An Update on the Investigation of Chronic Cerebrospinal Venous Insufficiency for the Treatment of Multiple Sclerosis

Context

Multiple sclerosis (MS) is a chronic progressive neurological disease common in young adults. Canada has one of the highest prevalence rates of MS in the world. MS causes significant disability due to mobility and vision problems, fatigue, incontinence, and cognitive impairment. The Public Health Agency of Canada estimated that the total costs associated with MS in 2000-2001 for hospitalization, treatment, and lost productivity due to morbidity and premature mortality were $950.5 million. Treatments involve suppressing or modifying the immune response, but there is currently no cure for MS.

Although MS is commonly believed to be an autoimmune disease, the evidence to support this concept has been questioned. An alternative hypothesis has been put forth by Dr. Paolo Zamboni, a former vascular surgeon and professor at the University of Ferrara in northern Italy. Dr. Zamboni believes a phenomenon termed chronic cerebrospinal venous insufficiency (CCSVI), an abnormality in blood drainage from the brain and spinal cord due to the narrowing of veins, may cause the buildup of iron deposits and contribute to inflammation and nervous system damage. Initial findings that CCSVI may be associated with MS were published in 2009 from a study of 65 patients with MS. Results from a second study suggested that treating CCSVI with endovascular angioplasty (the insertion of a tiny balloon or stent into blocked veins to improve blood flow), also referred to as the liberation procedure, is feasible and safe.

Results from other studies have not supported the hypothesis that CCSVI is present in patients with MS. Findings from a clinical trial published in April 2011, involving 499 participants, indicate that CCSVI may be a consequence rather than a cause of MS. The results showed that only 56.1% of MS patients had CCSVI. Furthermore, 42.3% of participants who had other neurological diseases and 22.7% of healthy controls also had CCSVI. It was also noted that CCSVI prevalence was significantly higher in patients with advanced progressive MS than those with non-progressive MS.

The CCSVI surgery for MS patients has not been approved by Health Canada and is not covered by provincial health insurance plans. In 2010, an estimated 3,000 Canadians travelled to clinics in the United States, Bulgaria, Poland, India, Costa Rica, and Mexico, each paying thousands of dollars for the procedure. Among them was an Ontario man who died in October 2010 from complications of the procedure, which he received in Costa Rica. Based on the risks associated with the CCSVI surgery and the inconclusive results of preliminary research, there have been recommendations that rigorous large-scale clinical trials are required to determine whether CCSVI is a clinically important factor in the development or progression of MS.

In light of the high prevalence of MS in Canada, the CCSVI procedure has sparked unprecedented interest and generated considerable debate in the medical and scientific communities. Politicians have faced increasing pressure from the public to provide funding for clinical trials.

Objectives

The purpose of this report is to review recent developments in the investigation of CCSVI for the treatment of MS. This report will update information presented in a previous Environmental Scan, released in December 2010. The following questions will be addressed:

- Which clinical trials in North America are currently studying the association of CCSVI with MS?
- What is the status of funding for CCSVI research in Canada?
- What other initiatives are taking place in Canada with regard to CCSVI?
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Findings

It is not intended that the findings of this Environmental Scan provide a comprehensive review of the topic. The results of this report are based on a limited literature search. This report is based on information gathered as of April 21, 2011.

Ongoing Clinical Trials

In June 2010, the National MS Society (USA) and the MS Society of Canada committed over $2.4 million to support seven diagnostic studies focused on the role of CCSVI in MS. The purpose of these studies is to examine the structure and function of veins draining the brain and spinal cord in individuals representing a spectrum of MS types, severities, and durations. Healthy volunteers and people with other diseases will be used for comparison. These diagnostic studies are not designed to treat CCSVI, but rather to confirm whether CCSVI contributes to MS disease activity, to identify the best imaging technology to evaluate the condition, and to resolve conflicting data from previous studies. The studies may also be used to design protocols for possible exploratory therapeutic trials that may be undertaken if blockages are found.

The two-year grants began in July 2010 and results are being closely monitored by a scientific expert working group to determine whether clinical trials are warranted. In January 2011, the MS Society of Canada published the first in a series of six-month progress reports from the seven research teams (Appendix 1). The research teams have established rigorous protocols, are successfully recruiting participants, and are on track to deliver data upon completion of the two-year projects. Diagnostic scanning procedures are underway at all but one of the study sites. The next update is expected in July or August 2011.

In addition to the studies funded by the MS societies, Canadian researchers in Ontario and British Columbia are studying the prevalence of CCSVI in MS patients compared with healthy people (Appendix 2). Three clinical trials are currently evaluating the safety and efficacy of endovascular angioplasty for the treatment of MS.

Federal and Provincial Funding for CCSVI Clinical Trials

In September 2010, federal Minister of Health Leona Aglukkaq announced that the federal government would not fund a pan-Canadian clinical trial until the results of studies currently underway and guidance from a scientific expert working group had been considered. This decision was based on recommendations formulated in August 2010 by an expert panel convened by the Canadian Institutes for Health Research (CIHR) and the MS Society of Canada. CIHR is also supporting a systematic review of diagnostic and therapeutic issues related to CCSVI. Results of this report are expected to be available in May 2011.

In October 2010, Saskatchewan invested $5 million to fund province-based clinical trials for the CCSVI procedure. The Saskatchewan Health Research Foundation launched a call for research proposals in December 2010. Funding decisions are expected to be announced in May 2011. The Yukon has expressed interest in teaming up with Saskatchewan. In April 2011, Yukon’s Minister of Health and Social Services, Glenn Hart, announced a $250,000 contribution to the Saskatchewan trials to ensure that Yukoners can participate in the trials.

In April 2011, Manitoba announced that it would join Saskatchewan by contributing $5 million to advance clinical trial research on the CCSVI procedure. Both provinces had been calling for a nationally coordinated trial, but Manitoba Minister of Health Theresa Oswald said they couldn’t wait any longer. The Manitoba Health Research Council will issue a call for research proposals and will follow protocols already developed by the Saskatchewan Health Research Foundation in a complementary research process. The registration of patients for the trials is expected to start before the end of 2011.

Provincial Ministries of Health in Quebec, Nova Scotia, and Prince Edward Island have expressed interest in supporting a pan-Canadian clinical trial, provided that evidence from ongoing studies is positive. Ontario has remained cautious, citing the need for more scientific research and consensus in the
The MS Society of Canada has announced it is reserving $1 million for a pan-Canadian therapeutic clinical trial if preliminary results indicate such a trial is warranted. The organization hopes to work with the provinces and federal government to secure the remaining funds if the trial is approved.

**Provincial Funding for the CCSVI Procedure**

New Brunswick is the only province currently funding the CCSVI procedure. In November 2010, New Brunswick Premier David Alward announced the creation of a $500,000 fund to help MS patients receive the CCSVI procedure outside Canada. Members of the medical community have voiced concerns over the decision to provide funding for medical treatment outside Canada, and the New Brunswick Medical Society hopes to be consulted as to how the money should be allocated. In December 2010, New Brunswick Minister of Health Madeleine Dubé communicated that details on how the fund would be dispersed were still being worked out, but the intent was for the money to be matched by contributions from the public.

**Provincial CCSVI Registries and Follow-Up Care**

Many Canadians with MS have reported difficulties in receiving follow-up care in Canada after undergoing the CCSVI procedure abroad. This includes the Ontario man who died from complications in October 2010, upon returning from the Costa Rican clinic where he received the procedure. It has been reported that he was unable to find a local physician who was willing to treat him. With no national standards for follow-up care, Newfoundland, Alberta, British Columbia, and Ontario are taking steps to improve the monitoring of patients who undergo the CCSVI procedure.

In September 2010, Newfoundland committed $320,000 to fund a provincially based observational study to track the progress of MS patients who have travelled overseas at their own expense to have the CCSVI procedure. In February 2011, New Brunswick Minister of Health and Community Services Jerome Kennedy announced that the budget for the study had increased by $80,000, and that 29 of the 40 proposed participants were enrolled. Participants will undergo an MRI exam before the procedure and will receive follow-up from local neurologists to collect data on their condition.

In December 2010, Alberta Minister of Health and Wellness Gene Zwozdesky announced that the Government of Alberta would commit up to $1 million for a three-year observational study to determine the safety and patient-reported impact of CCSVI treatment procedures received outside Canada. The study intends to track at least 500 Albertans who have MS, including those who have travelled overseas for the CCSVI procedure. Researchers at the University of Alberta and the University of Calgary will conduct the study in collaboration with other experts. As of March 2011, the research team is awaiting ethics approval for their research proposal and anticipates the enrolment of participants to start in May 2011. Once underway, those who participate will be asked to complete a questionnaire on their symptoms, medical history, and possible complications following surgery. This information will help health authorities better understand the requirements for follow-up care for those who have undergone the CCSVI procedure abroad. The province hopes to use information from this study to determine the future need for clinical trials.

In March 2011, Alberta released guidelines on how to monitor patients for complications following the CCSVI procedure. The document was created by a multidisciplinary group of Alberta physicians and is being distributed to members of the College of Physicians & Surgeons of Alberta. The document notes that the guidelines do not represent official College policy and should not be used by physicians as a substitute for individual clinical judgment. Alberta Health Services issued a position statement in August 2010, urging MS patients not to seek the CCSVI procedure.

In April 2011, the MS Clinic at the University of British Columbia Hospital received $700,000 over three years in provincial funding to establish a voluntary registry for MS patients who have undergone the CCSVI procedure in
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clinics outside Canada. The information will be used to assess the benefits and complications of the procedure and help establish province-wide post-care treatment guidelines.

In March 2011, the Ontario government announced that it is setting up a panel of medical experts to establish best practice guidelines for follow-up care and treatment of patients who receive the CCSVI procedure outside Canada. Medical experts and MS advocates expect the guidelines to be adopted across the country.

Canadian MS Monitoring System

In March 2011, federal Minister of Health Leona Aglukkaq announced that the Canadian Institute for Health Information (CIHI) will develop a nationwide system for measuring and monitoring the evolution and treatment of MS in Canada. The Canadian MS Monitoring System will be developed with initial funding from the Public Health Agency of Canada in collaboration with the Canadian Network of MS clinics and the MS Society of Canada. CIHI and its partners in the MS community will work with clinical and technical experts across Canada, patient representatives, and provincial and territorial governments to design and develop the monitoring system.

A standardized data collection approach will be built on existing provincial/territorial data systems, to avoid duplication. Information will be collected on a voluntary basis from the Canadian Network of MS Clinics, which treat an estimated 80% of MS patients in Canada.

Information from the monitoring system will be used to measure disease patterns across Canada, identify variations in the use of treatments, and monitor long-term patient outcomes associated with different treatment options, including complications associated with the liberation procedure. The data will be used to support patient care and decisions on health care resource allocation, and to identify priority areas for research. The registry will begin compiling data in April 2011 and it is hoped that its first findings will be reported in the fall. It is expected to be fully operational in early 2012. CIHI will produce publicly available reports once sufficient information is collected. The system will cost the federal government approximately $2 million to establish and an estimated $1.5 million in ongoing annual costs.

Other New and Emerging Therapies for MS

In March 2011, fingolimod (Gilenya, a sphingosine-1-phosphate analog) was approved by Health Canada as the first oral disease-modifying therapy for MS. Fingolimod was approved by the Food and Drug Administration (FDA) in September 2010 and by the UK’s drug regulator in April 2011.

Cladribine (a purine nucleoside analog) was granted a priority review designation by the FDA in July 2010. However, in March 2011, the FDA announced its decision not to approve cladribine without additional safety information.

Other health technologies currently being studied in clinical trials include monoclonal antibodies (such as rituximab, daclizumab, alemtuzumab, ocrelizumab, ofatumumab), statins (such as atorvastatin and simvastatin), laquinimod, oral fumarate, teriflunomide, filatricest, and autologous hematopoietic stem cell transplantation.

Conclusion

It is not yet established whether CCSVI contributes to MS disease activity, and there have been conflicting data as to the frequency of this condition in people with MS. Recent results from a large clinical trial suggest that CCSVI may be the result of the disease rather than a cause. It is hoped that findings from ongoing studies will provide clarity regarding the need for pan-Canadian therapeutic clinical trials.

Several provinces have provided funding for various studies to determine the safety and effectiveness of the CCSVI procedure for MS. Saskatchewan and Manitoba are in the process of launching clinical trials. Newfoundland, Alberta, and British Columbia are funding observational studies to track patients who have received the procedure overseas. Provincial Ministries of Health in Ontario, Quebec, Nova Scotia, and Prince Edward Island
have all expressed interest in supporting a pan-Canadian clinical trial, provided that evidence from ongoing studies is positive. The federal government intends not to fund a pan-Canadian clinical trial until ongoing studies indicate that CCSVI is indeed a hallmark in the disease process of MS.

Federal funding has been provided to develop the Canadian Multiple Sclerosis Monitoring System, which will track long-term patient outcomes associated with different treatment options, including complications associated with the CCSVI procedure. Alberta, British Columbia, and Ontario have taken steps to improve follow-up care for Canadians who travel abroad for the treatment. New Brunswick is the only province to promise funding to aid access to the CCSVI procedure outside Canada.

Scientific and medical organizations and experts across Canada have uniformly urged caution and rigorous study before the CCSVI procedure is recommended for use outside of clinical trials in MS patients. The recent approval of fingolimod has provided a new treatment choice for patients who have not responded to other MS therapies. Several other technologies are currently in the pipeline for the management of MS.

Complementing this Environmental Scan, CADTH prepared an Environmental Scan in December 2010 on the investigation of CCSVI for the treatment of MS, and a Rapid Response in December 2009 on surgical procedures targeting CCSVI for the treatment of MS. Both reports are available free of charge on the CADTH website.18,65

**North American Guidelines and Recommendations**


http://www.cihr-irsc.gc.ca/e/42381.html


**References**


2. Multiple Sclerosis Society of Canada [Internet]. Toronto: MS Society of Canada. MS experts estimate number of Canadians with MS is 55,000 to 75,000: medical update memo; 2006 May 2 [cited 2011 Apr 15]. Available from: http://mssociety.ca/en/research/medmmo-prev-may_02.htm


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35. Province of Manitoba [Internet]. Winnipeg (MB): Province of Manitoba; c2010. News release: Manitoba invests in multiple sclerosis support and research -- province pushes forward on multiple fronts for people living with MS: Oswald; 2010 Oct 15


43. New Brunswick 'liberation' fund for MS based on politics, not science: expert. Truro Daily News [Internet]. 2010 Dec 5 [cited 2011 Apr 18]. Available from:


### Appendix 1: Six-Month Progress for Seven MS Society-Funded CCSVI Studies

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<tr>
<th>Investigator, Location</th>
<th>Study Information</th>
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<tr>
<td>Dr. Brenda Banwell, Hospital for Sick Children, Toronto, Ontario</td>
<td>Research Ethics Board approval has been received. Participants are currently being enrolled to compare vein abnormalities in children and teenagers who have MS with healthy controls of the same age, using non-invasive MRI, ultrasound, and novel measures of venous flow. The team's ultrasound experts have received training in Dr. Zamboni's original techniques. A total of 60 participants, both healthy and with MS, will be enrolled. This population will allow for an examination of disease process at an early stage where other health conditions that might affect blood flow do not exist.</td>
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<td>Dr. Fiona Costello, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta</td>
<td>Research Ethics Board approval has been received. A cross-section of individuals with MS is currently being recruited for comparison with people who have other neurological diseases and healthy volunteers. The study will compare 3 Tesla MRI venography scans with ultrasound, as originally used by Dr. Zamboni. The team will assess whether linkages exist between venous abnormalities and different aspects and measures of MS activity and tissue damage. A total of 180 participants will be enrolled.</td>
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<td>Dr. Carlos Torres, Ottawa Hospital, University of Ottawa, Ottawa, Ontario</td>
<td>Research Ethics Board approval has been received and participants are currently being recruited. The study will use 3 Tesla MRI and Doppler ultrasound technology to explore differences in the anatomy of veins in the neck, chest, and spine and to assess iron deposits in the brain. Team members are slated to be trained using the ultrasound techniques originally used by Dr. Zamboni. The study will include 50 people with MS and 50 age-matched healthy volunteers.</td>
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<td>Dr. Anthony Traboulsee, MS Clinic at UBC Hospital, Vancouver Coastal Health and University of BC, Vancouver, British Columbia</td>
<td>Research Ethics Board approval has been received at both sites and research teams have begun to recruit and scan participants. Team radiologists met in February 2011 to ensure the consistency of protocols across sites. The prevalence of CCSVI in 200 people with and without MS will be studied using catheter venography, ultrasound, and magnetic resonance venography. Ultrasound technologies were trained in the techniques originally used by Dr. Zamboni. The study allows for the inclusion of family members of the MS patient, such as identical twins, in the control group. The study aims to determine the reliability and accuracy of different imaging techniques for screening of CCSVI.</td>
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<td>Dr. Katherine Knox, Saskatoon MS Clinic, University of Saskatchewan, Saskatoon, Saskatchewan</td>
<td>Institutional Review Board approval has not yet been received. The study will use MRI scans to generate detailed images of veins in the head and neck in 112 people with MS, 56 controls without MS, and 56 people with other neurological conditions. These images will be compared with results obtained from the ultrasound techniques used by Dr. Zamboni.</td>
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<td>Dr. Aaron Field, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin</td>
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### Investigator, Location

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| **Dr. Robert Fox,**  
Cleveland Clinic Foundation, Cleveland, Ohio<sup>71</sup> | Institutional Review Board approval has been received and recruitment is ongoing. The study will compare 90 people with MS and 80 healthy volunteers. The team will use the ultrasound techniques used by Dr. Zamboni, as well as magnetic resonance studies of the veins, MRI scans of the brain, and clinical measures to determine MS activity. The ultrasound team encountered several methodological challenges based on the published methodology and has developed a standardized protocol and analysis to achieve consistent results. To distinguish whether vein abnormalities are from atrophy (brain tissue volume loss) and not specifically MS, they are also comparing the MS group with people with atrophy from Alzheimer’s disease. Neck and spinal cord tissue obtained from MS patients via autopsy will be used for tissue-based evaluation of CCSVI and its possible relationship to MS. |
| **Dr. Jerry Wolinsky,**  
University of Texas Health Science Center, Houston, Texas<sup>72</sup> | Institutional Review Board approval has been received and the team has already scanned a significant number of participants. This study will replicate the ultrasound methods used by Dr. Zamboni to investigate the association of CCSVI with major clinical types of MS using non-MS control groups. A total of 275 people will be recruited. The team is currently having difficulty recruiting non-MS control subjects who don’t have a personal interest in the trial. The team will also assess whether other imaging methods can confirm the ultrasound findings and determine which technique is the most reliable to screen for CCSVI. |

CCSVI = chronic cerebrospinal venous insufficiency; MRI = magnetic resonance imaging; MS = multiple sclerosis.
### Appendix 2: Other Ongoing CCSVI Studies in North America

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<th>Investigator, Location</th>
<th>Study Information</th>
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<td><strong>Canada</strong></td>
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<td>Dr. Ian Rodger, St. Joseph’s Healthcare, Hamilton, in collaboration with Hamilton Health Sciences and McMaster University, Hamilton, Ontario&lt;sup&gt;21,23,73&lt;/sup&gt;</td>
<td>This study will use MRI and ultrasound tests to determine the prevalence of cerebrospinal venous abnormalities in 100 individuals who have MS compared with 100 people who do not have MS.</td>
<td>Public donations</td>
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<td>CCSVI MS Research Study</td>
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<td>Dr. Keith Chambers, False Creek Healthcare Centre, Vancouver, British Columbia&lt;sup&gt;24&lt;/sup&gt;</td>
<td>This study will compare brain blood vessel differences in 100 individuals who have MS with 100 people who do not have MS, using MRI.</td>
<td>False Creek Healthcare Centre</td>
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<td>CCSVI Blood Flow Study</td>
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<td><strong>United States</strong></td>
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<td>Dr. Adnan Siddiqui, University of Buffalo, Department of Neurosurgery, Buffalo, New York&lt;sup&gt;25&lt;/sup&gt;</td>
<td>This randomized, double-blind, placebo-controlled study will test the safety and efficacy of interventional endovascular therapy. In the first phase, 10 MS patients exhibiting CCSVI underwent minimally invasive venous angioplasties to determine whether the procedure could be performed safely. Investigators are currently enrolling 20 more participants for the second phase of the study.&lt;sup&gt;74&lt;/sup&gt; MS patients will be randomized to undergo either venous angioplasty or a “sham angioplasty” (i.e., catheter is inserted but there is no inflation of the balloon) to test the placebo effect. These subjects will be evaluated periodically over six months. If results are positive, the researchers will approach the University of Buffalo Institutional Review Board for an extension of the protocol to study a larger group of patients.</td>
<td>Public donations and Direct-MS Foundation</td>
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<tr>
<td>PREMiSe (Prospective Randomized Endovascular therapy in Multiple Sclerosis) Study</td>
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<td>Dr. Gary Siskin, Albany Medical Center, Albany, New York&lt;sup&gt;26&lt;/sup&gt;</td>
<td>This double-blind, randomized, controlled trial will determine whether venous angioplasty is an effective treatment for CCSVI and expects to enrol approximately 130 patients. The outcomes of two groups of patients will be compared. One group will have CCSVI diagnosed on a venogram and treated with angioplasty, and the second group will have CCSVI diagnosed on a venogram and treated with a sham procedure. Several outcomes will be evaluated over 24 months, including safety, efficacy, and quality of life.</td>
<td>Community Care Physicians, PC</td>
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<th>Investigator, Location</th>
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<td>Dr. Manish Mehta, The Vascular Group, PLLC, The Vascular Health Pavilion, Albany, New York²⁷</td>
<td>The study is a randomized, double-blind (sham procedure), placebo-controlled feasibility clinical trial with an expected enrolment of 600. The purpose is to evaluate the safety, feasibility, and efficacy of percutaneous transluminal angioplasty in treating extracranial venous obstructive lesions, and its influence on the clinical outcomes of MS patients who have been found to have CCSVI. Outcome measures evaluated over 24 months include adverse events, neurological assessment, MRI evaluation of MS lesions, and mortality.</td>
<td>The Vascular Group, PLLC</td>
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CCSVI = chronic cerebrospinal venous insufficiency; MRI = magnetic resonance imaging; MS = multiple sclerosis.

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