



multiple sclerosis
international federation

Multiple Sclerosis International Federation (MSIF) Statement

Chronic Cerebrospinal Venous Insufficiency (CCSVI)

24 May 2010

Introduction

Recent preliminary studies have suggested that a phenomenon called Chronic Cerebrospinal Venous Insufficiency (CCSVI), a reported abnormality in blood drainage from the brain and spinal cord, may contribute to nervous system damage in MS.

This hypothesis has been put forth by Dr. Paolo Zamboni from the University of Ferrara in Italy. Based on the results of his initial preliminary findings published in June 2009 from a study of approximately 65 patients, Dr. Zamboni and colleagues state that this pilot study warrants a larger and better controlled study to definitively evaluate the possible impact of CCSVI on the disease process in MS.

MSIF's *Principles for the Promotion of the Quality of Life*ⁱ include that "People with MS must be empowered to take control of the decisions affecting their lives and to self-manage the disease as much as possible. To encourage the highest possible degree of self management, they should be able to access a broad range of information, advice, and education regarding the nature of MS, its treatment, and methods for improving QOL".

The risks and benefits of procedures to treat CCSVI have not been established by properly controlled clinical trials. Unless and until strong supportive evidence is produced, and until the risks of treatment are thoroughly assessed, any procedures to mechanically correct the purported problem outside of a clinical trial are not recommended.

MSIF will continue to facilitate an open exchange of information amongst its members in relation to the research that is being undertaken. Several MS societies are promoting further research in CCSVI as a matter of urgency in order to evaluate the hypothesis of a link with MS, and what could be the short and long term benefits and risks of treatment.

Question 1 (Q): What is CCSVI?

Answer (A): Chronic cerebrospinal venous insufficiency is a reported abnormality caused by narrowing of the veins which drain oxygen depleted blood from the brain and spinal cord. It is theorised that the slowed draining of blood can cause reflux back into the brain and spine, leading to a lack of oxygen in the brain and iron deposition in the tissue.

Q 2: What is the connection between CCSVI and MS?

A: A recent study by Zamboni et al on 65 people with different types of MS (published in J Neurology Neurosurgery Psychiatry. 2009 Apr; 80 (4): 392-9. Epub. 2008 Dec 5.), compared with 235 people who were healthy or had other neurological disorders, reported abnormal venous flow in 100% of MS cases and in none of the people without MS. Venous drainage of the brain and spinal cord was examined using an ultrasound technique (Doppler). The researchers also noted that patterns of venous obstruction differed between people at different stages and courses of MS although there was no clear relationship between severity of MS and extent of venous obstruction. The treatment status of the people with MS did not appear to influence whether they showed signs of CCSVI.

A further study from the same group in Italy (Journal of Vascular Surgery, 2009 Dec 50:1348-58) looked at the effects on MS of improving venous blood flow by a technique called balloon dilation. This open-label study (not blinded or controlled – see Q3 below) evaluated the safety and preliminary outcomes of vascular surgery in 65 people with MS who had previously been diagnosed with CCSVI (35 individuals with relapsing-remitting MS, 20 with secondary-progressive MS, and 10 with primary-progressive MS). Some positive impacts were reported including a reduction in new brain lesions on MRI scans and reduction in the number of relapses experienced by some of the participants in the trial.

However, results were confounded by a number of factors including; restenosis in 47% of cases (meaning that internal jugular veins went back to having restricted blood flow after the procedure), inconsistency in the timing and type of MRI scans taken and the fact that participants remained on their Disease Modifying Treatments during the study period.

These are all major factors that need to be considered when data from the study is interpreted. Researchers conducting the study reported that further trials will need to be conducted to measure the benefits and risks of balloon dilation in people with MS.

Q 3: Why are blinded controlled trials important?

A: In controlled trials, “blinding” of participants and researchers as well as the use of a comparative control group are considered essential to ensure that the hopes and expectations of the participants and the researchers do not influence the assessment of the trial outcomes or the interpretation of the results. So far, none of the procedures conducted to correct CCSVI have been done in the context of a controlled trial.

Q 4: What does the latest CCSVI research show?

A: Preliminary results from a large ongoing Combined Transcranial and Extracranial Venous Doppler Evaluation study at the University at Buffalo

Medical Center aimed at investigating if CCSVI is associated with MS, were released on February 10, 2010. Doppler scan results were reported on five specific criteria that affect venous blood flow. Patients who met at least two of the criteria were considered to have CCSVI. 289 of the 500 patients enrolled had MS. Of these, at least 56 percent of the MS cohort met the criteria for CCSVI. The same was true for at least 22 percent of the 163 healthy controls and at least 42 percent of people with other neurological conditions. The results were substantially different from those reported by Dr Zamboni and suggest impaired venous flow is not specific for MS. The researchers concluded that further blinded studies are needed to determine the prevalence and significance of CCSVI in MS. A second stage of the study will involve screening a further 500 participants using more advanced screening methods.

Q 5: What further research is being undertaken into CCSVI?

A: MS Societies that fund MS research are interested in pursuing all promising avenues of MS research. In December 2009, the MS societies of Canada and USA issued an expedited international request for proposals on CCSVI and MS. Proposals were received from seven countries and final decisions will be announced on 14 June with projects anticipated to start on 1 July 2010. An international review panel of MS and vascular experts has been convened in cooperation with these MS Societies to ensure an expedited, coordinated response.

Several MS Societies, including those in Canada, Italy, Netherlands, United Kingdom and USA will also consider funding projects on CCSVI through their normal funding process. The Steering Committee of the Italian MS Foundation (FISM) will evaluate proposals on CCSVI that have been submitted through their annual call for projects in March. In addition, FISM is promoting an epidemiological study to confirm and extend Dr. Zamboni's findings by evaluating the prevalence of CCSVI in healthy controls, MS and other neurodegenerative diseases, other inflammatory diseases of the central nervous system and other systemic autoimmune diseases. This study plans to enroll 1690 subjects and will involve 15 clinical centres. FISM is also participating in a randomized controlled trial to evaluate the short and long term efficacy and risks of the venous dilation procedure on disease progression and symptoms. Both studies are likely to start in the second half of 2010.

The MS Society of Canada has also called on its government to make extra research funding available to speed up research on CCSVI.

Q 6: Does CCSVI cause MS?

A: At this point there is not enough evidence to draw conclusions on CCSVI and MS. Based on what has been published to date, we can only say that in some people MS may occur in association with impaired venous drainage of the central nervous system. However this phenomenon has also been observed in people who do not have MS.

There is not enough evidence to determine whether obstruction of veins causes MS, or is caused by MS, or even to determine when this obstruction may occur in the course of disease.

Q 7: How has CCSVI been treated?

A: Surgical procedures for CCSVI in MS have used balloon dilation to open up obstructed veins or insertion of stents into veins to help keep them open (endovascular surgery). These procedures have been performed on only a small number of MS patients.

Q 8: What is known about the risks involved in this treatment?

A: No studies testing the safety and effectiveness of treatments for CCSVI have reported detailed safety findings to date. Procedures involving stenting or balloon dilation of the jugular and Azygous veins for the treatment of CCSVI are of unknown safety.

It is known, however, that endovascular procedures, like any procedures, do carry risks. Balloon angioplasty and stenting both carry a small risk of elastic recoil, rupture of the vein and blood clots. The rates of restenosis (re-narrowing) are also high. Stenting carries additional risks because it requires that the patient takes anticoagulant drugs which could lead to bleeding and also because there is the possibility that the stent could come loose and migrate towards the heart.

This does not mean that these procedures would not be considered as a potential treatment in the future if further research proves that they are safe and effective at treating MS. At present treatments for CCSVI remain unproven and it is prudent that any such procedures only be performed as part of properly regulated controlled clinical trials, especially in light of adverse events reported to date.

Reports of CCSVI surgical procedures involving stents resulting in adverse events in persons with MS include one reported death. According to the Annals of Neurology, the person died of a haemorrhage in the brain while taking a blood thinner (anti-coagulant), which is commonly prescribed when stents are inserted into blood vessels. In another individual, a stent dislodged and moved to the heart, requiring emergency open heart surgery to remove the device. MS endovascular surgery was halted at Stanford University after these two adverse events occurred.

Q 9: Will the treatment of CCSVI be useful for the various forms of MS?

A: As research on this question is at a very early stage, it is currently unknown whether this type of treatment will be useful in any form of MS. More research is looking at possible links between CCSVI and MS, and/or its effects on MS symptoms and clinical studies on the effects of CCSVI treatment on MS are needed before it will be considered for approval in treating people with MS.

Dr. Zamboni has suggested that if further evidence supports the link between MS and CCSVI, its treatment may ultimately add to the arsenal of therapies available for MS. He emphasized the need for more research on his hypothesis,

and noted that it is still not proven whether CCSVI is a cause of MS or related to MS in some other manner. Dr. Zamboni also noted that people with MS should remain on their immunomodulatory therapies.

Q 10: Should I have treatment?

A: The risks and benefits of procedures to treat CCSVI have not been established by properly controlled clinical trials. Unless and until strong supportive evidence is produced, and until the risks of treatment are thoroughly assessed, any procedures to mechanically correct the purported problem outside of a clinical trial are not recommended.

ⁱ Article 1.5

http://www.msif.org/en/resources/msif_resources/msif_publications/quality_of_life_principles/principles_to_promote_the_quality_of_life/10_independence.html