Dr. Zamboni?

Based on scientific evidence, the Scientific Expert Working Group set up by CIHR recommended on June 28, 2011 the establishment of a Phase I/II clinical trial on CCSVI. The Minister of Health announced on June 29, 2011 that the Government of Canada would support this trial and asked CIHR to develop its terms of reference.

On November 30, 2011, CIHR released, in partnership with the Canadian MS Society, a request **for** research applications for a Phase I/II clinical trial. This study will allow us to better understand the procedure proposed by Dr. Zamboni to treat MS.

The applications received will undergo a rigorous and international review process to select **the** researcher team that will conduct the Phase I/II clinical trial. This process will be completed by mid-April 2012.

The selected team of researchers will recruit patients once they have received approval on their research protocol by their Institutional Ethics Review Board.

Through the Public Health Agency of Canada, the Government of Canada is also supporting the development of a new Canadian MS Monitoring System. This system developed by the Canadian Institute for Health Information in close collaboration with the Canadian Network of MS Clinics and the MS Society of Canada will increase our understanding of MS patterns in Canada and will provide information on disability, treatments, health outcomes, and quality of life. The monitoring system will be able to track

Canadians with MS who have chosen to have the procedure proposed by Dr. Zamboni abroad and monitor MS symptom changes over time and any complications.

Why a Phase I/II clinical trial and can MS patients participate in this trial?

In the Phase I of the trial, a small group of MS patients will be selected to evaluate the safety of the procedure proposed by Dr. Zamboni. The Phase II of the trial will then assess the efficacy of the intervention, as well as continue safety assessment in a larger group of MS patients.

What are the recommendations of Canadian health associations with respect to the CCSVI treatments offered abroad?

The Canadian Medical Association, the Association of Faculties of Medicine of Canada, and the Canadian Society for Vascular Surgery concur with CIHR's position on the need for an evidence-based approach to determine whether there is a link between CCSVI and MS. These associations are of the opinion that clinical trials on the safety and efficacy of angioplasty and/or stenting of the extracranial veins should be conducted, only if and when a link between CCSVI and MS can be clearly established.

Some professional associations such as the College des medecins du Quebec are recommending that MS patients "refrain from consulting any medical tourism clinics offering these treatments prematurely with little regard for their effectiveness and side effects." The College des medecins du Quebec is also of the opinion that should MS patients participate in controlled studies on venous angioplasty, such studies should be approved by a research ethics committee.

What follow-up is recommended for patients who chose to go abroad for Zamboni's procedure?

MS patients who have received a venous procedure abroad should be reassured that they will continue to be cared for by their physicians and/or regular MS specialists as any other patients.

The Ministry of Health and Long-Term Care for Ontario has produced guidelines to primary care providers in regard to follow-up care of patients who undergo the procedure abroad. These guidelines are available at http://www.health.gov.on.ca/en/public/publications/ministry_reports/ms_ccvsi/ms_ccvsi.aspx#.

Some provincial Health Associations such as the College des medecins du Quebec, l'Association des radiologistes du Quebec and l'Association des neurologues du Quebec have also issued a set of recommendations regarding follow-up for these patients (available at http://www.cmq.org/en/MedecinsMembres/Profil/Commun/AProposOrdre/~media/6ED37CAF460D4E5BAEA98FBB319F3376.ashx?sc_lang=en&41127).

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' Zamboni, P., Galeotti, R., Menegatti, E., Malagoni, A.M., Tacconi, G., Dall'Ara, S., Bartolomei, I., and Salvi F. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis.. *J Neurol Neurosurg Psychiatry*. April 2009. Vol 80(4):392-399.

" Laupacis, A, Lillie, E., Dueck. A., Straus. S., Perrier, L., Burton. J., Aviv, R., Thorpe, K., Feasby. T.. and Spears. J. Association between chronic cerebrospinal venous insufficiency and multiple sclerosis: a meta-analysis. *Canadian Medical Association Journal*. November 8. 2011. Vol 183(16): 1203-1212.

''' Dome, H., Zaidat, O. O., Fiorella, D., Hirsh, J., Prestigiacomo, C, Albuquerque, F., and Tarr, R. W. Chronic cerebrospinal venous insufficiency and the doubtful promise of an endovascular treatment for multiple sclerosis. *J. NeuroIntervent. Surg*. December 2010. Vol 2(4):309-311.