Multiple Sclerosis and Chronic Cerebrospinal Venous Insufficiency

A Preliminary Evidence Review

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The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the Ontario Health Technology Assessment Series. When the conduct of a full evidence-based analysis is not feasible, an evidence update or a preliminary evidence review may be conducted.

Disclaimer

This preliminary evidence review was prepared by the Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care, for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data, and information provided by experts and applicants to the Medical Advisory Secretariat to inform the analysis. Because this is a preliminary evidence review, it may not reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review. This preliminary evidence review may be superseded by another report on the same topic. Please check the Medical Advisory Secretariat Website for a list of all MAS and OHTAC publications:
Rationale for the Preliminary Evidence Review

A review on the effectiveness and safety of imaging investigations and treatment of chronic cerebrospinal venous insufficiency (CCSVI) in patients with multiple sclerosis (MS) was requested by the Ministry of Health and Long-Term Care. A preliminary evidence review was conducted by the Medical Advisory Secretariat (MAS) in order to determine whether there was sufficient evidence to conduct a full evidence-based review on CCSVI in MS patients.

Recent reports in the scientific and medical community and the media have led to great interest in a novel approach in the management of multiple sclerosis.

Condition

Multiple sclerosis (MS) is a complex disease defined as a chronic inflammatory presumed autoimmune disease of the central nervous system. Inflammation is believed to be the primary cause of nervous system damage to myelin sheaths (fatty substance covering axons of nerve cells) which causes grey and white matter to degenerate, leaving lesions in the brain and spinal cord. The factors that initiate the inflammation, however, are unknown. Brain atrophy is the end point of irreversible tissue loss in MS, but the underlying mechanisms are diverse, complex and still under investigation. (1)

CNS system damage is usually manifested through attacks, known as relapses, to vision, sensation, coordination and strength either temporarily or permanently. Cognitive impairment, fatigue, pain, mobility limitations and visual disturbances are all commonly reported impacting on quality of life and activities of daily living. It is the leading cause of acquired neurological disability in young and middle aged people in the developed world. (2;3)

Treatments for MS have been variably defined as halting the disease progression, reversing neurological deficits or preventing MS. (2) Four distinct clinical patterns of disease have been identified: relapsing-remitting (RRMS); secondary progressive (SPMS); primary progressive (PPMS); and progressive relapsing (PRMS). RRMS is the most common form of the disease and the disease pattern for which drug therapies are more effective. Currently there are six different parenteral formulations of disease-modifying drugs approved for MS treatment and many others are in different stages of investigation or awaiting regulatory approval. (4)

Technology/ Theory

Chronic cerebrospinal venous insufficiency (CCSVI) was first described by Paolo Zamboni in 2007. (5) CCSVI has been defined as a syndrome characterized by stenoses of the internal jugular (IJ) and/or azygous (AZ) veins, the principal pathways of extracranial venous drainage, with opening of collaterals and insufficient drainage proven by cerebral MRI perfusional study. These abnormalities in extracranial venous outflow mechanism have been suggested to be a possible causal mechanism for the increased iron deposits in MS plaques. (6) This theory is related to the observation that plaques in MS are known to be venocentric and that histological examination of involved veins sometimes reveals characteristics similar to those observed in chronic venous insufficiency such as fibrin cuffs, perivenous iron deposits in the form of extracellular haemosiderin and iron rich macrophages.
Regulatory Status

Endovascular interventions for CCSVI in MS patients, such as angioplasty or stenting for venous insufficiency of the IJ or the AZ veins, do not have regulatory approval in Canada.

Status in Ontario

Interventions for CCSVI in MS patients are not insured in Canada. Kuwait is the only jurisdiction where the publicly funded health care system provides endovascular treatment to MS patients with blocked veins and abnormal blood flow in their central nervous system. Treatment for CCSVI in MS patients is performed in the United States, Bulgaria, Poland and other countries through private clinics. In Ontario, patients with MS are having imaging investigations for CCSVI performed at private imaging centers and are traveling to other countries for treatment.

Current Evidence

Clinical Trials

Imaging Investigations on CCSVI in MS

Researchers at the University of Ferrara in Italy have reported on a prospective study involving the intracranial venous haemodynamics in 89 consecutively referred MS patients and 60 healthy age sex matched volunteer controls. (5) Patients taking immunosuppressive (azathioprine, methylprednisolone) or immunomodulatory (interferon-beta or glatiramer acetate) drugs within 6 months of recruitment were excluded. Significant haemodynamic alterations were found in MS patients. The reflux-bidirectional flow detected in the cranial veins was anatomically related to plaque disposition and significantly associated with worse disability scores. The value of cerebral Doppler venous haemodynamics was further investigated by researchers at the University of Ferrara in 120 patients with clinically defined MS and 200 controls. (6) CCSVI in MS patients was further investigated with a combined transcranial and extracranial color-Doppler examination to clarify the parameters of anomalous venous outflow. (7)

Researchers from the SUNY Imaging Group in Buffalo NY recently reported the preliminary results on the design and interim results of the first 500 subjects enrolled in a prospective survey evaluating the prevalence of CCSVI in MS patients at the April 2010 annual scientific conference of the American Academy of Neurology. The interim estimated prevalence rate of CCSVI, defined by the presence of two or more vascular abnormalities in the IJ or AZ veins, was reported to be significantly higher ($p < .001$) in MS patients than in healthy control subjects (62.5% versus 25.5%).

The study aims to recruit 1700 consecutive patients at one MS center and includes: 1000 adult patients with possible and definite MS, 300 with other neurodegenerative disease, and 300 age sex matched normal adult controls, 50 pediatric patients with acquired demyelinating diseases (MS and acute disseminated encephalomyelitis) and 50 pediatric normal controls. Investigations will include Doppler scan of head and neck and MRI evaluations blinded to patient’s clinical status.

Endovascular Intervention for CCSVI in MS

At this time, there are no published randomized controlled trials or clinical trials with comparative groups involving Multiple Sclerosis and CSSVI
Multiple sclerosis and CCSVI

One prospective clinical trial has been published in 2009 from the research group at the University of Ferrara in Italy reporting on the feasibility, safety and vascular and neurologic outcomes of percutaneous angioplasty (PTA) performed in 65 adult MS patients. (8) Patients were consecutively referred and had a mean age of 41.7 years and a mean disease duration of 8.6 years. They were diagnosed with MS according to the revised McDonald criteria and included patients with the relapsing remitting (n=35), secondary progressive (n=20) and primary progressive (n=10) forms of the disease. Patients were followed up for 18 months with imaging (echo color Doppler, selective venography, contrast phlebography) and independent neurologic investigations. Outcomes included: echo Doppler hemodynamics; venous pressure; patency rates; gadolinium enhanced MRI lesions; disease severity (Multiple Sclerosis Functional Composite Score; disease specific HRQOL (Multiple Sclerosis Quality of Life-54 Instrument); and relapse rate.

This small study reported significantly decreased relapse, decreased MRI active brain lesions, increased HRQOL and functional outcomes. However, patients in the relapsing-remitting subgroup of MS patients were more likely to experience these improvements than patients in the primary and secondary progressive subgroups. No relapses were detected in patients in whom successful reversal of vein blockages was maintained in follow-up. Recurrence of stenosis after angioplasty was dependent on the location and the type of vessel malformation and was significantly higher (p < .0001) in the IJ (43%) than the AZ (4%) treated veins. However, the small sample size, lack of controls, unblinded neurologic evaluations, and inconsistent MRI protocols limit the conclusions that can be drawn from these study findings.

A second collaborative study between the Italian Group at the University of Ferrara and at SUNY Imaging Group in Buffalo, NY is underway to evaluate angioplasty of cerebral venous stenosis in a controlled trial. Consecutive patients referred to their centers will be randomized for treatment to two groups, one group to immediate treatment and the second group to act as a control group to be treated at least 6 months later.

Upcoming Research

Since the 2009 published report of the Italian clinical intervention trial for CCSVI in MS patients which received intense media and public interest on both sides of the Atlantic, the Multiple Sclerosis Society of Canada and the US National Multiple Sclerosis Society have each issued RFPs for CSSVI related research. Both societies have received multiple submissions and are jointly reviewing proposals by an independent international research committee. The funding decisions are expected in mid June 2010 and trials are to be underway in July.

One submission involves an Ontario research group at St Joseph’s Healthcare Hamilton and McMaster University who are well advanced with their study plans and will be recruiting 200 participants (100 MS patients and an equal number of healthy age and gender matched control subjects) starting in early July. Their study is aimed at rigorously testing the CCVSI hypothesis in MS using both ultrasound and MR imaging diagnostic techniques. The study does not involve any surgical intervention(s). The results are anticipated early in 2011.

The SUNY Imaging Group in Buffalo is awaiting funding decisions to complete the final recruitment phase of their research study (prospective imaging study of the next 1200 of 1700 subjects).

Conclusion

The initial reports on intravascular interventions to remove blockages in cranial veins in MS patients are encouraging. There are however, several key areas for investigation and these include:

1. The nature of the association between CCSVI and multiple sclerosis (or other neurodegenerative diseases)?

2. The criteria for a CCSVI diagnosis and the optimal neuro imaging technologies to investigate the vascular haemodynamics and structural abnormalities of CCSVI?
3. The clinical pathological consequences of extracranial venous blockage and haemodynamic disturbances?

4. The safety, effectiveness and durability of the endovascular treatments, angioplasty and stenting for cranial stenotic veins in MS patients?
References


