Association between chronic cerebrospinal venous insufficiency and multiple sclerosis: a meta-analysis

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See related commentary by Fox at www.cmaj.ca/lookup/doi/10.1503/cmaj.111506

ABSTRACT

Background: It has been proposed by Zamboni and colleagues that multiple sclerosis is caused by chronic cerebrospinal venous insufficiency, a term used to describe ultrasound-detectable abnormalities in the anatomy and flow of intra- and extracerebral veins. We conducted a meta-analysis of studies that reported the frequency of chronic cerebrospinal venous insufficiency among patients with and those without multiple sclerosis.

Methods: We searched MEDLINE and EMBASE as well as bibliographies of relevant articles for eligible studies. We included studies if they used ultrasound to diagnose chronic cerebrospinal venous insufficiency and compared the frequency of the venous abnormalities among patients with and those without multiple sclerosis.

Results: We identified eight eligible studies: all included healthy controls, and four of them also included a control group of patients with neurologic diseases other than multiple sclerosis. Chronic cerebrospinal venous insufficiency was more frequent among patients with multi-

ple sclerosis than among the healthy controls (odds ratio [OR] 13.5, 95% confidence interval [CI] 2.6–71.4), but there was extensive unexplained heterogeneity among the studies. The association remained significant in the most conservative sensitivity analysis (OR 3.7, 95% CI 1.2–11.0), in which we removed the initial study by Zamboni and colleagues and added a study that did not find chronic cerebrospinal venous insufficiency in any patient. Although chronic cerebrospinal venous insufficiency was also more frequent among patients with multiple sclerosis than among controls with other neurologic diseases (OR 32.5, 95% CI 0.6–1775.7), the association was not statistically significant, the 95% CI was wide, and the OR was less extreme after removal of the study by Zamboni and colleagues (OR 3.5, 95% 0.8–15.8).

Interpretation: Our findings showed a positive association between chronic cerebrospinal venous insufficiency and multiple sclerosis. However, poor reporting of the success of blinding and marked heterogeneity among the studies included in our review precluded definitive conclusions.

M ultiple sclerosis is a chronic demyelinating and degenerative disease of the central nervous system. The exact cause remains unknown, but most evidence favours an autoimmune mechanism.[1] In 2006, Zamboni and colleagues proposed that multiple sclerosis is caused by abnormalities in the direction and pathway of cerebral venous flow, leading to deposition of iron in the brain, which triggers an autoimmune reaction.[2] They reported that patients with multiple sclerosis had a higher frequency of abnormalities of anatomy and flow in the internal jugular, deep cerebral, vertebral and azygos veins than individuals without multiple sclerosis had.[3,4] They called this condition chronic cerebrospinal venous insufficiency. They further described detection of this

condition by means of transcranial and extracranial Doppler ultrasonography. This method of detection requires the evaluation of five ultrasound parameters that assess both venous blood flow and anatomy.[3,5] Chronic cerebrospinal venous insufficiency is diagnosed if a patient has an abnormality in two or more of the five parameters.

There is controversy about the frequency and role of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis[6,7] and whether the frequency differs between patients with and those

A summary for patients that explains the purpose, design and main findings of this study is available in Appendix 1, at www.cmaj.ca/lookup/suppl /doi:10.1503/cmaj.111074/-/DC1.

without multiple sclerosis. We performed a systematic review and meta-analysis of all peer-reviewed reports of studies that compared the frequency of chronic cerebrospinal venous insufficiency among patients with and those without multiple sclerosis.

Methods

Literature search

We searched the MEDLINE and EMBASE electronic databases for articles reporting the frequency of chronic cerebrospinal venous insufficiency among patients with and those without multiple sclerosis published from 2005 to June 28, 2011. No language restrictions were imposed. The search was done as part of a larger

systematic review of all methods of evaluating the cerebral and azygos veins in patients with multiple sclerosis. The detailed search strategy, carried out by an information scientist (L.P.), is shown in Appendix 1 (available at www.cmaj.ca /lookup/suppl/doi:10.1503/cmaj.111074/-/DC1). We examined reference lists of all articles that met the eligibility criteria and of review articles to identify studies that may have been missed by the database searches. We also contacted experts to verify that no relevant studies were omitted.

Study selection

Studies were eligible if they met all of the following criteria: they reported original data in a peer-reviewed publication; they used Doppler ultrasonography to detect chronic cerebrospinal venous insufficiency; and they assessed patients who had multiple sclerosis and had at least one control group (healthy controls or patients with neurologic diseases other than multiple sclerosis).

The titles and abstracts of all studies identified were screened independently by two of us (A.L. and S.S.). Studies that appeared to be relevant were selected and the full-text versions assessed independently by the same two reviewers. Disagreements were resolved by consensus or involvement of a third reviewer (A.D.).

Data extraction and analysis

Two reviewers independently extracted data about the study characteristics, the methodologic quality of the studies (assessed using items derived from the Newcastle–Ottawa Quality Assessment Scale tool for observational studies[8]), patient characteristics and ultrasound results. Disagreements were resolved by consensus.

We used the Cochrane Review Manager 5.1, version 5.1.2, to generate odds ratios and forest plots, to determine whether there was a statistical association between chronic cerebrospinal venous insufficiency and multiple sclerosis (using a random-effects model) and to assess heterogeneity of the studies.[9] Heterogeneity was quantified using the I^2 statistic.

To test the robustness of the main results, we conducted sensitivity analyses, which included the removal of the initial study by Zamboni and colleagues[4] and the addition of a study by Doepp and colleagues[10] that did not find chronic cerebrospinal venous insufficiency in any patient.[10]

Results

Identification of eligible studies

Of the 471 records found initially, we identified 10 studies that used Doppler ultrasonography and met our inclusion criteria (Figure 1). Of
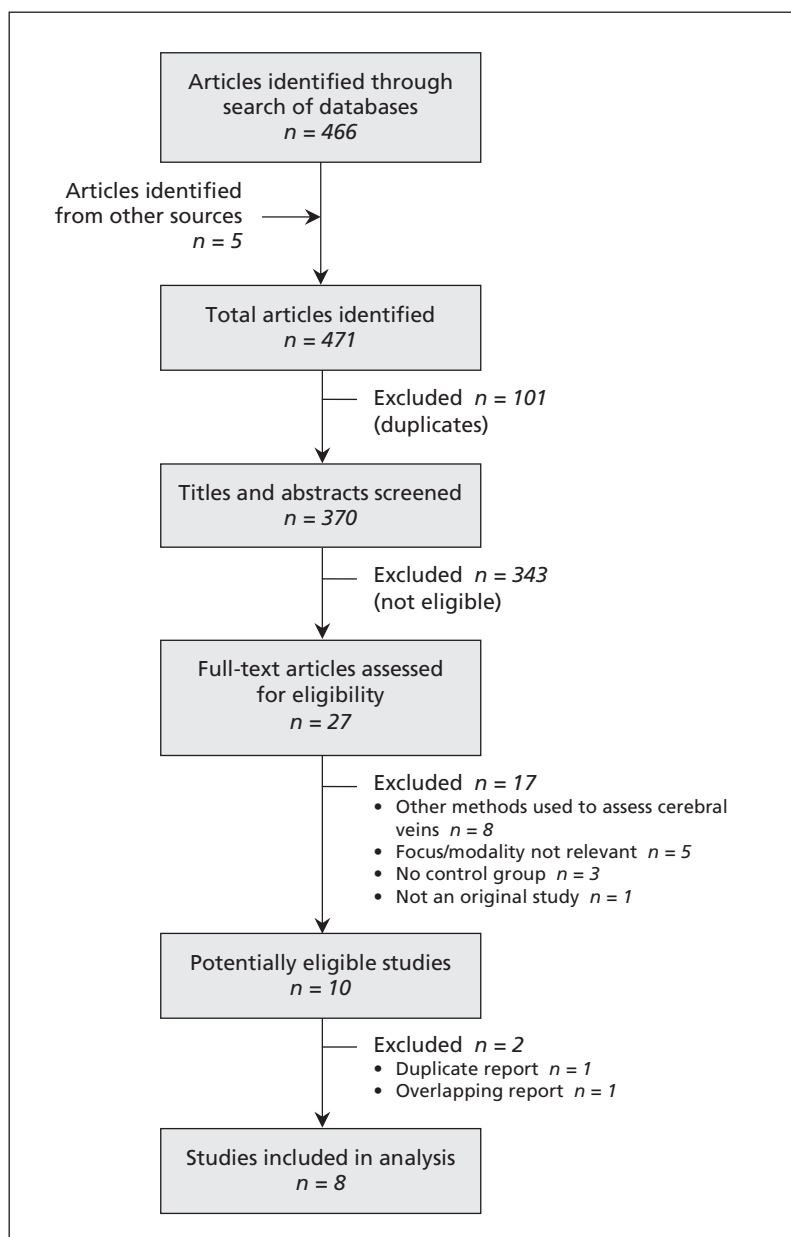

Figure 1: Results of literature search and identification of eligible studies.

three studies from Zamboni's group,[3–5] two described the same patients and reported the same results,[3,5] and two appeared to describe overlapping patients[3,4] but did not report dates of enrolment. We included what appeared to be the most recent study by Zamboni and colleagues with the largest number of patients[4] and excluded the other two studies. Thus, eight studies were included in the meta-analysis.[4,10–16]

Study characteristics

The studies were conducted in Italy (n = 3), Germany (n = 3), Jordan (n = 1) and the United States (n = 1). Most enrolled a small number of patients with multiple sclerosis (range 10–310) and controls (range 7–210) (Tables 1, 2 and 3). All eight studies included healthy controls, and four also included controls with neurologic diseases other than multiple sclerosis. All studies except that by Centonze and coworkers[13] described their assessment of the five ultrasound parameters for chronic cerebrospinal venous insufficiency as well as the

ultimate diagnosis of the condition. Both Zamboni and colleagues[4] and Krogias and coworkers[14] included healthy individuals and patients with neurologic diseases other than multiple sclerosis as controls, but they did not report the results for these two groups separately. No controls in either of these studies had chronic cerebrospinal venous insufficiency. However, for the analysis of the individual ultrasound parameters, if one or more controls in the study by Zamboni and colleagues fulfilled the criteria for a parameter, we considered all of the controls to be healthy controls in the analysis of that parameter because 75% of their controls were healthy controls. Similarly, if one or more of the controls in the study by Krogias and coworkers fulfilled the criteria for a parameter, we considered all of the controls to be patients with other neurologic diseases in the analysis of that parameter because 71% of their controls had such diseases.

Most of the studies did not describe clearly how patients were identified for enrolment and

Table 1: Characteristics of studies included in meta-analysis that compared the frequency of chronic cerebrospinal venous insufficiency among patients with and without multiple sclerosis (MS)

Study	No. of patients with MS	No. of controls		Ultrasound equipment used	Blinding
		Healthy controls	Patients with neurologic diseases other than MS		
Al-Omari et al.[11]	25	25	NA	Philips ATL HDI 5000 with 4–7-MHz linear probe and/or 5–8-Mhz curved probe; transcranial exam not performed (probe not available)	Not blinded
Baracchini et al.[12]	50	110	60	Philips iU22 xMatrix; 5–10-MHz linear array probe for extracranial exam, 1–3-MHz phased array probe for transcranial exam	Described as blinded but did not describe how blinding was ensured or whether blinding was tested
Centonze et al.[13]	84	56	NA	Esaote Biomedica MyLab-Vinco 25 with 11–3-MHz LA322 linear probe	Described blinding process but did not describe whether blinding was achieved
Doepp et al.[10]	56	20	NA	Toshiba PowerVision 6000; 7.5-MHz linear transducer for extracranial exam, 2.5-MHz probe for transcranial exam	Not blinded
Krogias et al.[14]	10	2	5	Not described	Not blinded
Mayer et al.[15]	20	20	NA	Phillips iU22 with L9-3 probe to assess internal jugular veins and vertebral veins; S5-1 probe used to assess intracranial veins	Described blinding process but did not describe whether blinding was achieved
Zamboni et al.[4]	109	132	45	Esoate Biosound MyLab 25; 7.5–10 MHz for extracranial exam, 2.5 MHz for intracranial exam	Described as blinded but did not describe how blinding was undertaken or whether blinding was achieved
Zivadinov et al.[16]	310	163	26	Esaote-Biosound MyLab Gold 25 equipped with 2.5- and 7.5–10-MHz transducers	Described blinding process but did not describe whether blinding was achieved

Note: NA = not applicable.

appeared to enrol a convenience sample (Table 4). Three studies were not blinded (Table 1). The method of blinding of the ultrasound technician and the interpreter of the images was poorly described in two studies,[4,12] reasonably well-described in two others[13,16] and well-described in one study.[15] However, the success of blinding was not reported by any study.

Although one study described the ultrasound technique used in great detail,[16] the training of ultrasonographers and radiologists in assessing this relatively novel entity, and in ensuring quality control, was generally poorly described (Table 4). Two of the studies indicated that their ultrasonographers were trained by Zamboni's group.[13,16] No study described a run-in period during which intra- and interobserver reliability was determined to be good, although one study described intraobserver variability.[16]

Most of the patients with multiple sclerosis had relapsing–remitting disease; those in the study by Baracchini and colleagues[12] had clinically isolated syndrome (Table 2). Most patients were taking disease-modifying agents. The mean age, proportion of women and mean Expanded Disability Status Scale scores (range 1.5–5.8) were typical of patients with clinically isolated syndrome and multiple sclerosis (Table 2).

Frequency of chronic cerebrospinal venous insufficiency

The diagnosis of chronic cerebrospinal venous insufficiency requires that a patient have an abnormality in at least two of the following five ultrasound parameters:[3,4] (1) reflux in the internal jugular veins or vertebral veins for more than 0.88 seconds, assessed in the supine and sitting position without use of the Valsalva manoeuvre;

(2) reversal of flow in at least one of the deep cerebral veins; (3) stenoses of the internal jugular vein identified on high-resolution B-mode imaging; (4) flow in the internal jugular veins or vertebral veins not detectable by Doppler ultrasonography; and (5) reverted postural control of the main cerebral venous outflow pathway (internal jugular veins). [A diagram of the five vascular abnormalities is available online at www .cmaj.ca/lookup/suppl/doi:10.1503/cmaj.111506 /-/DC1. — Ed.]

Figure 2 displays the results of the meta-analyses of data on the frequency of chronic cerebrospinal venous insufficiency among patients with multiple sclerosis compared with healthy controls and with controls who had a neurologic disease other than multiple sclerosis.

In the comparisons with healthy controls, the frequency of chronic cerebrospinal venous insufficiency among patients with multiple sclerosis varied markedly, from none[10,15] to 100%[4] (Figure 2). The association between chronic cerebrospinal venous insufficiency and multiple sclerosis also varied markedly, from an odds ratio (OR) of 0.32 (95% CI 0.01–8.3) to an OR of 58 035.0 (95% CI 1142.2– 2 948 755.8). The pooled analysis revealed a statistically significant association between chronic cerebrospinal venous insufficiency and multiple sclerosis, as compared with healthy controls (OR 13.5, 95% CI 2.6–71.4); however, there was extensive heterogeneity among study results ($I^2 = 89\%$).

In terms of the five individual parameters, patients with multiple sclerosis had significantly higher odds than healthy controls of having reflux in the internal jugular or vertebral veins (OR 13.7, 95% CI 2.0–93.8), although there was

Table 2: Characteristics of patients with multiple sclerosis (MS) included in studies

Study	Type of MS; no. of MS patients			Age, yr	Female, %	EDSS score	Use of disease-modifying medications, %	Duration of MS, yr
	Clinically isolated syndrome	Relapsing–remitting	Other					
Al-Omari et al.[11]	0	21	4	35*	52	NA	NA	NA
Baracchini et al.[12]	50	0	0	33*	70	1.5†	28	NA
Centonze et al.[13]	0	69	15	39*	62	NA	82	NA
Doepp et al.[10]	0	41	15	42*	65	2.7*	NA	10*
Krogias et al.[14]	0	2	8	42†	30	5.8†	NA	NA
Mayer et al.[15]	0	17	3	42*	65	3†	90	13*
Zamboni et al.[4]	0	69	40	40†	59	2†	NA	6†
Zivadinov et al.[16]	21	191	98	48†	76	3†	89‡	12†

Note: EDSS = Expanded Disability Status Scale, NA = not available.
*Mean.
†Median.
‡Calculation based on 289 patients (excludes patients with clinically isolated syndrome).

extensive heterogeneity among study results ($I^2 = 85\%$). The other parameters were also more frequent among patients with multiple sclerosis than among healthy controls, but these trends did not reach statistical significance (Figure 3).

In the comparisons with controls who had other neurologic diseases, chronic cerebrospinal venous insufficiency was more frequent among patients with multiple sclerosis (Figure 2), but the association was not statistically significant (OR 32.5, 95% CI 0.59–1775.7) and heterogeneity among the study results was large ($I^2 = 90\%$). Again, the only individual ultrasound parameter that was significantly more frequent among patients with multiple sclerosis than among controls with other neurologic diseases was reflux in the internal jugular or vertebral veins (OR 6.7, 95% CI 1.3–34.8; $I^2 = 73\%$) (Figure 4).

Sensitivity analyses

Because Zamboni and colleagues were the first to describe chronic cerebrospinal venous insufficiency (and therefore their study could be considered hypothesis-generating) and because the OR found in their study was extremely high,[4] we repeated the meta-analysis with their study removed. The odds of chronic cerebrospinal venous insufficiency being more frequent among patients with multiple sclerosis than among healthy controls decreased from an OR of 13.5 to 4.7 (95% 1.5–14.6), but the association remained statistically significant with considerable heterogeneity ($I^2 = 73\%$) (Figure A in Appendix 2, available at www.cmaj.ca/lookup/suppl/doi: 10.1503/cmaj.111074/-/DC1).

When we repeated the meta-analysis after changing zero to one in each cell for the study by Doepp and colleagues, in which none of the patients with multiple sclerosis or healthy controls had chronic cerebrospinal venous insufficiency, the results were similar to those of the primary analysis (OR 8.8, 95% CI 1.9–42.0; $I^2 = 88\%$) (Figure B in Appendix 2).

Table 3: Characteristics of participants included in control groups

Study	No. of participants	Age, yr	Female, %
Healthy controls			
Al-Omari et al.[11]	25	34‡	52
Baracchini et al.[12]			
Group 1*	50	33‡	70
Group 2†	60	63‡	53
Centonze et al.[13]	56	42‡	64
Doepp et al.[10]	20	41‡	60
Mayer et al.[15]	20	34‡	50
Zamboni et al.[4]			
Group 1*	60	37§	53
Group 2†	72	58§	60
Zivadinov et al.[16]	163	47§	54
Controls with neurologic diseases other than MS			
Baracchini et al.[12]	60	64‡	53
Krogias et al.[14]	7	40§	29
Zamboni et al.[4]	45	60§	44
Zivadinov et al.[16]	26	50§	73

Note: MS = multiple sclerosis, NA = not applicable.
*Healthy controls in group 1 were matched with MS patients.
†In the study by Baracchini et al., healthy controls in group 2 were matched with controls who had neurologic diseases other than MS; in the study by Zamboni et al., healthy controls in group 2 were older than the median age of the European MS population.
‡Mean.
§Median.

Table 4: Methodologic quality of studies included in meta-analysis*

Study	Experience level		Case definition		Representativeness of patients	
	Was evidence provided that operator had adequate experience to conduct test?	Was evidence provided that interpreter had adequate experience to interpret results?	Were patients examined to confirm that they had MS?	Were controls examined to confirm that they did not have MS or to confirm other neurologic diagnosis?	How were patients identified for enrolment?	Were controls matched to cases by sex and age?
Al-Omari et al.[11]	No	No	Not sure	No	Convenience	Yes
Baracchini et al.[12]	No	No	Yes	No	Consecutively	Yes
Centonze et al.[13]	Yes	Yes	Yes	No	Convenience	Yes
Doepp et al.[10]	No	No	Yes	No	Convenience	Yes
Krogias et al.[14]	No	No	Not sure	No	Convenience	Not sure
Mayer et al.[15]	No	No	Not sure	No	Convenience	No
Zamboni et al.[4]	Yes	Yes	Not sure	No	Convenience	Yes
Zivadinov et al.[16]	Yes	Yes	Yes	Yes	Convenience	No

Note: MS = multiple sclerosis.
*Methodologic quality was assessed using items derived from the Newcastle–Ottawa Quality Assessment Scale tool for observational studies.[8]

In the next sensitivity analysis, we removed the study by Zamboni and colleagues and changed zero to one in each cell for the study by Doepp and colleagues, thus providing the most conservative estimation of the odds of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis versus healthy controls. This analysis yielded a substantially weaker but still statistically significant association compared with the primary analysis (OR 3.7, 95% CI 1.2–11.0; $I^2 = 72\%$) (Figure C in Appendix 2).

The exclusion of studies that were reported as not blinded[10,11,14] produced similar results to the primary analysis comparing patients with multiple sclerosis and healthy controls (OR 11.4, 95% CI 1.8–73.2; $I^2 = 91\%$) (Figure D in Appendix 2).

When we removed the study by Zamboni and colleagues from the meta-analysis comparing patients with multiple sclerosis and those with other neurologic diseases, the association was greatly weakened (OR 3.5, 95% CI 0.8–15.8) and heterogeneity was reduced ($I^2 = 37\%$) (Figure E in Appendix 2).

When we assumed that all patients in the study by Zivadinov and colleagues[16] (in whom ultrasound parameter two [reversal of flow in at least one of the deep cerebral veins] could not be assessed) were negative for that parameter, or when we removed patients with clinically isolated syndrome from the multiple sclerosis group, there was no material effect on the results.

Interpretation

We found a strong and statistically significant association between chronic cerebrospinal venous insufficiency and multiple sclerosis. However, the large amount of heterogeneity among the study results prevents a definitive conclusion. The source of the heterogeneity is not clear. It is not obviously caused by differences in the definition of chronic cerebrospinal venous insufficiency, patient characteristics or the methodologic quality of the studies.

We also could not identify any factor that accounted for the large and problematic difference between the studies in the frequency of chronic cerebrospinal venous insufficiency among patients with multiple sclerosis. Although small samples may be partly responsible, the magnitude of the difference strongly suggests that other factors are important. One obvious possibility is differences in ultrasound technique. It is crucial that ultrasonographers agree upon the technique to be used to diagnose chronic cerebrospinal venous insufficiency, and on a method to ensure quality control.
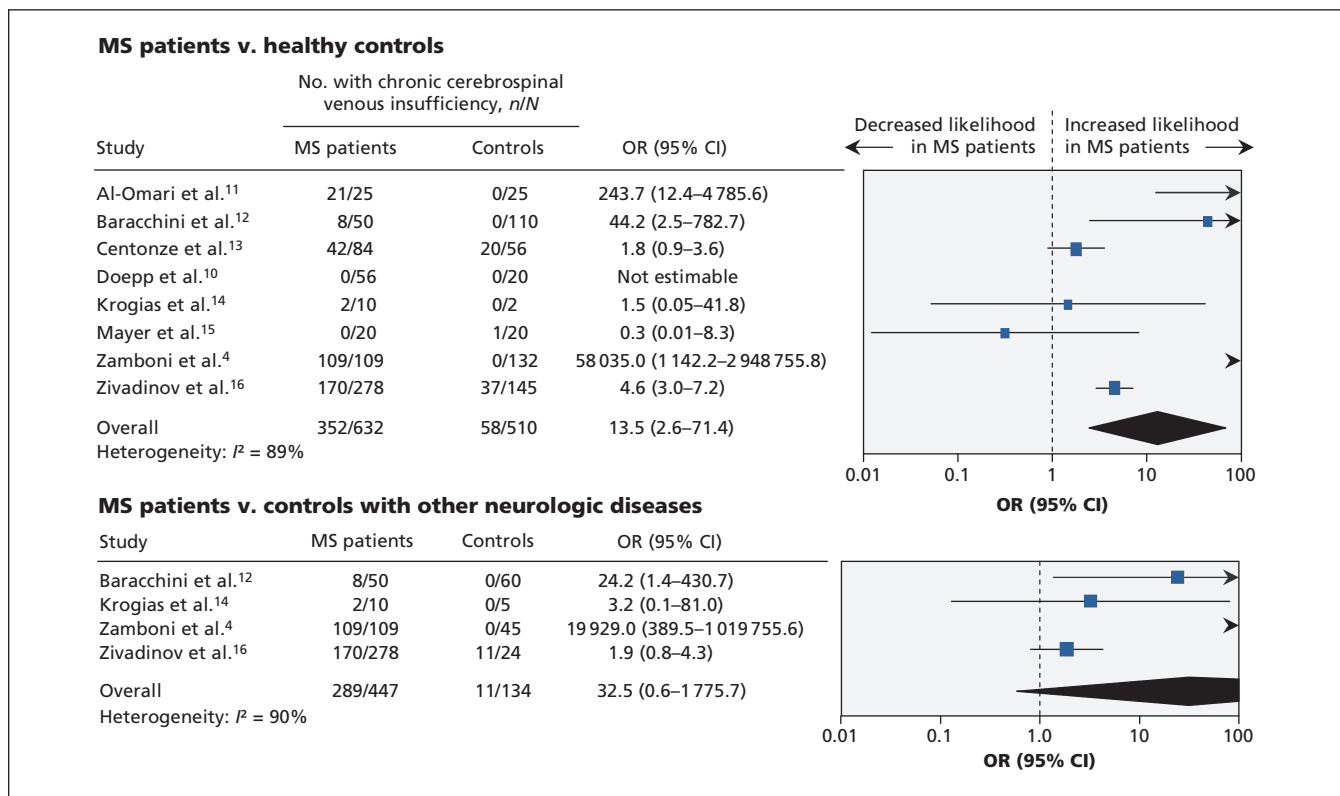
Figure 2: Meta-analysis of diagnosis of chronic cerebrospinal venous insufficiency (presence of at least two parameters) in patients with multiple sclerosis (MS) versus healthy controls (top panel) and controls with other neurologic diseases (bottom panel). An odds ratio greater than 1.0 indicates an increased likelihood of a diagnosis of chronic cerebrospinal venous insufficiency in MS patients versus controls. CI = confidence interval, OR = odds ratio.

Parameter 1

Study	No. fulfilling criteria for parameter, n/N		OR (95% CI)
	MS patients	Healthy controls	
Al-Omari et al.[11]	18/25	6/25	8.1 (2.3–28.9)
Baracchini et al.[12]	12/50	0/110	71.8 (4.2–1241.0)
Doepp et al.[10]	0/56	0/20	Not estimable
Krogias et al.[14]	1/10	0/2	0.8 (0.02–25.9)
Mayer et al.[15]	0/20	0/20	Not estimable
Zamboni et al.[4]	76/109	0/132	605.2 (36.6–10 017.0)
Zivadinov et al.[16]	137/310	33/163	3.1 (2.0–4.9)
Overall	244/580	39/472	13.7 (2.0–93.8)

Heterogeneity: I^2 = 85%

Parameter 2

Study	MS patients	Healthy controls	OR (95% CI)
Baracchini et al.[12]	0/50	0/110	Not estimable
Doepp et al.[10]	1/56	0/20	1.1 (0.04–28.3)
Krogias et al.[14]	1/10	0/2	0.8 (0.02–25.9)
Mayer et al.[15]	0/20	0/20	Not estimable
Zamboni et al.[4]	55/109	0/132	269.9 (16.4–4 447.0)
Zivadinov et al.[16]	110/236	15/118	6.0 (3.3–10.9)
Overall	167/481	15/402	6.9 (0.6–74.9)

Heterogeneity: I^2 = 75%

Parameter 3

Study	MS patients	Healthy controls	OR (95% CI)
Baracchini et al.[12]	8/50	0/10	44.2 (2.5–782.7)
Doepp et al.[10]	0/56	0/20	Not estimable
Krogias et al.[14]	0/10	0/2	Not estimable
Mayer et al.[15]	13/20	16/20	0.5 (0.1–1.9)
Zamboni et al.[4]	30/109	1/177	66.8 (9.0–498.8)
Zivadinov et al.[16]	197/310	63/163	2.8 (1.9–4.1)
Overall	248/555	80/492	6.0 (0.9–40.3)

Heterogeneity: I^2 = 86%

Parameter 4

Study	MS patients	Healthy controls	OR (95% CI)
Al-Omari et al.[11]	0/25	0/25	Not estimable
Baracchini et al.[12]	3/50	1/110	7.0 (0.7–68.6)
Doepp et al.[10]	5/56	1/20	1.9 (0.2–17.0)
Krogias et al.[14]	3/10	0/2	2.3 (0.1–62.7)
Mayer et al.[15]	0/20	1/20	0.3 (0.01–8.3)
Zamboni et al.[4]	35/109	1/177	83.2 (11.2–618.9)
Zivadinov et al.[16]	30/310	12/163	1.4 (0.7–2.7)
Overall	76/580	16/517	3.5 (0.7–18.5)

Heterogeneity: I^2 = 76%

Parameter 5

Study	MS patients	Healthy controls	OR (95% CI)
Al-Omari et al.[11]	4/25	0/25	10.7 (0.5–209.6)
Baracchini et al.[12]	8/50	6/110	3.3 (1.1–10.1)
Doepp et al.[10]	4/56	3/20	0.4 (0.1–2.2)
Mayer et al.[15]	0/20	0/20	Not estimable
Zamboni et al.[4]	61/109	21/177	9.4 (5.2–17.1)
Zivadinov et al.[16]	35/310	11/163	1.8 (0.9–3.6)
Overall	112/570	41/515	2.9 (0.96–8.6)

Heterogeneity: I^2 = 81%

Forest plot axes: Decreased likelihood in MS patients ← | → Increased likelihood in MS patients. OR (95% CI) scale: 0.01, 0.1, 1.0, 10, 100.
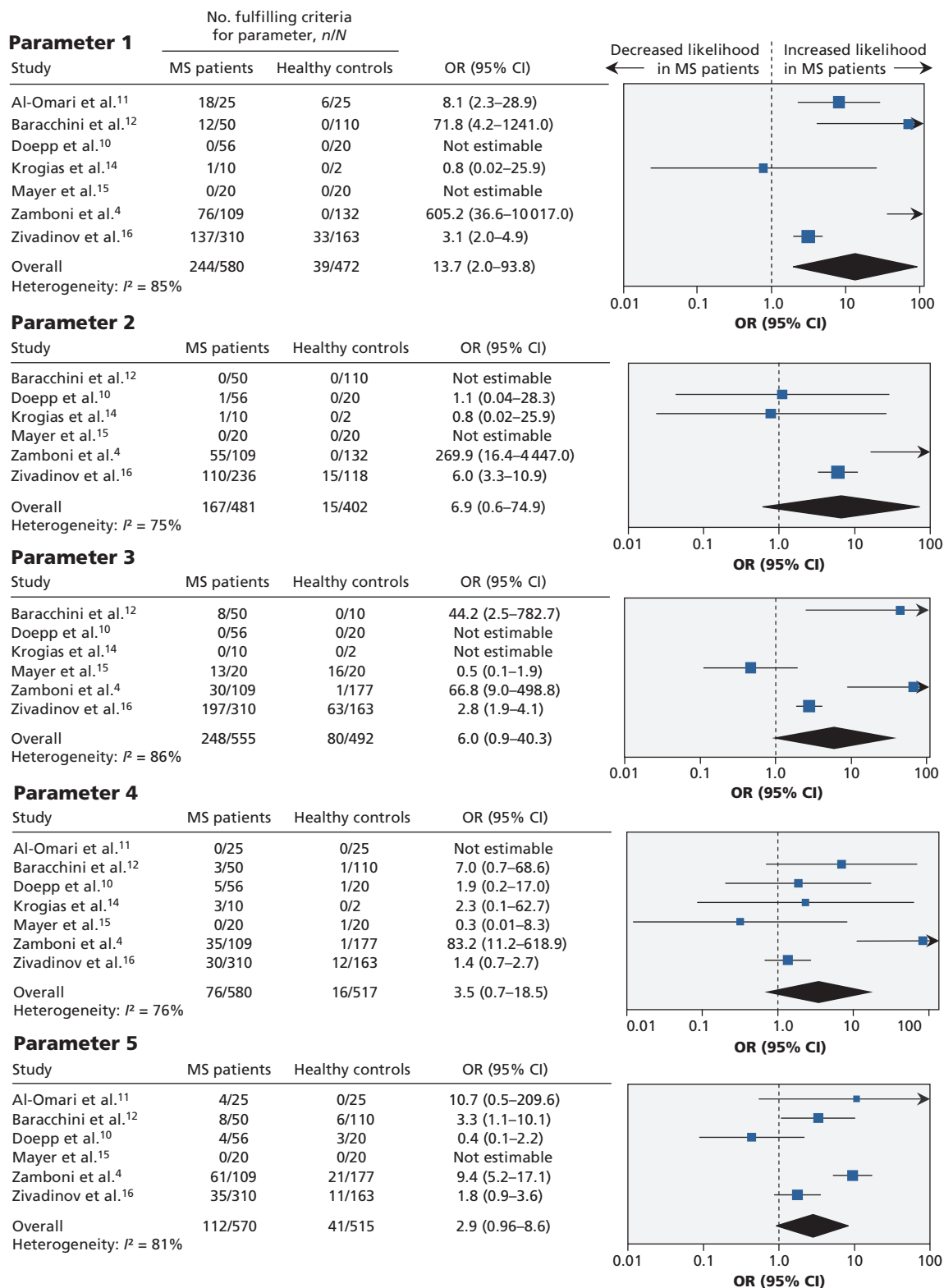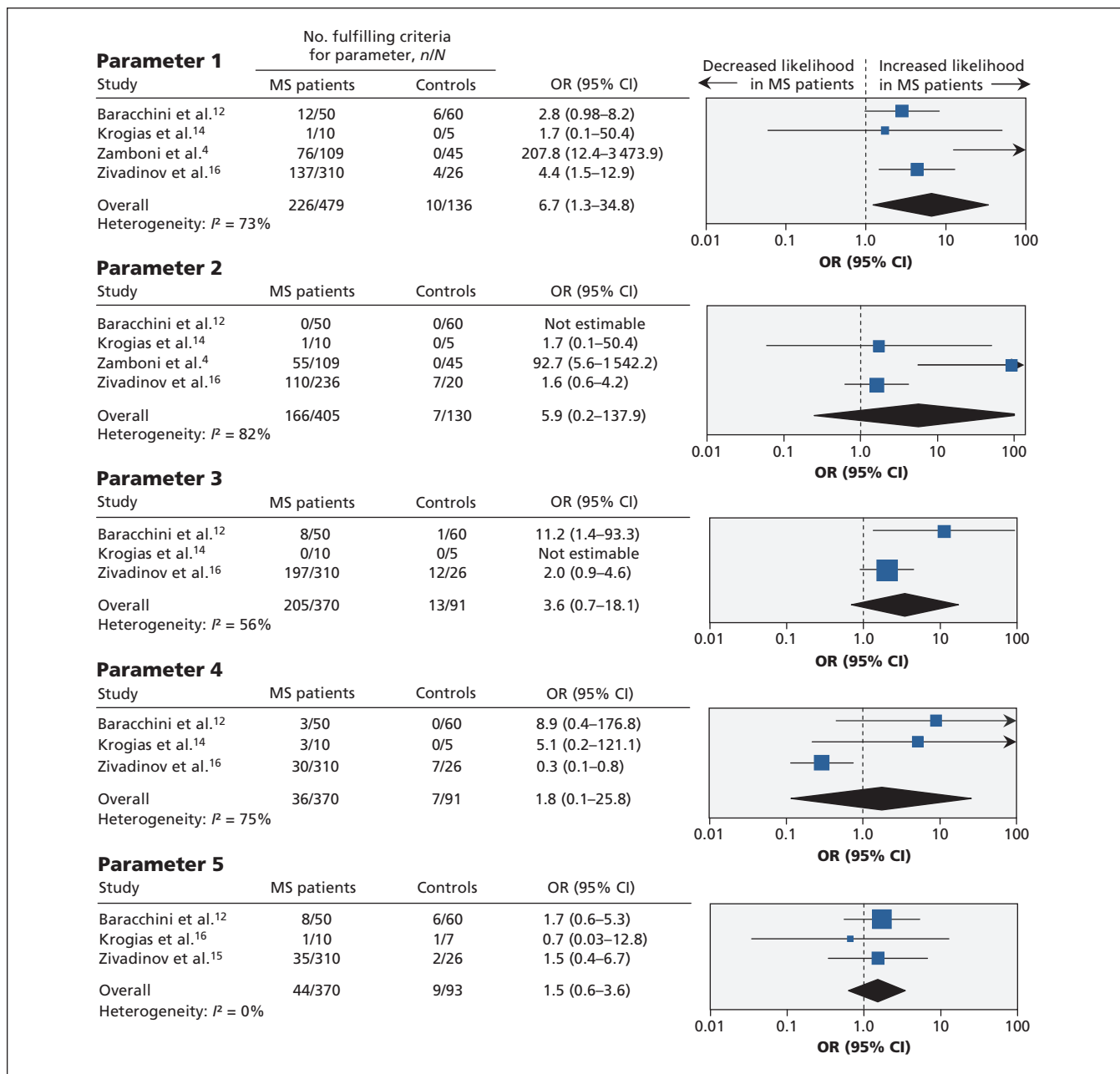
Figure 3: Meta-analysis of individual parameters of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis (MS) versus healthy controls. (1) Reflux in internal jugular veins or vertebral veins; (2) flow reversal in deep cerebral veins; (3) stenoses of internal jugular vein; (4) flow not detectable in internal jugular veins or vertebral veins; and (5) reverted postural control of main cerebral venous outflow pathway (internal jugular veins). An odds ratio greater than 1.0 indicates an increased likelihood of the parameter being present in MS patients versus controls. CI = confidence interval, OR = odds ratio.

Reflux in the deep cerebral veins is the most technically challenging of the ultrasound parameters to identify. One study was unable to assess it at all,[11] and another was unable to assess it in 28% of patients.[16] Another study, which we excluded from our systematic review because it did not have a control group of people without multiple sclerosis, was also unable to evaluate the deep cerebral veins.[17] This questions the appropriateness of having a diagnostic parameter that is difficult to assess and emphasizes the

importance of training ultrasonographers in how to assess the deep cerebral veins.

Because ultrasonography is so operator-dependent, the lack of blinding in three studies, and the lack of a description of how well blinding was achieved in all of the other studies, is of concern. Future studies should report the mechanism and success of blinding in detail. The intra- and interobserver variability of the diagnosis of chronic cerebrospinal venous insufficiency also needs assessment. Zivadinov and

Figure 4: Meta-analysis of individual parameters of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis (MS) versus controls with other neurologic diseases. (1) Reflux in internal jugular veins or vertebral veins; (2) flow reversal in deep cerebral veins; (3) stenoses of internal jugular vein; (4) flow not detectable in internal jugular veins or vertebral veins; and (5) reverted postural control of main cerebral venous outflow pathway (internal jugular veins). An odds ratio greater than 1.0 indicates an increased likelihood of the parameter being present in MS patients versus controls. CI = confidence interval, OR = odds ratio.

colleagues assessed the intrarater reliability of the diagnosis of the condition in 28 patients (11 with multiple sclerosis) one week apart and found an agreement of 89% and a kappa value of 0.75.[16] The diagnosis differed between raters in 11% (3/28) of patients. Another paper about reproducibility did not provide data in a manner allowing interpretation similar to the above.[18] More studies of the reproducibility of the assessment of chronic cerebrospinal venous insufficiency are needed.

An association between chronic cerebrospinal venous insufficiency and multiple sclerosis does not mean that the condition causes multiple sclerosis. Indeed, some observations, including a subgroup analysis of the methodologically sound study by Zivadinov and colleagues,[16] suggest that chronic cerebrospinal venous insufficiency may be a consequence of multiple sclerosis. In the study by Zivadinov and colleagues, the frequency of chronic cerebrospinal venous insufficiency was roughly inversely correlated to the duration of multiple sclerosis: 38% (8/21) among patients with clinically isolated syndrome, 49% (94/191) among those with relapsing–remitting multiple sclerosis and 73% (58/80) among those with secondary progressive multiple sclerosis. Another study, which used angiography in 42 patients with multiple sclerosis, found stenosis of the jugular or azygos vein in 9% (1/11) of patients with clinically isolated syndrome, 33% (6/18) of those with early relapsing–remitting multiple sclerosis and 89% (12/13) of those with late multiple sclerosis (average duration 14 years).[19] These observations are not definitive, and further research examining the link between chronic cerebrospinal venous insufficiency and duration of multiple sclerosis is needed.

Limitations

Only eight studies were eligible for our review, and many of them were small. Three studies were not blinded, and none of the others reported the success of blinding. The description of the ultrasound technique was limited in some studies, so it is unclear whether the techniques differed across the studies. As with most systematic reviews, there is the potential for publication bias. However, the question about whether chronic cerebrospinal venous insufficiency is associated with multiple sclerosis is so controversial that we feel positive and negative studies are both likely to be published. Finally, we did not have access to individual patient data and therefore were unable to explore whether the frequency of chronic cerebrospinal venous insufficiency was affected by individual factors such as age, sex and type of multiple sclerosis.

Conclusion

We found a strong association between chronic cerebrospinal venous insufficiency and multiple sclerosis. However, poor reporting of the success of blinding and marked heterogeneity among the studies included in our review precluded definitive conclusions. Further high-quality studies, using identical ultrasound protocols, are needed to definitively determine whether chronic cerebrospinal venous insufficiency is more frequent among patients with multiple sclerosis than among those without it. Our meta-analysis will need to be updated as the results of future studies become available.

References

1. Bar-Or A. The immunology of multiple sclerosis. *Semin Neurol* 2008;28:29-45.
2. Zamboni P. The big idea — iron-dependent inflammation in venous disease and proposed parallels in multiple sclerosis. *J R Soc Med* 2006;99:589-93.
3. Zamboni P, Galeotti R, Menegatti E, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2009;80:392-9.
4. Zamboni P, Menegatti E, Galeotti R, et al. The value of cerebral Doppler venous haemodynamics in the assessment of multiple sclerosis. *J Neurol Sci* 2009;282:21-7.
5. Bartolomei I, Salvi F, Galeotti R, et al. Hemodynamic patterns of chronic cerebrospinal venous insufficiency in multiple sclerosis. Correlation with symptoms at onset and clinical course. *Int Angiol* 2010;29:183-8.
6. Khan O, Filippi M, Freedman MS, et al. Chronic cerebrospinal venous insufficiency and multiple sclerosis. *Ann Neurol* 2010;67:286-90.
7. Worthington V, Kilestein J, Eikelenboom MJ, et al. Normal CSF ferritin levels in MS suggest against etiologic role of chronic venous insufficiency. *Neurology* 2010;75:1617-22.
8. Wells GA, Shea B, O'Connell D, et al. *The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses.* Ottawa (ON): The Ottawa Hospital Research Institute. Available: www.ohri.ca/programs/clinical_epidemiology /oxford.asp (accessed 2011 June 25).
9. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions.* Version 5.1.0. The Cochrane Collaboration; 2011. Available: www.cochrane-handbook.org (accessed 2011 June 25).
10. Doepp F, Paul F, Valdueza JM, et al. No cerebrocervical venous congestion in patients with multiple sclerosis. *Ann Neurol* 2010;68:173-83.
11. Al-Omari MH, Rousan LA. Internal jugular vein morphology and hemodynamics in patients with multiple sclerosis. *Int Angiol* 2010;29:115-20.
12. Baracchini C, Perini P, Calabrese M, et al. No evidence of chronic cerebrospinal venous insufficiency at multiple sclerosis onset. *Ann Neurol* 2011;69:90-9.
13. Centonze D, Floris R, Stefanini M, et al. Proposed chronic cerebrospinal venus insufficiency criteria do not predict MS risk nor MS severity. *Ann Neurol* 2011;70:51-8.
14. Krogias C. Schroder A, Wiendl H, et al. "Chronic cerebrospinal venous insufficiency" and multiple sclerosis: critical analysis and first observation in an unselected cohort of MS patients [article in German]. *Nervenarzt* 2010;81:740-6.
15. Mayer CA, Pfeilschifter W, Lorenz MW, et al. The perfect crime? Chronic cerebrospinal venous insufficiency not leaving a trace in MS. *J Neurol Neurosurg Psychiatry* 2011;82:436-40.
16. Zivadinov R, Marr K, Cutter G, et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. *Neurology* 2011;77:138-4.
17. Simka M, Kostecki J, Zaniewski M, et al. Extracranial Doppler sonographic criteria of chronic cerebrospinal venous insufficiency in the patients with multiple sclerosis. *Int Angiol* 2010;29:109-14.
18. Menegatti E, Genova V, Tessari M, et al. The reproducibility of colour Doppler in chronic cerebrospinal venous insufficiency associated with multiple sclerosis. *Int Angiol* 2010;29:121-6.
19. Yamout B, Herlopian A, Issa Z, et al. Extracranial venous stenosis is an unlikely cause of multiple sclerosis. *Mult Scler* 2010;16:1341-8.

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