

OHTAC Recommendation

Multiple Sclerosis and Chronic Cerebrospinal Venous Insufficiency

*Presented to the Ontario Health Technology
Advisory Committee in May 2010*

May 2010

Issue Background

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. The Ontario Health Technology Advisory Committee (OHTAC) met on May 28, 2010 to determine whether there was sufficient evidence to conduct a full evidence-based review on the effectiveness and safety of imaging investigations and treatment of chronic cerebrospinal venous insufficiency (CCSVI) in patients with multiple sclerosis (MS). The determination was based on a preliminary evidence review by the Medical Advisory Secretariat (MAS).

Clinical Indication

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 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.

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.

Treatments for MS have been variably defined as halting the disease progression, reversing neurological deficits or preventing MS. 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.

The Technology

Chronic cerebrospinal venous insufficiency (CCSVI) was first described by Paolo Zamboni in 2007. CCSVI has been defined as a syndrome characterized by stenoses (blockages) of the internal jugular (IJ) and/or azygous (AZ) veins which are the principal pathways of extracranial venous drainage. These abnormalities in extracranial venous outflow have been suggested to be a possible causal mechanism for the increased iron deposits in MS plaques. This theory is also 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 peripheral chronic venous insufficiency. Treatment for CCSVI has involved balloon angioplasty or stents to open the blocked vessels.

Regulatory Status

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

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.

Evidence

The current published evidence on the imaging and treatment of CCSVI in MS patients is limited.

Imaging Investigations on CCSVI in MS

There are several reports on the imaging investigations on CCSVI in MS patients.

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. Patients taking immunosuppressive or immunomodulatory 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 subjects.

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 included 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 treatment of CCSVI in patients with MS.

One prospective clinical trial published in 2009 from the research group at the University of Ferrara in Italy has reported on the feasibility, safety and vascular and neurologic outcomes of percutaneous angioplasty (PTA) performed in 65 adult MS patients. 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 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. The design involves the randomization of consecutive patients referred to their centers to two treatment 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 published report in 2009 of the Italian clinical intervention trial for CSSVI 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 CCSVI 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. These include clarifying the relationship between CCSVI and MS, particularly as some of these vascular anomalies have been reported in healthy control subjects. There are also uncertainties about the appropriate imaging investigations to diagnose CCSVI, the vascular and anatomic properties that define CCSVI, the indications for angioplasty and/or stenting and the safety, effectiveness and durability of these procedures.

OHTAC Recommendations

- OHTAC has undertaken a preliminary evidence review of the safety and effectiveness of endovascular treatments for chronic cerebrospinal venous insufficiency in patients with multiple sclerosis and is unable to make any recommendation at this time due to the paucity of available evidence. OHTAC regards this treatment as experimental at this time.
- OHTAC will continue to closely monitor new evidence and will provide its recommendation when more published peer reviewed evidence is available.
- In the interim, OHTAC recommends that patients with MS desiring these investigations be encouraged to participate in clinical trials.