Patient summary

Systematic reviews of the evidence regarding chronic cerebral spinal venous insufficiency (CCSVI) and multiple sclerosis

November 21, 2011 Report to the Canadian Institutes of Health Research from the Canadian CCSVI Systematic Review Group

Why did we write this report?

In November 2009, Dr. Paolo Zamboni reported that all multiple sclerosis (MS) patients had abnormalities in the veins in their neck or chest that could be diagnosed using ultrasound. He called these abnormalities *chronic cerebrospinal venous insufficiency* (CCSVI). He found no CCSVI in people who did not have MS, and suggested that CCSVI was a cause of MS.

Dr. Zamboni has also suggested that treating a narrowing or stenosis in one or more neck vein improves the symptoms of people with relapsing-remitting MS. This is usually done by blowing up a balloon within the narrowing, or less frequently by inserting a stent. In our report, we call these treatments "endovascular therapy".

Dr. Zamboni's findings have been controversial. Experts in many fields of medicine and research caution that it is almost unheard of to have a risk factor that occurs in 100% of people with a disease and 0% of people without a disease. Concerns have also been raised about the quality of Dr. Zamboni's treatment study because, among other criticisms, he did not report on a comparison "control" group of MS patients who did not undergo endovascular therapy. Dr. Zamboni himself has called for randomized trials of endovascular therapy in order to better understand the benefits and harms of the treatment.

In December 2010, the Canadian Institutes of Health Research (CIHR) indicated that they wanted an independent group of researchers to regularly update the scientific literature about CCSVI and MS. They invited interested groups to apply for a grant to do this, and our group was awarded that grant. We presented our first report to the CIHR in late June 2011, and indicated that we would update the report about every 4 months with the results of newly published studies. This report is the first update, and includes studies published since June 2011.

What did we do?

This study is an update of the systematic review that was presented to the Canadian Institutes of Health Research in June, 2011 (http://www.stmichaelshospital.com/pdf/research/CIHR-final-report-CCSVI.pdf). We examined all peer reviewed papers related to CCSVI and MS, focusing particularly on the methods of diagnosing CCSVI, whether CCSVI was found to be more common in people with MS than those without MS, and what is known about the benefits and harms of treating MS patients with endovascular therapy. When a paper is "peer reviewed" it has been carefully reviewed by several specialists in a

variety of fields who do not work with the authors of the paper (in this case; experts in MS, statistics, ultrasound, vascular surgery, radiology, medicine and others) in order to detect any problems such as inappropriate analyses or methods, or conflicts of interest. In order to be included in our review, each paper had to meet a minimum scientific quality standard.

Why did we only look at peer-reviewed publications?

Although peer review doesn't guarantee high quality science, it does increase the chances that a study is of good quality. These papers also provide much more detail about the study than do "abstracts" that are presented at meetings.

Why is it important to highlight articles that meet a certain quality standard?

Poor quality science can produce information that is misleading, incomplete or wrong, and can expose people to harm.

What did we find?

Is CCSVI found more often in people with MS than in people without MS?

- Since the publication of our meta-analysis in the Canadian Medical Association Journal which looked at whether CCSVI is more common in people with MS than those without MS, 2 new studies have been published. Given that both studied a small number of patients, it is not surprising that the results of the initial meta-analysis did not change much with the addition of these 2 new studies. In total, 9 studies with a total of 1262 participants diagnosed CCSVI with an ultrasound test, and *compared people with MS with healthy people*. When the information from all of the studies was combined, CCSVI was nearly 13 times more likely to be found in people with MS than in healthy people.

- However, there was a large difference in results between the studies. Some studies found a much lower frequency of CCSVI than other studies. Some studies found no difference in the frequency of CCSVI in people with MS compared with healthy people, while others found a large difference. It is unusual to find such a large variation in results among studies, and the reason for these differences is not clear. Therefore, the overall finding of the meta-analysis that CCSVI is more common in people with MS than in healthy people needs to be viewed with caution.

- When Zamboni's study was removed from the analysis and the remaining 8 studies were combined (given that it is common for the initial description of a new entity in medicine to find much more dramatic results than studies that are completed afterward by others), CCSVI was found to be 4 times more frequent in people with MS than in healthy people.

- In total, we found 5 studies with 610 participants that diagnosed CCSVI with ultrasound and *compared people with MS to people with other neurological diseases.* Although CCSVI was found more frequently in people with MS compared with people with other neurological diseases, this difference was not statistically significant, and could therefore have occurred by chance. Removal of Zamboni's study did not change this result.

Diagnosis of CCSVI with ultrasonography

- Ultrasound tests are very dependent upon the person who is doing the ultrasound. For example, the result can be affected by how much pressure is put on the neck with the ultrasound probe, the position the patient is scanned in, and the experience of the person doing the ultrasound. It is possible that the difference in results among the studies mentioned in the previous section is because the people doing the ultrasound sometimes knew whether the person they were examining had MS or not, thus accidentally influencing their interpretation or reading of the results. For example, those reading the ultrasound might be more likely to say that a borderline abnormality is definitely abnormal if they know the person has MS than if they know the person does not have MS.

- A recent study of over 700 MS patients that was conducted in 5 Italian and 1 Canadian centre found a large variation in the frequency with which the various CCSVI parameters were positive. This occurred even though the ultrasound personnel were trained by Dr. Zamboni, suggesting that more work needs to be done to standardize the method of diagnosing CCSVI.

- A large Italian study looking at the frequency of CCSVI in people with and without MS is underway. They are studying 1200 people with MS: 400 healthy people and 400 people with other neurological diseases. This will be by far the largest study of the ultrasound diagnosis of CCSVI. The results of this study, as well as the results of other on-going studies, will be very informative.

Benefits of endovascular therapy for MS

- We believe that only randomized trials in which patients with MS are randomly allocated to undergo endovascular therapy or a control therapy, provide good evidence about the benefits of treatment.

    - Zamboni recently published a study of 15 patients in which half received endovascular treatment when they entered the study and half received endovascular therapy six months later. The study was not truly randomized, and given the small number of patients, it is not possible to reliably comment on the benefits of endovascular treatment from this study.
    - Four studies have followed patients after endovascular therapy using a variety of quality of life, functional and x-ray outcomes. Each reported benefits from the therapy. However, because they were not randomized studies and did not study a control group, it is not possible to reliably comment on the benefits of endovascular therapy on the basis of these studies.

Harms of endovascular therapy

    - Six studies reported about the type and frequency of complications at the time of endovascular therapy in a total of 1148 patients. There were no deaths, and serious side effects occurred in less than 2% of patients. The most frequent serious side-effect was a heart rhythm disorder during the procedure, which occurred in between 1-2% of

patients. Some of these required admission to hospital, and in one instance admission to an intensive care unit.

- Some patients have suffered serious side effects days to weeks after endovascular therapy, including movement of the stent, serious bleeding, a blood clot to the lung, a clot of the internal jugular vein requiring surgical removal of the clot, and death. This information comes from individual case reports. Careful long-term follow-up studies of groups of patients who have undergone endovascular therapy are needed to determine how frequently these complications occur.

Re-stenosis after endovascular therapy

- Re-stenosis (recurrence of blockage of the vein) 6 to 18 months after endovascular therapy has been reported in between 29% and 47% of patients.

What's the bottom line right now?

Although our meta-analysis found that CCSVI was more common in people with MS compared to those without MS, the very large difference in results between the 9 studies is unusual, unexplained and worrying. The results of ongoing studies, using a standardized and reproducible ultrasound methodology, will hopefully clarify this issue.

It is important to remember that an association between CCSVI and MS does not mean that CCSVI causes MS. If there is an association, it could be that MS causes CCSVI, or that CCSVI happens to occur more frequently in people with MS without causing the disease. Indeed, the studies that we reviewed had a tendency to find a higher frequency of CCSVI in people who had MS for a long time (compared to those who were recently diagnosed), suggesting that CCSVI doesn't cause MS. However, more research is needed on this issue.

Endovascular therapy is associated with a small risk of serious complications in about 2% of patients; the most common serious side-effect is a heart rhythm abnormality. Between one quarter and one half of patients who undergo endovascular therapy develop re-stenosis of the treated veins in the subsequent 6 to 18 months. The impact of treatment on radiological and patient-relevant outcomes is not clear at this time.

What are we doing next?

We are aware of a number of studies on this topic that should be published in the next year or two. Therefore, we will continue to update our systematic review on a regular basis (about every 3-4 months).

Who are we?

We are 10 researchers from the University of Toronto and the University of Calgary, with a variety of expertise: caring for individuals with MS and performing MS research, vascular surgery, neurosurgery, statistics, health technology assessment and the conduct of systematic reviews.

How was this study funded?

We received a grant from the Canadian Institutes of Health Research (CIHR) to conduct this study. The funds were used to hire a research coordinator (Erin Lillie). None of the rest of us received any payment to undertake this study. Neither the CIHR nor its Scientific Expert Working Group on MS had any influence on the conduct of this study.

Do we have any potential conflicts of interest?

Dr. Laupacis is a Data Safety Monitoring Board member for studies of two drugs for patients with MS, funded by Novartis Pharmaceuticals. Dr. Burton has received unrestricted educational support and honoraria for speaking and educational engagements from TEVA Neuroscience Canada, EMD Serono and Biogen Idec Canada.

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