Systematic reviews of the evidence regarding chronic cerebrospinal venous insufficiency (CCSVI) and multiple sclerosis - Summary of the First Report for CIHR Expert Panel, September 23, 2011

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Executive Summary

Introduction and Background

Venous abnormalities and MS: Multiple sclerosis (MS) is a chronic demyelinating and degenerative disease of the central nervous system. The exact cause remains unknown, but evidence over the better part of a century has demonstrated that it is immune-mediated and likely an autoimmune disease. In 2006, Zamboni and colleagues proposed that MS is caused by abnormalities in the anatomy and flow of the cerebral veins, which he has called chronic cerebrospinal venous insufficiency (CCSVI). CCSVI as described by Zamboni et al is detected by transcranial and extracranial Doppler ultrasound. It requires the evaluation of 5 ultrasound parameters, and a diagnosis of CCSVI is given if a patient has an abnormality in 2 or more of the 5 parameters. Investigators have used other techniques to study cerebral venous flow and anatomy, including magnetic resonance venography and direct venography.

Treatment of CCSVI: In connection with the CCSVI-MS hypothesis, endovascular therapy (venoplasty or stenting of extracranial veins) has been proposed as a possible treatment option for patients with MS. Venoplasty involves
the insertion of a catheter into the vein that has a stenosis, and inflation of a balloon to dilate that stenosis. Stenting involves placement of a stent after a stenosis has been dilated (similar to the stents used for arterial stenting).

Purpose and Methods

Purpose: The primary purpose of this systematic review was to examine the evidence evaluating the association between venous abnormalities and MS. The secondary purpose was to systematically review the current evidence about the benefits and harms of endovascular treatment for MS, focusing on high quality studies.

Methods: This systematic review only focused on studies published in the peer-reviewed literature. Studies that used ultrasound and magnetic resonance venography (MRV) to assess CCSVI were eligible if they compared MS patients with patients without MS [either healthy controls (HC) or patients with other neurological diseases (OND)]. Because of the side-effects of contrast venography (CV), it would not be appropriate to expose control patients to CV. Therefore, CV studies were eligible even if they did not have a non-MS control group. Only randomized trials were eligible for the assessment of the benefits of endovascular treatment for MS. To assess the harms of endovascular treatment, we accepted observational studies of >10 patients. An extensive literature search of peer-reviewed publications, with no language restrictions, was undertaken to identify eligible studies published up to June 2011. Studies using ultrasound were statistically combined using a random effects model.

Results and Interpretation

Ultrasound: 8 studies\textsuperscript{2-9} compared the frequency of CCSVI diagnosed with ultrasound in MS patients versus HC, and 4 studies compared MS patients with OND\textsuperscript{2,4,7,9}. CCSVI was diagnosed more frequently in patients with MS than in HC [odds ratio (OR) 13.5, 95% confidence interval (CI): 2.6-71.4], but there was extensive heterogeneity. There continued to be a statistically significant association in the most conservative analysis, which involved removing Zamboni's initial study and adding a study in which no CCSVI was found in any patient (OR 3.7, 95% CI: 1.2-11.0). The 4 studies that compared MS patients and OND patients found a higher frequency of CCSVI in MS patients, but this finding was not statistically significant (OR 32.5, 95% CI: 0.6-1775.7); removal of Zamboni's study resulted in an OR of 3.5, 95% CI: 0.8-15.8). None of the studies that used ultrasound reported the success of blinding of the technicians or radiologists.

Although this systematic review found a strong and statistically significant association between chronic cerebrospinal venous insufficiency and multiple sclerosis, the large amount of heterogeneity among study results (both in the frequency of CCSVI in patients with MS and in the association of CCSVI with MS) prevents a definitive conclusion. The source of the heterogeneity is not clear. It is not obviously caused by patient characteristics or the methodological quality of the studies. For further details about the systematic review, please refer to the CMAJ publication entitled: Systematic review of the association between chronic cerebrospinal venous insufficiency and multiple sclerosis.

MRV and CV: Only 3 small studies\textsuperscript{10-12} evaluated MRV findings in patients with MS and HC, and they found no statistically significant differences in the frequency of venous abnormalities in patients with and without MS. One study of CV in 42 patients with MS found that 1/11 (9%) of patients with clinically isolated syndrome had extracranial venous stenosis, compared to 6/18 (33%) of patients with early relapsing remitting MS and 11/13 (85%) of patients with long-standing MS\textsuperscript{13}.

Studies of Endovascular Therapy for MS: Randomized trials are widely recognized as the most valid study design to assess the benefits of treatment. This is especially true for a disease like MS which is characterized by spontaneous relapses and remissions, is treated with a number of drugs and other therapies (which can be confounders of the treatment effect), and the likelihood of a placebo effect associated with endovascular treatment. No randomized trials have been reported of endovascular therapy for MS; therefore the impact of this intervention upon the symptoms and signs of MS cannot be reliably assessed. Although the best evidence about the harms of endovascular therapy is derived from randomized trials, well-conducted observational studies can provide valid information about the harms associated with a procedure.

Only two studies\textsuperscript{14-15} have reported the frequency of short-term complications of endovascular therapy; in 66 and 331 patients. No deaths were reported. Post-intervention bleeding, stent thrombosis (with no important clinical consequences) and transient atrial fibrillation were reported, but all occurred in less than 2% of patients. Thus, despite rare reports of death after endovascular interventions for CCSVI, the frequency of severe side-effects appears low. Stents are associated with a risk of stent migration, and presumably a higher frequency of major bleeding because of the more intense and longer use of anti-thrombotic therapy. However, the magnitude of the excess risks associated with stent insertion compared to venoplasty alone is not known. These studies did not
appear to systematically follow patients for complications beyond the immediate post-procedure period.

Conclusions

Venous abnormalities and MS: A meta-analysis of 8 studies\textsuperscript{2,9} found a positive association between CCSVI and MS patients (compared to HC) that was statistically significant, even when a "conservative" analysis was conducted. However, poor reporting of the success of blinding, and the marked heterogeneity of the results do not allow definitive conclusions to be drawn. More high quality studies are needed to determine definitively whether CCSVI is more frequent in patients with MS as compared to those without MS. It is also urgent that ultrasonographers agree on a standardized method to diagnose CCSVI. Furthermore, it is important to note that should future studies establish an association between CCSVI and MS, this does not necessarily mean that CCSVI causes MS.

Unfortunately, the current literature about MRV in MS does not allow firm conclusions to be drawn about either the frequency of MRV abnormalities in MS patients and those without MS, or the correlation between MRV and ultrasound in the assessment of extra-cranial veins. Only one small venographic study\textsuperscript{15} has been conducted in relatively unselected patients with MS.

Studies of Endovascular Therapy for MS:
Two studies\textsuperscript{14-15} reported peri-procedure complications of endovascular therapy in a total of 396 patients. There were no deaths, and serious peri-procedure side-effects occurred in <2% of patients.

The complete report on Systematic reviews of the evidence regarding chronic cerebral spinal venous insufficiency (CCSVI) and multiple sclerosis can be found on St. Michael’s Hospital Website.

References


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