

## Appendix 1: Patient summary

### The results of a systematic review of studies that have examined whether chronic cerebrospinal venous insufficiency (CCSVI) is more common in people with multiple sclerosis (MS) than in people without MS

#### Why did we do this study?

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

The findings of Dr. Zamboni's group have been controversial, with experts in many fields of medicine and research cautioning 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. As well, concerns have been raised about the quality of their study. Therefore, there has been a call for CCSVI to be studied by research groups other than Dr. Zamboni's.

Our study reviews the existing scientific literature, from Zamboni's group and others, to determine whether CCSVI is more common in people with MS than those without MS. Our study does not examine the benefits and risks of treating CCSVI.

#### What did we do?

We reviewed all of the scientific papers related to CCSVI and MS that were published in the peer-reviewed scientific literature. When a paper is "peer reviewed," it is 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, medicine and others) in order to detect any problems such as inappropriate analyses or methods, or conflicts of interest. To be included in our review, each paper had to meet a minimum scientific quality standard.

#### Why did we look at only peer-reviewed publications?

Although peer review does not guarantee high-quality science, it does increase the chances that a study is of good quality.

#### Why did we include only articles that met a certain quality standard?

Poor-quality science can produce information that is misleading, incomplete or wrong, which can expose people to harm. Given the importance of the CCSVI–MS topic, we felt it was important that all papers included in our study reached a minimum quality standard.

#### What did we find? Is CCSVI found more often in people with MS than in people without MS?

- We found 8 studies that diagnosed CCSVI with ultrasound and **compared MS patients with healthy people**. When the results from all of the studies were combined, we found that CCSVI was almost 14 times more likely to be found in people with MS than in healthy people. However, there was a large difference in results among the studies, with some studies finding a much lower frequency of CCSVI than others, and some studies finding no difference in the

frequency of CCSVI between people with MS and healthy people. It is unusual to find such a large difference in results between studies, and the reason for the difference is not clear. Therefore, these results need to be viewed with caution.

- When we removed the study by Zamboni's group from the analysis and combined the remaining 7 studies (it is common for the initial description of a new entity in medicine to find much more dramatic results than studies done afterwards by others), CCSVI was found to be almost 5 times more frequent in people with MS than in healthy people.
- Of the 8 studies, 4 studies also ***compared MS patients with patients who had other neurologic diseases***. CCSVI was much more likely to be found in people with MS than in people with other neurologic diseases, although there were large differences in results among the studies; when we removed the study by Zamboni's group from the analysis, we found that CCSVI was almost 4 times more likely to be found in people with MS than in people with other neurologic diseases.
- Ultrasound studies 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 in which the patient is scanned, and the experience of the person doing the ultrasound. The difference in results between the studies may have been 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.

### **What's the bottom line right now?**

Our review of the scientific literature found that CCSVI appears to be more common in people with MS than in people without MS. However, the very large difference in results between the 8 studies is unusual, unexplained and worrying. The results of ongoing studies will hopefully help clarify the 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 tended to find a higher frequency of CCSVI in people who had MS for a long time, compared with those who were recently diagnosed, suggesting that CCSVI does not cause MS. However, more research is needed on this issue.

### **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 be updating our systematic review on a regular basis (about every 3–4 months) as these studies become available.

### **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.

**Where can we see the full scientific report?**

Our paper is published in *CMAJ* and is available online at [www.cmaj.ca/lookup/doi/10.1503/111074](http://www.cmaj.ca/lookup/doi/10.1503/111074).