Ontario
Health Quality Ontario
Qualité des services de santé Ontario

Update on Multiple Sclerosis and Chronic Cerebrospinal Venous Insufficiency: A Preliminary Evidence Review

December 2011

Suggested Citation

This report should be cited as follows:

Medical Advisory Secretariat, Health Quality Ontario. Update on multiple sclerosis and chronic cerebrospinal venous insufficiency: a preliminary evidence review. [Internet]. Toronto, ON. Medical Advisory Secretariat; 2011 December; 1-19. Available from: www.hqontario.ca/en/mas/per/pdfs/rev_CSSVI_update_December.pdf

Permission Requests

All inquiries regarding permission to reproduce any content in this preliminary evidence review should be directed to: MASinfo@hqontario.ca.

Enquiries from the public:

The Medical Advisory Secretariat
Health Quality Ontario
20 Dundas Street West, 10th floor
Toronto, Ontario
CANADA
M5G 2C2
Tel: 416 323-6868, ext. 261
Toll-free 1-866-623-6868
Email: MASinfo@hqontario.ca.

Media Enquiries:

416-323-6868, ext. 288

About Preliminary Evidence Reviews

Preliminary evidence reviews summarize existing evidence and information about health services and technologies that the Medical Advisory Secretariat (MAS) and the Ontario Health Technology Advisory Committee (OHTAC) have been asked to review, but for which there is insufficient evidence available to conduct a full evidence-based analysis. In each instance, OHTAC will have determined that a full review is not possible. In some instances, OHTAC may wish to make recommendations based on the information available in the preliminary evidence review.

About the Medical Advisory Secretariat

Effective April 5, 2011, MAS became a part of Health Quality Ontario (HQO), an independent body funded by the Ministry of Health and Long-Term Care. The mandate of MAS is to provide evidence-based recommendations on the coordinated uptake of health services and health technologies in Ontario to the Ministry of Health and Long-Term Care and to the health care system. This mandate helps to ensure that residents of Ontario have access to the best available and most appropriate health services and technologies to improve patient outcomes.

To fulfill its mandate, MAS conducts systematic reviews of evidence and consults with experts in the health care services community. The resulting evidence-based analyses are reviewed by OHTAC—to which MAS also provides a secretariat function—and published in the *Ontario Health Technology Assessment Series.*

Disclaimer

This preliminary evidence review was prepared by MAS for OHTAC and developed from the 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 MAS to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This analysis may be superseded by an updated publication on the same topic. Please check the MAS website for a list of all preliminary evidence reviews:
http://www.health.gov.on.ca/english/providers/program/mas/tech/pub_pe_review.html

Table of Contents

List of Abbreviations

CCSVI	Chronic cerebrospinal venous insufficiency
CI	Confidence interval(s)
IQR	Inter-quartile range
MAS	Medical Advisory Secretariat
MS	Multiple sclerosis
OHTAC	Ontario Health Technology Advisory Committee
RRMS	Relapsing-remitting MS
SD	Standard deviation
SPMS	Secondary-progressive MS

Background

MS is a chronic progressive neurologic disease believed to have an autoimmune origin. (1) 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. (1)

Ongoing Studies

Seven studies funded by the Multiple Sclerosis Society of Canada and the National Multiple Sclerosis Society in the United States have been examining the association between CCSVI and MS and the imaging technology most appropriate for investigating cerebrospinal blood flow abnormalities. (1) These studies, however, are not evaluating the treatment of CCSVI. (1) Two additional Canadian studies are evaluating the prevalence of CCSVI in MS patients compared with its prevalence in healthy control groups. (1)

Objective of Analysis

The objective of this analysis was to evaluate the prevalence of chronic cerebrospinal venous insufficiency (CCSVI) in patients with multiple sclerosis (MS) compared with control groups without MS.

Rationale for the Updated Preliminary Evidence Review

In May 2010, the Medical Advisory Secretariat (MAS) published a preliminary evidence review on Multiple Sclerosis and Chronic Cerebrospinal Venous Insufficiency. (2) The review concluded that although initial reports on intravascular interventions to remove blockages in cranial veins in multiple sclerosis (MS) patients were encouraging, unanswered questions nevertheless remained. (2) These included questions about the proposed condition known as chronic cerebrospinal venous insufficiency (CCSVI) and MS; the criteria for diagnosing CCSVI; and the neuroimaging technologies used for investigating CCSVI. (2)

In May 2010, the Ontario Health Technology Advisory Committee (OHTAC) made recommendations on CCSVI and MS (3) (Appendix 1) based on the results of the preliminary evidence review (2) conducted by the Medical Advisory Secretariat.

One of the OHTAC recommendations was that the literature should be monitored for new studies on the subject so that updated recommendations could be made once more published peer-reviewed evidence became available. (3)

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

Preliminary Evidence Review

Research Question

What is the prevalence of CCSVI in patients with MS compared with its prevalence in healthy controls?

Research Methods

Patient Population

The patient population consisted of patients with MS in whom the prevalence of CCSVI was evaluated.

Literature Search

Search Strategy

A literature search was performed on March 11, 2011 using OVID MEDLINE and OVID EMBASE for studies published since January 1, 2010. (Search terms are provided in Appendix 2.) Automatic literature search alerts were created so that studies published after the literature search was performed could be identified. Literature search updates issued until July 25, 2011 were included in this review. Reference lists were also examined for any additional relevant studies not identified through the search. Eligible studies included in the preliminary evidence review originally published by the Medical Advisory Secretariat in May 2010 (2) were also included.

Inclusion Criteria

- studies, systematic reviews, and meta-analyses that compared the prevalence of CCSVI in patients with MS with control groups, either healthy or with other neurologic diseases
- studies in English
- overall study sample size ≥ 20 subjects

Exclusion Criteria

- uncontrolled studies, systematic reviews, and meta-analyses of the prevalence of CCSVI in patients with MS

Outcomes of Interest

- prevalence of CCSVI

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 results of the studies were entered in tables as reported in the publications.

Quality of Evidence

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria as presented below. Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up. (5) The potential effects of further evidence on decision-making were also rated according to the following GRADE definitions:

High Further research is very unlikely to change confidence in the estimate of effect.

Moderate Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very low Any estimate of effect is very uncertain.

Results of the Preliminary Evidence Review

Two eligible studies were published before May 2010 (4;6) and 6 eligible studies have been published since the previous preliminary evidence review. (7-12)

Table 2: Body of Evidence Examined According to Study Design*

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	
Large RCT	
Small RCT	
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with contemporaneous controls	
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	8
Case series	
Retrospective review, modelling	
Studies presented at an international conference or other sources of grey literature	
Expert opinion	
Total	

*RCT indicates randomized controlled trial; source: Goodman et al. (13)

The studies identified comprised cross-sectional evaluations of the prevalence of CCSVI in patients with MS compared with healthy control groups. (4;6-12) One study also evaluated the prevalence of CCSVI in patients with other neurologic diseases. (9)

Most patients included in the studies presented with relapsing-remitting MS (RRMS), but some studies included patients with secondary-progressive MS (SPMS) and other forms of MS. Only 2 studies used control groups matched to MS patients by age and gender. (11;12) Details about patient recruitment and participation rates were not provided in most studies.

Six studies used Doppler ultrasound to evaluate CCSVI (4;6;8-10;12) and 2 studies used 3T magnetic resonance imaging (MRI) to evaluate the cervical and cerebral venous outflow. (7;11) Table 3 provides additional information on study characteristics and results.

Considerable inconsistencies were observed in the study results. For example, 4 studies using Doppler ultrasound to diagnose CCSVI observed a higher prevalence of CCSVI in patients with MS compared with healthy controls (4;6;8;9), while 2 studies using Doppler ultrasound did not observe a difference between the two groups. (10;12) Two studies using 3T MRI to evaluate abnormalities in cerebral or

cranial venous flow did not observe a difference between patients with MS and healthy controls. (7;11) One of the studies using 3T MRI frequently observed findings suggestive of anomalies of cranial venous outflow anatomy 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 control groups. (7)

One study did not find a statistically significant difference in the prevalence of CCSVI between patients with MS compared with 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, that CCSVI may be a consequence of MS. (9)

Table 3: Prevalence of CCSVI among Multiple Sclerosis Patients*

Study	Study Characteristics	Study Population	Prevalence of CCSVI in MS	Prevalence of CCSVI – Healthy Controls	Prevalence of CCSVI – Other neurologic diseases
Zivadinov et al. (9) (2011) US N= 289 (MS) Controls: N= 163 [healthy controls (HC)] N= 26 (other neurological diseases)	• **Study Design** Cross-sectional, single centre, blinded* • **Recruitment** Not described in detail • **Outcome** Prevalence of ≥ 2 CCSVI criteria • **Exclusion criteria** Relapse and steroid treatment 30 days prior to enrolment • **CCSVI measurement** Transcranial and extracranial echo-colour Doppler	• **Median Age (IQR)** MS: 48 (16) yrs HC: 47 (18.5) yrs OND: 50 (21.5) yrs • **Male gender** MS: 68 (23.5%) HC: 75 (46.0%) OND: 7 (26.9%) • **MS type** RRMS: 191 (66.1%) SPMS: 80 (27.7%) PPMS: 11 (3.8%) PRMS: 1 (0.3%) • **Median EDSS (IQR)** 3.0 (4.0) • **Median duration MS (IQR)** 12 (13) yrs	**CCSVI** Overall: 162 (56.1%)‡ RRMS: 94 (49.2%) SPMS (relapsing): 17 (89.5%) SPMS (non-relapsing): 41 (67.2%) PPMS: 6 (54.5%) PRMS: 0	**CCSVI** 37 (22.7%)‡ p < .001 vs. MS	**CCSVI** 11 (42.3%)‡ Not statistically significant vs. MS
Mayer et al. (10) (2011) Germany N=20 (MS) N=20 [healthy controls (HC)]	• **Study Design** Cross-sectional, single centre, blinded* • **Recruitment** Not described in detail • **Outcome** Prevalence of ≥ 2 CCSVI criteria (slightly modified criteria used) • **Exclusion criteria** Relapse 30 days prior to enrolment • **CCSVI measurement** Ultrasound by trained expert sonographer	• **Mean Age ± SD** MS: 42.2 ± 13.3 yrs HC: 34.3 ± 11.0 yrs • **Male gender** MS: 7 (35%) HC: 10 (50.0%) • **MS type** RRMS: 17 (85.0%) SPMS: 3 (15.0%) • **Median EDSS (range)** 3 (0-6.5) • **Mean MS duration ± SD** 13.1 ± 11.1 yrs • **MS patients on medication** 18 (90%) • **Mean # relapses in prior 12 months ± SD** 0.9 ± 1.1	**CCSVI** 0	**CCSVI** 1 (5%) p 1.0 vs. MS	**Not performed**

Wattjes et al. (11) (2011) Netherlands N= 20 (MS) N= 20 [healthy controls (HC)] – age- and gender-matched to MS patients	• **Study Design** Cross-sectional, single centre, blinded* • **Recruitment** Patients attending the MS clinic • **Outcome** Prevalence of extracranial venous stenosis • **Exclusion criteria** • **Outcome assessment** Magnetic resonance venography, 3T MRI	• **Mean Age ± SD** MS: 35.1 ± 9.0 yrs HC: 34.5 ± 9.2 yrs • **Male gender** NR • **MS type** RRMS: 19 (95.0%) PPMS: 1 (5.0%) • **Median EDSS (range)** 2.3 (0-6) • **Mean MS duration ± SD** 8.7 ± 6.2 yrs • **MS patients on medication** 14 (70%) • **Mean treatment duration** 37 months	**Anomalous venous system** 10 (50%) **Extracranial stenosis** 8 (40%) **Intracranial stenosis** 4 (20%) **Intracranial and/or extracranial stenosis** 10 (50%) **Venous backflow or reflux** 0	**Anomalous venous system** 8 (40%) **Extracranial stenosis** 7 (35%) **Intracranial stenosis** 1 (5%) **Intracranial and/or extracranial stenosis** 8 (40%) **Venous backflow or reflux** 0	**Not performed**
Doepp et al. (12) (2010) Germany N=56 (MS) N=20 (healthy controls (HC)) age- and gender-matched to MS patients	• **Study Design** Cross-sectional, single centre • **Recruitment** Patients attending the MS clinic • **Outcome** Prevalence of CCSVI • **Exclusion criteria** Relapse 30 days prior to enrolment • **Outcome assessment** Conventional arterial Doppler ultrasound	• **Mean Age ± SD** MS: 42.0 ± 11.0 yrs HC: 41.0 ± 12.0 yrs • **Male gender** MS: 20 (36%) HC: 8 (40%) • **MS type** RRMS: 41 (73.2%) SPMS: 1 (26.8%) • **Mean EDSS ± SD** 2.7 ± 1.9 • **Mean MS duration ± SD** 9.8 ± 8.8 yrs • **MS patients on medication** 14 (70%) • **Mean treatment duration** 37 months	**CCSVI** 0	**CCSVI** 0	**Not performed**
Sundstrom et al. (7) (2010**)** Sweden	• **Study Design** Cross-sectional, single centre • **Recruitment** Patients attending the MS	• **Median Age (range)** MS: 31.0 (19-56) yrs HC: 31.0 (24-52) yrs • **Male gender** MS: 8 (38.0%)	No significant differences between MS and HC in cerebral blood flow **<u>Venous magnetic resonance angiography in</u>**		**Not performed**

N=21 (MS) N=20 (healthy controls (HC)	clinic in whom an MRI investigation was clinically indicated • **Outcome** Prevalence of extracranial venous stenosis • **Exclusion criteria** • **Outcome assessment** 3T MRI	HC: 12 (60%) • **MS type** RRMS: 21 (100%) • **Median EDSS (range)** 2.0 (0-3.5) • **Mean MS duration (range)** 5.0 (1-25) yrs	**MS** No stenosis: 18 (85.7%)		
Zamboni et al. (8) (2011**)** Italy N= 16 (MS) N=8 (healthy controls (HC)	• **Study Design** Cross-sectional, blinded* • **Recruitment** Consecutive MS patients treated with disease-modifying agents • **Outcome** Prevalence of CCSVI • **Exclusion criteria** Relapse 30 days prior to enrolment • **Outcome assessment** Echo-Colour Doppler	• **Mean Age ± SD** MS: 36.1 ± 7.3 yrs HC: 33.1 ± 7.3 yrs • **Male gender** MS: 6 (37%) HC: 2 (25%) • **MS type** RRMS: 16 (100%) • **Mean EDSS ± SD** 2.4 ± 0.9 • **Mean MS duration ± SD** 7.5 ± 1.9 yrs • **Mean treatment duration** 14 (70%)	**CCSVI** 16 (100%)	**CCSVI** 0 $p < .001$ vs. MS (Fisher's exact test)	**Not performed**
Zamboni et al. (4) (2009**)** Italy N= 65 (MS) N= 60 (healthy controls (HC), age- and gender-matched N=82 (healthy older controls) N=48 (older controls not affected by neurological diseases) N=45 (other neurological diagnosis)	• **Study Design** Cross-sectional • **Recruitment** Not described in detail • **Outcome** Prevalence of CCSVI • **Exclusion criteria** List of concomitant diagnoses • **Outcome assessment** Extracranial echo-colour Doppler	• **Median Age (IQR)** MS: 41 (34-48) yrs Controls: 37-60 yrs • **Male gender** MS: 30 (46%) HC: 109 (46%) • **MS type** RRMS: 35 (53.8%) SPMS: 20 (30.8%) PPMS: 10 15.4%) • **Median EDSS (IQR)** 2.5 (1-5) • **Mean MS duration ± SD** Not reported • **Treatment usage** Not reported	**CCSVI individual criteria (Table 1)** 1. 46 (71%) 2. 40 (61%) 3. 24 (37%) 4. 34 (52%) 5. 36 (55%) Number of patients with ≥ 2 CCSVI criteria not provided.	**CCSVI individual criteria (Table 1)** **Pooled control groups** 1. 0 2. 0 3. 1 (0%) 4. 7 (3%) 5. 25 (35%) None had ≥ 2 CCSVI criteria.	**Not performed**

Zamboni et al. (6) (2009**)** Italy **(**N= 120 (MS) N= 60 (healthy controls (HC), age- and gender-matched) N=80 (healthy older controls) N=60 (other neurological diagnosis)	• **Study Design** Cross-sectional • **Recruitment** Not described in details • **Outcome** Prevalence of CCSVI • **Exclusion criteria** List of concomitant diagnoses • **Outcome assessment** Extracranial echo-colour Doppler	• **Median Age (IQR)** MS: 40 (12) yrs Controls: 37-58 yrs • **Male gender** MS: 30 (46%) HC: 109 (46%) • **MS type** RRMS: 69 (57.5%) SPMS: 31 (25.8%) PPMS: 9 (7.5%) • **Median EDSS (IQR)** 2 (3) • **Median MS duration (IQR)** 6 (10) • **MS Treatment** Not reported	**CCSVI** 109 (100%)	**CCSVI** 0	**Not performed**

*CCSVI chronic cerebrospinal venous insufficiency; EDSS Expanded Disability Status Scale; HC healthy controls; IQR inter-quartile range; MRI magnetic resonance imaging; MS multiple sclerosis; PPMS primary progressive MS; PRMS progressive-relapsing MS; RRMS relapsing-remitting MS; SD standard deviation; SPMS secondary progressive MS; yr year
* Rater was blinded to subject underlying condition and MS or control status
‡ Includes borderline CCSVI

Grading of Evidence

The quality of evidence in studies of the prevalence of CCSVI in patients with MS compared with healthy controls was considered very low, as evaluated based on the GRADE Working Group criteria. (14) Table 4 provides a summary of the evaluation.

Table 4: GRADE Quality of Evidence: Prevalence of CCSVI in Patients with Multiple Sclerosis compared with Healthy Controls

Outcome	Design	Quality	Consistency	Directness	Other Modifying Factors	Summary of Findings	Overall Quality
Prevalence of CCSVI in Multiple Sclerosis vs. Healthy Controls	8 controlled cross-sectional studies	▪ **Subject selection** No details about recruitment or participation rate provided in the studies ▪ **Measure of outcomes** No limitation ▪ **Losses to f-up** Not applicable ▪ **Blinding of outcome measurement** In some studies the ultrasound reader was not blinded to the patient status/ underlying condition	Important inconsistency across study results (-1)	▪ **Patient population** No limitations ▪ **Outcome** No limitations	▪ **Sparse data** No limitation ▪ **Precision** No limitation ▪ **Publication bias** Could not be evaluated	Some studies observed a higher prevalence of CCSVI in MS patients compared with healthy controls, however some studies did not find a difference in CCSVI prevalence between the 2 groups. The reasons for these inconsistencies could not be explained with the data available.	
	Low	Low	Very Low	→	→	→	**Very Low**

Conclusions

- 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.

Appendices

Appendix 1: OHTAC Recommendations on Multiple Sclerosis and Chronic Cerebrospinal and Venous Insufficiency (May 2010)

OHTAC Recommendations (May 2010) (3)

- 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.

Appendix 2: Literature Search Strategies

Search date: March 11, 2011

Database: Ovid MEDLINE(R) <1948 to March Week 1 2011>
Search Strategy:
---
1 exp Multiple Sclerosis/ or (multiple sclerosis or ms).ti,ab. (165228)
2 exp Venous Insufficiency/ or exp Angioplasty/ (51309)
3 exp Cerebrovascular Circulation/ (41983)
4 exp Hyperemia/ (4503)
5 2 or 3 or 4 (97237)
6 1 and 5 (590)
7 (chronic cerebrospinal venous insufficiency or ccsvi or (liberation adj2 (therap* or treatment* or procedure*))).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (58)
8 6 or 7 (614)
9 limit 8 to humans (489)
10 limit 9 to yr="2010 -Current" (66)

Database: EMBASE <1980 to 2011 Week 09>
Search Strategy:
---
1 exp multiple sclerosis/ (53930)
2 (multiple sclerosis or ms).ti,ab. (200233)
3 1 or 2 (212255)
4 exp chronic vein insufficiency/ (2444)
5 exp ANGIOPLASTY/ (53399)
6 exp brain circulation/ (18473)
7 exp HYPEREMIA/ (7869)
8 or/4-7 (81780)
9 (chronic cerebrospinal venous insufficiency or ccsvi or (liberation adj2 (therap* or treatment* or procedure*))).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] (88)
10 3 and 8 (458)
11 9 or 10 (505)
12 limit 11 to human (391)
13 limit 12 to yr="2010 -Current" (61)

References

(1) 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

(2) 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

(3) 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

(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) Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. 2011 Apr;64(4):407-15.

(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.

(13) Goodman, C. Literature searching and evidence interpretation for assessing health care practices. Stockholm, Sweden: The Swedish Council on Technology Assessment in Health Care; 1993 81 p. SBU-Report No 119E.

(14) 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.