

OHTAC Recommendation

Update on Multiple Sclerosis and Chronic Cerebrospinal Venous Insufficiency

*Presented to the Ontario Health Technology
Advisory Committee in July, 2011*

December 2011

Rationale

In May 2010, the Medical Advisory Secretariat (MAS) published a preliminary evidence review (PER) on Multiple Sclerosis and Chronic Cerebrospinal Venous Insufficiency. (1) The review concluded that although the initial reports on intravascular interventions to remove blockages in cranial veins in multiple sclerosis (MS) were encouraging, unanswered questions nevertheless remained. (1) These included questions about the association between the proposed condition known as chronic cerebrospinal venous insufficiency (CCSVI) and MS; about the criteria to diagnose CCSVI; and the neuroimaging technologies used to investigate CCSVI. (1)

In May 2010, the Ontario Health Technology Advisory Committee (OHTAC) made recommendations on CCSVI and MS (2) (Appendix 1) based on the results of the preliminary evidence review (1) conducted by MAS.

One of OHTAC's recommendations was that the literature be monitored for new evidence on the subject so that recommendations could be updated once more published peer-reviewed evidence became available. (2)

This update therefore incorporates the evidence from the studies published on the prevalence of CCSVI in patients with MS published before and after the May 2010 MAS preliminary evidence review.

Background

MS is a chronic progressive neurologic disease believed to have an autoimmune origin. (3) A more recent theory proposes that an abnormality in the drainage of blood from the brain and spinal cord, CCSVI, may be associated with MS. (3)

Ongoing Studies

Seven studies funded by the MS Society of Canada and the United States National MS Society to investigate the association between CCSVI and MS and the most appropriate imaging technology to investigate cerebrospinal blood flow abnormalities are currently ongoing. (3) These studies are not evaluating the treatment of CCSVI. (3) Two additional ongoing Canadian studies are evaluating the prevalence of CCSVI in MS patients compared to healthy individuals. (3)

OHTAC Findings

The objective of this analysis was to evaluate the prevalence of CCSVI in patients with MS compared to healthy control groups.

CCSVI was defined as the presence of ≥ 2 of the criteria below as described in a study by Zamboni et al. (4)

Table 1: Criteria Used to Define CCSVI*

1. Reflux constantly present in the internal jugular veins and/or vertebral veins in sitting and supine posture
2. Reflux in the deep cerebral veins
3. High-resolution B-mode evidence of proximal internal jugular veins stenoses
4. Flow not Doppler-detectable in the internal jugular veins and/or vertebral veins despite numerous deep inspirations with the head at 0° and +90°
5. Reverted postural control of the main cerebral venous outflow pathways

*Source: Zamboni et al (4)

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria. (5)

Two eligible studies had been published before May 2010 (4;6) and 6 eligible studies have been published since the previous preliminary evidence review. (7-12) The studies identified consisted of cross-sectional evaluations of the prevalence of CCSVI in patients with MS compared to healthy controls. (4;6-12) One study also evaluated the prevalence of CCSVI in patients with other neurologic diseases. (9) Six studies used Doppler ultrasound to evaluate CCSVI (4;6;8-10;12) and two studies used 3T magnetic resonance imaging (MRI) to evaluate cervical and cerebral venous outflow. (7;11)

Considerable inconsistency was observed in the study results. For example, in 4 studies using Doppler ultrasound to diagnose CCSVI, a higher prevalence of CCSVI in patients with MS compared to healthy controls was observed (4;6;8;9) while in 2 studies using Doppler ultrasound no difference between the two groups was observed. (10;12) Two studies using 3T MRI to evaluate abnormalities in cerebral or cranial venous flow did not report a difference between patients with MS and healthy controls. (7;11) One of the studies using 3T MRI observed findings suggestive of anomalies of cranial venous outflow anatomy frequently in both MS patients and healthy controls, and concluded that these abnormal findings are likely to reflect anatomical variants of venous drainage instead of clinically relevant venous outflow obstructions. (11) The second study that used 3T MRI to evaluate cerebral venous outflow did not observe any significant differences between patients with MS and healthy controls in cerebral venous flow. (7)

One study did not find a statistically significant difference in the prevalence of CCSVI between patients with MS and patients with other neurologic diseases. (9) The authors concluded that their findings suggest that CCSVI does not have a primary causative role in MS, but given the higher prevalence of CCSVI in progressive forms of MS, CCSVI may be a consequence of MS. (9)

The quality of the evidence for the studies on the prevalence of CCSVI in patients with MS compared with healthy controls was considered very low based on the GRADE Working Group criteria. (5)

Conclusions

- The quality of the body of evidence was considered very low.
- Four new studies did not show an increased prevalence of CCSVI or cerebral venous flow abnormalities in MS patients versus healthy controls.
- A large cross-sectional study published in July 2011 showed a higher prevalence of CCSVI in MS patients versus healthy controls. The study did not observe an increased prevalence of CCSVI in MS patients versus patients with other neurological diseases.
- Considerable inconsistency was observed in study results.
- Ongoing studies in Canada and the United States are evaluating both the association between CCSVI and MS and the most appropriate imaging technology to diagnose CCSVI.

OHTAC Recommendations

- OHTAC has undertaken a preliminary evidence review of the safety and effectiveness of endovascular treatments for the proposed condition known as 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.
- Evidence concerning the prevalence of chronic cerebrospinal venous insufficiency available up to July 2011 was reviewed by OHTAC and no changes to the May 2010 recommendations were deemed necessary.
- 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.

References

- (1) Medical Advisory Secretariat. Multiple sclerosis and chronic cerebrospinal venous insufficiency: a preliminary evidence review. Toronto, ON: Medical Advisory Secretariat; 2010 May 1 [cited: 2011 Jul 25]. 7 p. Available from: http://www.health.gov.on.ca/english/providers/program/mas/tech/rapid_review.html
- (2) Ontario Health Technology Advisory Committee. OHTAC recommendation. Multiple sclerosis and chronic cerebrospinal venous insufficiency. Toronto, ON: Ontario Health Technology Assessment Committee; 2011 [cited: 2011 Jul 25]. 5 p. Available from: http://www.health.gov.on.ca/english/providers/program/ohtac/tech/recommend/rec_ccsvi_20100611.pdf
- (3) Canadian Agency for Drugs and Technologies in Health. An update on the investigation of chronic cerebrospinal venous insufficiency for the treatment of multiple sclerosis. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2011 Apr 1 [cited: 2011 Jul 25]. 14 p. Available from: <http://www.cadth.ca/en/products/environmental-scanning/environmental-scans/environmental-scans-20>
- (4) Zamboni P, Galeotti R, Menegatti E, Malagoni AM, Tacconi G, Dall'Ara S et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry. 2009 Apr;80(4):392-9.
- (5) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S et al. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490.
- (6) Zamboni P, Menegatti E, Galeotti R, Malagoni AM, Tacconi G, Dall'Ara S et al. The value of cerebral Doppler venous haemodynamics in the assessment of multiple sclerosis. J Neurol Sci. 2009 Jul 15;282(1-2):21-7.
- (7) Sundstrom P, Wahlin A, Ambarki K, Birgander R, Eklund A, Malm J. Venous and cerebrospinal fluid flow in multiple sclerosis: a case-control study. Ann Neurol. 2010 Aug;68(2):255-9.
- (8) Zamboni P, Menegatti E, Weinstock-Guttman B, Dwyer MG, Schirda CV, Malagoni AM et al. Hypoperfusion of brain parenchyma is associated with the severity of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis: a cross-sectional preliminary report. BMC Med. 2011;9:22.
- (9) Zivadinov R, Marr K, Cutter G, Ramanathan M, Benedict RH, Kennedy C et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. Neurology. 2011 Jul 12;77(2):138-44.
- (10) Mayer CA, Pfeilschifter W, Lorenz MW, Nedelmann M, Bechmann I, Steinmetz H et al. The perfect crime? CCSVI not leaving a trace in MS. J Neurol Neurosurg Psychiatry. 2011 Apr;82(4):436-40.
- (11) Wattjes MP, van Oosten BW, de Graaf WL, Seewann A, Bot JC, van den Berg R et al. No association of abnormal cranial venous drainage with multiple sclerosis: a magnetic resonance venography and flow-quantification study. J Neurol Neurosurg Psychiatry. 2011 Apr;82(4):429-35.

- (12) Doepp F, Paul F, Valdueza JM, Schmierer K, Schreiber SJ. No cerebrocervical venous congestion in patients with multiple sclerosis. *Ann Neurol*. 2010 Aug;68(2):173-83.