Signature: © Pol J Radiol, 2014; 79: 323-327
DOI: 10.12659/PJR.890690

Polish Journal of Radiology
www.PolRadiol.com
ORIGINAL ARTICLE

Received: 2014.03.15
Accepted: 2014.04.08
Published: 2014.09.19

Evaluation of Hemodynamic Properties of Cerebral Venous Drainage in Patients with Multiple Sclerosis: A Case-Control Study

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Ali Babaei Jandaghi[1,2 ABCDEF], **Dayan Amanian**[1 ABCDEF], **Seyed Ali Roudbari**[1 ABCDEF], **Alireza Rajabzadeh Kanafi**[1 ABCDEF], **Ramin Pourghorban**[3 ABCDEF]

[1] Department of Radiology, Poursina Hospital, Guilan University of Medical Sciences, Rasht, Iran
[2] Guilan Road Trauma Research Center, Guilan University of Medical Sciences, Rasht, Iran
[3] Department of Radiology, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Author's address: Ramin Pourghorban, Department of Radiology, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, e-mail: ramin_p2005@yahoo.com

Summary

Background: The purpose of this study was to compare patients with multiple sclerosis and healthy control subjects as regards hemodynamics of cerebral venous drainage.

Material/Methods: Between December 2012 and May 2013, 44 consecutive patients with multiple sclerosis and 44 age- and sex-matched healthy subjects underwent the B-mode, color Doppler, and duplex Doppler evaluations of the internal jugular vein (IJV) and vertebral vein. The following four parameters were investigated: IJV stenosis, reversal of postural control of the cerebral venous outflow pathways, absence of detectable blood flow in the IJVs and/or vertebral veins, and reflux in the IJVs and/or vertebral veins in the sitting or supine position.

Results: In the study group, IJV stenosis, postural control reversal of the cerebral venous outflow pathways, and absence of flow in the IJVs and/or vertebral veins were found in 3 (6.8%), 2 (4.5%), and 3 (6.8%) patients, respectively. In the control group, IJV stenosis (P=0.12), postural control reversal of the cerebral venous outflow pathways (P=0.50), and absence of flow (P=0.12) were not detected. Abnormal reflux was found neither in multiple sclerosis patients nor in healthy subjects.

Conclusions: No significant difference in the cerebral venous drainage through the IJV or vertebral vein was found between patients with multiple sclerosis and healthy subjects within any of the investigated ultrasonographic parameters.

MeSH Keywords: Hemodynamics • Jugular Veins • Multiple Sclerosis • Ultrasonography, Doppler • Venous Insufficiency

PDF file: http://www.polradiol.com/abstract/index/idArt/890690

Background

Multiple sclerosis is a chronic inflammatory disease of unknown pathogenesis causing demyelination of the central nervous system. The potential association between multiple sclerosis and venous reflux into the skull or spine was first described by Schelling [1]. However, the hypothesis of chronic cerebrospinal venous insufficiency (CCSVI) as a causative factor in multiple sclerosis has been recently implicated by Zamboni et al. [2–5]. Extracranial multiple venous strictures have been postulated to produce substitute collateral circles and reflux into both extracranial and intracranial venous systems. Although the alternative pathways may prevent intracranial hypertension, they will get overloaded with time, and the cerebral venous outflow regulation may be hampered. As a result, transmural venous pressure will be elevated, with local erythrocytes being extravasated. The latter may cause perivenous iron deposits with venotopic location typical of multiple sclerosis plaques. Zamboni et al. [2,4] claimed a strong association between multiple sclerosis and CCSVI, and based on their findings, several attempts have been made to treat multiple sclerosis patients with percutaneous transluminal angioplasty [5,6]. Nevertheless, given the controversial results from some other studies, the role of CCSVI in multiple sclerosis is still debated, and further investigations seem to be necessary for this controversy. Furthermore, the proposed treatment has not gained universal acceptance to date.

The purpose of our study was to determine if there is any difference in hemodynamics of cerebral venous drainage between patients with multiple sclerosis and their control subjects, by using extracranial grayscale and color Doppler studies.

Material and Methods

Our institutional review board approved this prospective study. Written informed consent was obtained, with patients' confidentiality being maintained during the study.

Study subjects

This prospective study was performed between December 2012 and May 2013. The study population comprised 44 consecutive patients with a definite diagnosis of multiple sclerosis according to the revised McDonald criteria [7]. Forty-four age- and sex-matched control subjects were also included in the study. Exclusion criteria included history of cerebrovascular diseases, migraine, congenital or acquired vascular malformations (e.g., Budd-Chiari syndrome, Klippel-Trénaunay-Weber syndrome, Parkes Weber syndrome, vein of Galen malformation, or dural arteriovenous fistulae), any kinds of vasculitis (e.g., Behçet's disease or Takayasu arteritis), subclavian steal syndrome, vertebral artery dissection, intracranial hypertension, thrombophilia, thrombosis of jugular or deep cerebral veins, central venous access placement, tricuspid regurgitation, and right-sided heart failure. Those with a relapse or steroid treatment within 30 days before the study were also excluded.

Imaging technique

The evaluation was performed in a blinded manner by a radiologist with more than 8 years of experience in extracranial Doppler studies by a SonixOP system (Ultrasonix Medical Corporation, Richmond, Canada) with a 7.5–12 MHz linear array probe, which had B-mode, color Doppler, and duplex Doppler capabilities. Bilateral internal jugular veins (IJVs) and vertebral veins were interrogated in both the supine and sitting positions. Given the physiological change in the diameter of cervical veins during deep inspiration or expiration, the patients were asked to breathe quietly during the examination and all measurements were done in breath-holding time. In addition, the utmost caution was exercised to avoid collapse of the cervical veins by probe compression during the examination.

The following four criteria, used by Zamboni et al. [2,4] and claimed not to occur in healthy subjects were assessed by the examiner: B-mode evidence of stenoses of IJVs, reversal of postural control of the cerebral venous outflow pathways, absence of flow in the IJVs and/or vertebral veins, and reflux in the IJVs and/or vertebral veins in the sitting or supine position.

B-mode evidence of stenoses of IJVs

The whole cervical region was explored on grayscale imaging, and bilateral IJVs were meticulously followed on their entire course using a transverse approach. The narrowest portion of the IJV was examined on each side, and in the axial section, a line was drawn manually around the wall of the vessel. Therefore, the cross-sectional area (CSA) could have been calculated by a dedicated software on the ultrasound machine. Since a cross-sectional area of <0.3 cm^2 was never found in healthy subjects [8], the mentioned value was defined as a threshold below which the vessel was considered stenotic.

Reversal of postural control of the cerebral venous outflow pathways

The IJVs are the major exit pathways of cerebral blood for the brain in the supine position. They may collapse with the vessel area being reduced in the upright position [9]. Postural change in the IJV area was interpreted by ÄCSA, calculated as supine CSA minus its counterpart upright CSA. A positive result meant that the vessel diameter in the supine position was larger than that in the sitting position. A decrease in CSA during the supine position, i.e. negative ÄCSA, was regarded as reversal of postural control of the cerebral venous outflow pathways.

Absence of flow in the IJVs and/or vertebral veins

The distal part of the vertebral veins was examined near the vertebral artery and above the clavicle. Next, the course of the vein was attempted to be followed with a transducer. The lack of a color Doppler- and duplex Doppler-detectable flow in the vertebral vein was recorded after a thorough search. Similarly, IJVs were scanned to find any evidence of no detectable flow.

Reflux in the IJVs and/or vertebral veins in the supine or sitting position

The direction of blood flow in the IJVs and vertebral veins was examined bilaterally. As mentioned earlier, the evaluation was performed in breath-holding time. The previously retrograde flow in the cervical veins was searched for in spectral imaging, with the evaluation of reverse flow in both the supine and sitting position. Reflux time of >0.88 seconds was considered abnormal [10].

Statistical analysis

All continuous data were expressed as mean±standard deviation, and categorical data were presented as proportions. Statistical analyses were carried out using SPSS version 17.0 (SPSS Inc, Chicago, Illinois, USA). Differences in each categorical variable between the two groups were tested for significance using Fisher's exact test. In 20 randomly selected patients, ultrasound examination was repeated with a time interval of 4 weeks, and inter-examination variability was evaluated by Bland and Altman analysis. P values of less than 0.05 were considered statistically significant.

Results

The study group consisted of 44 patients with multiple sclerosis (41 women and 3 men; mean age 32±9 years). Forty-four age- and sex-matched healthy subjects (41 women and 3 men; mean age 32±9 years) were considered as the control group. In the study group, mean duration of the disease was 6 years (range of 2–12 years). All patients

Table 1. Number of patients with the criteria parameters in the study (n=44) and control (n=44) groups.

	No. (%) of the study group affected on the right side	No. (%) of the study group affected on the left side	No. (%) of the healthy subjects affected on the right side	No. (%) of the healthy subjects affected on the left side
IJVs stenosis	2 (4.5%)	1 (2.3%)	0 (0.0%)	0 (0.0%)
Reverse of postural control	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Absent IJV flow	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Absent vertebral vein flow	1 (2.3%)	2 (4.5%)	0 (0.0%)	0 (0.0%)
Abnormal IJV and/or vertebral vein reflux	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

IJV – internal jugular vein.

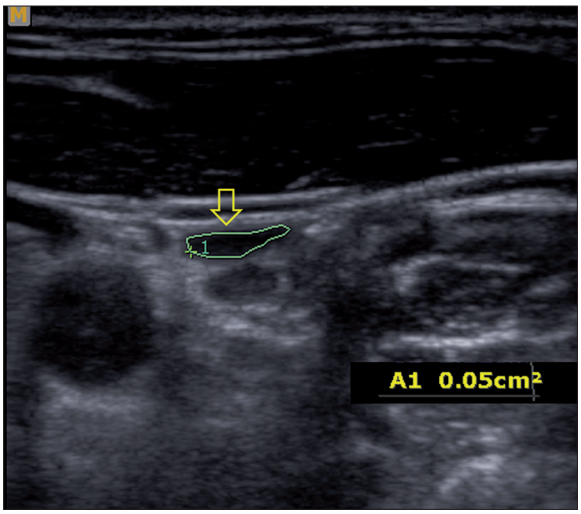

Figure 1. A 30-year-old female with multiple sclerosis. Grayscale ultrasound examination of the right IJV (open arrow) shows CSA of 0.05 cm^2.

were on medication, with none of them being on steroid treatment within 30 days before the study. IJVs and vertebral veins were successfully insonated in all cases. The sonographic findings of the cervical veins in both groups are summarized in Table 1.

In the study group, the area of the right IJV was 0.05 cm^2 (Figure 1) and 0.26 cm^2 (4.5%) in 2 patients, and the area of the left IJV was 0.26 cm^2 in 1 (2.3%) patient. The measured area of IJVs in the remaining patients was >0.3 cm^2, whereas no evidence of IJV stenosis was found in healthy subjects on grayscale imaging. However, the difference in the prevalence of IJV stenosis between the two groups was not statistically significant (right side, P=0.25; left side, P=0.12; both sides, P=0.12).

The negative ΔCSA of IJV was found in only 1 multiple sclerosis patient (supine CSA, 0.05 cm^2; sitting CSA, 0.1 cm^2) on the right side; the remaining patients and all healthy control subjects had no evidence of the reversal of postural control of the cerebral venous exit pathways, indicating no statistically significant difference between the groups (P=0.50).

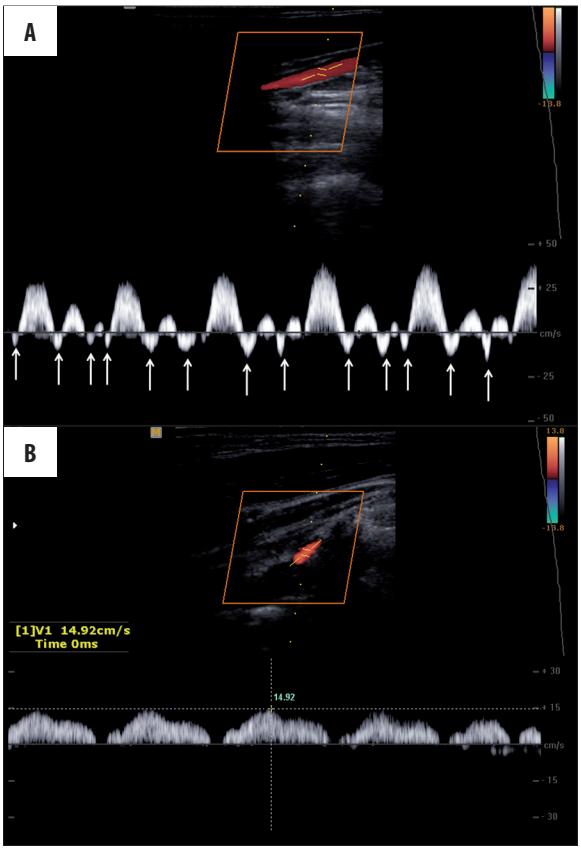

Figure 2. A 31-year-old female with multiple sclerosis. (**A**) Spectral Doppler examination of the left IJV shows blood reflux (arrows) with duration of about 0.35 seconds. (**B**) Duplex Doppler study of the left vertebral vein shows normal antegrade flow with no evidence of blood reflux.

Absence of detectable blood flow in the IJVs veins was seen in neither the study group nor the control subjects. In patients with multiple sclerosis, blood flow could not be detected in the vertebral veins by color Doppler and spectral imaging in 1 (2.3%) and 2 (4.5%) patients on the right and left sides, respectively. In contrast, vertebral vein blood flow was detected in all healthy subjects. However, no significant difference was found in the prevalence of absent blood flow in the vertebral veins between the two groups (right side, P=0.50; left side, P=0.25; both sides, P=0.12).

On spectral imaging of multiple sclerosis patients, unilateral blood reflux in IJV was observed in 3 (mean duration, 0.39 seconds) and 1 (duration, 0.35 seconds) patients on the right and left sides, respectively. Two patients had both-sided IJV reflux (first case, right reflux duration, 0.50 seconds, left reflux duration, 0.50 seconds; second case, right reflux duration, 0.62 seconds, left reflux duration, 0.75 seconds). Similarly, two patients had vertebral vein reflux, albeit with a duration of <0.88 seconds (right side, n=1, duration, 0.40 seconds; left side, n=1, duration, 0.25 seconds). Venous reflux was not detected in either the remaining patients or the control subjects (Figure 2). Hence, there was no difference in the prevalence of abnormal venous reflux between patients with multiple sclerosis and healthy subjects.

Inter-examination variability was evaluated in 20 patients. Paired t-test showed no significant change between the first and second time (P=0.85), indicating a good inter-examination agreement.

Discussion

Since the determination of CCSVI by Zamboni et al. [2] as a causative factor in the development of multiple sclerosis plaques, several studies with controversial results have been conducted in this regard. In the previous studies, variable imaging modalities, including extracranial and intracranial ultrasound, digital subtraction venography, and magnetic resonance venography were used to assess the relationship between CCSVI and pathogenesis of multiple sclerosis. Some studies confirmed that the prevalence of CCSVI in multiple sclerosis patients was significantly higher, compared to their control subjects [11–17]. In contrast, the results of other investigations contradicted those of Zamboni et al. [18–35].

The following four investigators found equivocal results: Zivadinov et al. [36] reported a higher prevalence of CCSVI in multiple sclerosis, but with modest sensitivity and specificity. Floris et al. [37] found a slight, albeit not statistically significant difference in the prevalence of CCSVI between multiple sclerosis patients and healthy subjects. Lanzillo et al. [38] found that CCSVI was more common in multiple sclerosis patients. However, its prevalence was more related to the patient's age. Chambers et al. [39] found an increased prevalence of IJV variations in their patients. However, the causal role of CCSVI in multiple sclerosis was not supported.

In the present study, we investigated the potential relationship between multiple sclerosis and abnormal hemodynamics of cerebral venous drainage in our patients using real-time ultrasonography of the cervical veins. Four extracranial grayscale and color Doppler ultrasound parameters were examined in the case-control study. The criteria were similar to those adopted in the majority of the previous studies, i.e., B-mode IJV stenoses, reversal of postural control of the cerebral venous pathways, lack of detectable blood flow in IJVs and/or vertebral veins, and IJV and/or vertebral vein blood reflux in the supine or sitting position.

In the current study, despite a higher prevalence of the first three above-mentioned parameters in multiple sclerosis patients (as compared to their age- and sex-matched healthy subjects), the difference between the two groups was not significant. The remainder criterion was not detected in any of our patients. However, blood reflux with a duration of <0.88 seconds was detected in 6 and 2 patients within IJVs and vertebral veins, respectively. Moreover, the overall prevalence of three of extracranial ultrasound parameters was low in our multiple sclerosis patients, for unknown reasons. On the other hand, none of the healthy subjects in our control group showed evidence of CCSVI on grayscale or color Doppler imaging.

It was suggested that pulsations or surges in cerebral venous pressure may cause chronic venous inflammatory changes, and the resultant increased permeability would promote extravasation of erythrocytes [40]. The latter might be responsible for iron deposition in a perivenular or venocentric location typical for multiple sclerosis plaques. Although it was proposed that multiple sclerosis plaques may develop from CCSVI and consequent iron deposition, to date, the association between multiple sclerosis and the proposed ultrasound criteria remained controversial. The current study does not support the hypothesis that CCSVI has a potential role in multiple sclerosis pathogenesis. Hence, it may cast doubt on any attempts to treat multiple sclerosis with percutaneous cervical venoplasty.

The major limitation of this study was a relatively small number of enrolled patients and their control subjects. Although the authors had performed a sample size calculation based on the prevalence of ultrasound markers of CCSVI, the negative result of our study regarding the difference in hemodynamics of cerebral venous drainage between patients with multiple sclerosis and healthy subjects, and also the fact that abnormal cerebral venous outflow pathways were seen exclusively in our multiple sclerosis patients may merit further investigations with a larger sample size even in the absence of statistical significance. Secondly, the results of the present study are limited to extracranial Doppler-adopted criteria. Therefore, correlations with findings from other imaging modalities seems necessary for clarifying the actual prevalence of CCSVI in multiple sclerosis patients. Thirdly, the operator dependency of grayscale and Doppler ultrasound may impact the results of venous examinations. Hence, conduction of all ultrasonographic examinations by only one sonographer is a further limitation of our study. Fourthly, the vertebral veins are generally difficult to identify with ultrasound. Also, the limitations of ultrasound examination are subject to equipment quality, and patient-related factors.

Conclusions

In summary, given the lack of Doppler evidence in favor of a significant higher prevalence of chronic cerebrospinal venous insufficiency in multiple sclerosis, the role of abnormal cerebral venous drainage as an etiological factor of multiple sclerosis remained in doubt, and our results called into question whether percutaneous transluminal angioplasty is rational in the treatment of multiple sclerosis. Hence, further investigations may be warranted to confirm or refute the CCSVI hypothesis.

References:

1. Schelling F: Damaging venous reflux into the skull or spine: relevance to multiple sclerosis. Med Hypotheses, 1986; 21: 141–48
2. Zamboni P, Menegatti E, Weinstock-Guttman B et al: The severity of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis is related to altered cerebrospinal fluid dynamics. Funct Neurol, 2009; 24: 133–38
3. Singh AV, Zamboni P: Anomalous venous blood flow and iron deposition in multiple sclerosis. J Cereb Blood Flow Metab, 2009; 29: 1867–78
4. Zamboni P, Menegatti E, Galeotti R et al: The value of cerebral Doppler venous hemodynamics in the assessment of multiple sclerosis. J Neurol Sci, 2009; 282: 21–27
5. Zamboni P, Galeotti R, Menegatti E et al: A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency. J Vasc Surg, 2009; 50: 1348–58
6. Ferral H, Behrens G, Tumer Y, Riemenschneider M: Endovascular diagnosis and management of chronic cerebrospinal venous insufficiency: retrospective analysis of 30-day morbidity and mortality in 95 consecutive patients. Am J Roentgenol, 2013; 200: 1358–64
7. Polman CH, Reingold SC, Banwell B et al: Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol, 2011; 69: 292–302
8. Lichtenstein D, Saïfi R, Augarde R et al: The Internal jugular veins are asymmetric. usefulness of ultrasound before catheterization. Intensive Care Med, 2001; 27: 301–5
9. Gisolf, J, van Lieshout JJ, van Heusden K et al: Human cerebral venous outflow pathway depends on posture and central venous pressure. J Physiol, 2004; 560: 317–27
10. Nedelmann M, Eicke BM, Dieterich M: Functional and morphological criteria of internal jugular valve insufficiency as assessed by ultrasound. J Neuroimaging, 2005; 15: 70–75
11. Zamboni P, Galeotti R, Menegatti E et al: Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry, 2009; 80: 392–99
12. Al-Omari MH, Rousan LA: Internal jugular vein morphology and hemodynamics in patients with multiple sclerosis. Int Angiol, 2010; 29: 115–20
13. 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
14. SMcTaggart RA, Fischbein NJ, Elkins CJ et al: Extracranial venous drainage patterns in patients with multiple sclerosis and healthy controls. Am J Neuroradiol, 2012; 33: 1615–20
15. Patti F, Nicoletti A, Leone C et al: Multiple sclerosis and CCSVI: a population-based case control study. PLoS ONE, 2010; 7: e41227
16. Ciccone MM, Galeandro AI, Scicchitano P et al: Multigate quality Doppler profiles and morphological/hemodynamic alterations in multiple sclerosis patients. Curr Neurovasc Res, 2012; 9: 120–27
17. Zaniewski M, Kostecki J, Kuczmik W et al: Neck duplex Doppler ultrasound evaluation for assessing chronic cerebrospinal venous insufficiency in multiple sclerosis patients. Phlebology, 2013; 28: 24–31
18. Doepp F, Paul F, Valdueza JM et al: No cerebrocervical venous congestion in patients with multiple sclerosis. Ann Neurol, 2010; 68: 173–83
19. Krogias C, Schröder A, Wiendl H et al: "Chronic cerebrospinal venous insufficiency" and multiple sclerosis: critical analysis and first observation in an unselected cohort of MS patients. Nervenarzt, 2010; 81: 740–46
20. Worthington V, Killestein J, Eikelenboom MJ et al: Normal CSF ferritin levels in MS suggest against etiologic role of chronic venous insufficiency. Neurology, 2010; 75: 1617–22
21. Tsivgoulis G, Mantatzis M, Bogiatzi C et al: Extracranial venous hemodynamics in multiple sclerosis: a case-control study. Neurology, 2011; 77: 1241–45
22. Mayer CA, Pfeilschifter W, Lorenz MW et al: The perfect crime? CCSVI not leaving a trace in MS. J Neurol Neurosurg Psychiatry, 2011; 82: 436–40
23. Centonze D, Floris R, Stefanini M et al: Proposed chronic cerebrospinal venous insufficiency criteria do not predict multiple sclerosis risk or severity. Ann Neurol, 2011; 70: 51–58
24. Baracchini C, Perini P, Calabrese M et al: No evidence of chronic cerebrospinal venous insufficiency at multiple sclerosis onset. Ann Neurol, 2011; 69: 90–99
25. Marder E, Gupta P, Greenberg BM et al: No cerebral or cervical venous insufficiency in US veterans with multiple sclerosis. Arch Neurol, 2011; 68: 1521–25
26. Zivadinov R, Lopez-Soriano A, Weinstock-Guttman B et al: Use of MR venography for characterization of the extracranial venous system in patients with multiple sclerosis and healthy control subjects. Radiology, 2011; 258: 562–70
27. Blinkenberg M, Akeson P, Sillesen H et al: Chronic cerebrospinal venous insufficiency and venous stenoses in multiple sclerosis. Acta Neurol Scand, 2012; 126: 421–27
28. Amato M, Saia V, Hakiki B et al: No association between chronic cerebrospinal venous insufficiency and pediatric-onset multiple sclerosis. Mult Scler, 2012; 18: 1791–96
29. Kantarci F, Albayram S, Demirci NO et al: Chronic cerebrospinal venous insufficiency: does ultrasound really distinguish multiple sclerosis subjects from healthy controls? Eur Radiol, 2012; 22: 970–79
30. Garaci FG, Marziali S, Meschini A et al: Brain hemodynamic changes associated with chronic cerebrospinal venous insufficiency are not specific to multiple sclerosis and do not increase its severity. Radiology, 2012; 265: 233–39
31. Comi G, Battaglia M, Bertolotto A et al: Observational case-control study of the prevalence of chronic cerebrospinal venous insufficiency in multiple sclerosis: results from the CoSMo study. Mult Scler, 2013; 19: 1508–17
32. Barreto AD, Brod SA, Bui TT et al: Chronic cerebrospinal venous insufficiency: case-control neurosonography results. Ann Neurol, 2013; 73: 721–28
33. Imperiale D, Melis F, Giaccone C et al: Chronic cerebrospinal venous insufficiency in multiple sclerosis: a sonographer-blinded case-control study. Clin Neurol Neurosurg, 2013; 115: 1394–98
34. Leone MA, Raymkulova O, Naldi P et al: Chronic cerebrospinal venous insufficiency is not associated with multiple sclerosis and its severity: a blind-verified study. PLoS ONE, 2013; 8: e56031
35. Van den Berg PJ, Van den Berg GB et al: Occurrence of CCSVI in patients with MS and its relationship with iron metabolism and varicose veins. Eur J Neurol, 2013; 20: 519–26
36. Zivadinov R, Marr K, Cutter G et al: Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. Neurology, 2011; 77: 138–44
37. Floris R, Centonze D, Fabiano S et al: Prevalence study of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis: preliminary data. Radiol Med, 2012; 117: 855–64
38. Lanzillo R, Mancini M, Liuzzi R et al: Chronic cerebrospinal venous insufficiency in multiple sclerosis: a highly prevalent age-dependent phenomenon. BMC Neurol, 2013; 13: 20
39. Chambers B, Chambers J, Cameron H et al: Chronic cerebrospinal venous insufficiency is not more prevalent in patients with mild multiple sclerosis: a sonographer-blinded, case-control ultrasound study. Mult Scler, 2013; 19: 749–56
40. Adams CW: Perivascular iron deposition and other vascular damage in multiple sclerosis. J Neurol Neurosurg Psychiatry, 1988; 51: 260–65