The controversy on chronic cerebrospinal venous insufficiency

Paulo Zamboni,† Erica Menegatti,† Savino Occhionorelli,† Fabrizio Salvi‡
†Vascular Diseases Center, University of Ferrara; ‡Bellaria Neuroscience, Bellaria Hospital Bologna, Italy

Abstract

The objective of this review is to analyze the actual scientific controversy on chronic cerebrospinal venous insufficiency (CCSVI) and its association with both neurodegenerative disorders and multiple sclerosis (MS). We revised all published studies on prevalence of CCSVI in MS patients, including ultrasound and catheter venography series. Furthermore, we take into consideration other publications dealing with the pathophysiological consequences of CCSVI in the brain, as well as recent data characterizing the pathology of the venous wall in course of CCSVI. Finally, safety and pilot data on effectiveness of endovascular CCSVI treatment were further updated.

Studies of prevalence show a big variability in prevalence of CCSVI in MS patients assessed by established ultrasonographic criteria. This could be related to high operator dependency of ultrasound. However, 12 studies, by the means of more objective catheter venography, show a prevalence >90% of CCSVI in MS. Global hypoperfusion of the brain, and reduced cerebral spinal fluid dynamics in MS was shown to be related to CCSVI. Postmortem studies and histology corroborate the 2009 International Union of Phlebology (UIP) Consensus decision to insert CCSVI among venous malformations. Finally, safety of balloon angioplasty of the extracranial veins was certainly demonstrated, while prospective data on the potential effectiveness of endovascular treatment of CCSVI support to increase the level of evidence by proceeding with a randomized control trial (RCT).

Taking into account the current epidemiological data, including studies on catheter venography, the autopic findings, and the relationship between CCSVI and both hypoperfusion and cerebro-spinal fluid flow, we conclude that CCSVI can be definitively inserted among the medical entities. Research is still conclusive in elucidating the CCSVI role in the pathogenesis of neurological disorders. The controversy between the vascular and the neurological community is due to the great variability in prevalence of CCSVI in MS patients by the means of venous ultrasound assessment. More reproducible and objective CCSVI assessment is warranted. Finally, current RCT may elucidate the role of CCSVI endovascular treatment.

The controversial problem of chronic cerebrospinal venous insufficiency in multiple sclerosis

Chronic cerebrospinal venous insufficiency (CCSVI) is a syndrome characterized by stenosis or obstructions of the internal jugular (IJV) and/or aygos (AZ) veins with disturbed flow and formation of collateral venous channels.1,2 Venous narrowings are primary obstructions, mainly related to segmental hypoplasia or, more frequently, to intraluminal defects like webs, fixed valve leaflets, membrane, inverted valve orientation, etc.3-5

Venous anomalies are a field in which experts still have to agree upon many things. The basis and foundation of venous anomalies are not entirely clear yet. Venous lesions are described as truncal venous malformations.6-8 Developmental arrest in advanced stages of vascular trunk formation during fetal life can result in such truncal venous malformations. Lesions caused by incomplete development of axial veins result in aplasia, hypoplasia or hyperplasia of the vessel or as a defective vessel with obstruction from intraluminal lesions (e.g., vein web, malformed valve, or septum) or dilatation (e.g., jugular vein ectasia/aneurysm). Radiological studies of healthy subjects did not demonstrate these types of lesions;6,9 while CCSVI-like lesions were described associated to myelopathies.9,20 Despite the above and other scientific evidences,21-24 in clinical practice, due to the inherent variability of the cerebral venous system and the lack of standards, it is difficult to accurately detect CCSVI using current magnetic resonance imaging (MRI) and echo-color Doppler (ECD) sonography techniques, as well as its possible association with neurodegenerative disorders such as MS-something that has generated considerable scientific controversy. There are a lot of opinion papers, and some original contributions, pointing against the existence and the association of CCSVI in MS.25,28

The core of the controversy: the ultrasonographic prevalence of chronic cerebrospinal venous insufficiency in multiple sclerosis

The neurological community did not accept from the beginning, the intrusion of the vascular procedure for CCSVI in MS treatment. The harshest were Khan et al.26 with a statement that endovascular procedures in MS were research endeavors, and that these invasive endovascular procedures should be discouraged until there is conclusive evidence to justify their indication in MS. A Canadian group27 comments on Call for liberation in Edmonton and the mobilizing power of the media and the Internet. Because of the pressure from MS groups the Canadian Institutes of Health Research with MS Society held an expert panel in August 2009, which concluded that in absence of clear and convincing evidence for CCSVI, the performance of an interventional venous angioplasty trial with its attendant risk to MS patients is not appropriate at this time. The authors also27 stated that more effort needs to be devoted to improving scientific literacy of the public, politicians and the media, in order to prevent an diverting public resources to testing what will probably turn out to be ineffective or harmful therapies. Rikkers et al.28 state that recent randomized trials did not show a difference in the prevalence of venous stenosis between groups of patients with or without MS, comparing the studies of Doepp and other Authors.29-34

In an everyday growing field of studies and papers trying to demonstrate either positive or negative association of CCSVI with MS we will discuss the results of studies published so far. Ultrasound in the form of duplex scanning uses a combination of physiological measurements as well as anatomical imaging and has been used for the detection of CCSVI by differ-
ent centers with variable results. Ultrasound is, of course, an ideal screening tool because it is non-invasive, economic, etc. However, these studies show very variable results, which we aim to comment. We were able to observe interesting grouping of results into two main groups; those with a CCSVI prevalence higher than 60%, from 60%-100%12,15-19 and those with absence of such lesions,20,21 or CCSVI prevalence under 60%22-31 (Table 1). This variability could be the result of differences in technique, training, experience or criteria used.40 For future avoidance of such variable results, and in order to ensure a high reproducibility of duplex scanning with comparable accuracy between centers, all investigators are invited to follow the protocol with standard methodology and criteria.40 Moreover, a recent meta-analysis done by Laupacis et al.41 showed a positive association between CCSVI and MS. The group performed a systematic review and meta-analysis of all reports from 2005 till June 2011, comparing the frequency of CCSVI and MS. Their findings proved a significant association between CCSVI and MS even after exclusion of the first study by Zamboni, due to the fact that it, being the first study, may be considered hypothesis-generating and because of the extremely high Odds Ratio found in the study. The meta-analysis was repeated after inclusion of Doepp’s study,31 in which none of the patients or controls had CCSVI, but the findings were similar to those in the primary analysis. The group concluded a strong association between CCSVI and MS with marked heterogeneity due to reduced reporting of patient blinding.

Table 1. Prevalence of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis and healthy controls in the main published study.

| Author (ref)       | MS patients | CCSVI | Total | Controls CCSVI |
|--------------------|-------------|-------|-------|----------------|
| Zamboni et al., 2009 | 65 (100%)   | 65    | 0     |                |
| Zivadinov et al., 2011 | 162 (56.1%) | 289   | 374 (22.7%) |                |
| Doepp et al., 2011  | 0 (0%)      | 56    | 0 (0%) |                |
| Mayerer et al., 2011 | 0 (0%)      | 20    | 1 (5%) |                |
| Baracchini et al., 2011 | 8 (16%)    | 50    | 1 (2%) |                |
| Al Omari et al., 2010 | 21 (84%)   | 25    | 0 (0%) |                |
| Sinka et al., 2010  | 64 (91%)    | 70    | -     |                |
| Bastianello et al., 2011 | 610 (86%) | 710   | -     |                |
| Marder et al., 2011  | 0 (0%)      | 18    | -     |                |
| Zivadinov et al., 2011 | 10 (100%)  | 10    | -     |                |

MS, multiple sclerosis; CCSVI, chronic cerebrospinal venous insufficiency.

Negative studies showing traces of venous abnormalities

Doepp et al.42 reported no CCSVI in MS patients,29 but their results did show a significant reduction of venous outflow in MS patients when their position changed from supine to upright, which points towards a disturbed venous outflow. One of the major regulators of cerebral venous outflow is the posture, due to the gravitational gradient between the cerebral parenchymal veins (30 mmHg) and the base of the neck (0 mmHg). Doepp et al.39 demonstrate a much larger change in blood flow volume in normals compared to MS patients when the subjects go from a supine to upright position. They find a change of 128 mL/min and 36 mL/min for the right and left sides respectively for MS patients. But they find a much larger change of 266 mL/min and 165 mL/min for their normal subjects. This result actually suggests the presence of CCSVI proven with a different protocol. The causes of reduced outflow changing posture to upright can be from intraluminal septum, membrane, immobile valve affecting the hydrostatic pressure gradient.42 However, high quality Doppler flow measurement at the terminal LV shows a restricted outflow in CCSVI with increased flow though the collaterals respect to controls.43 The presence of such blockages in the extracranial and extravertebral cerebral veins have been proven by using catheter venography, a more objective method respect to ECD.14-18 More interestingly, Dacou et al. communicated at European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) the results of a post-mortem study clearly showing a highest prevalence of jugular septimization with possible hemodynamic consequences in MS patients in respect to controls.21 This result is confirmed by another autopic study.22 Baracchini et al. reported 16% of CCSVI in MS patients at disease onset, compared to 2% of CCSVI in healthy controls.33 This finding suggests that CCSVI represents a nine times higher risk factor for disease onset, showing increased susceptibility to MS in CCSVI subjects. Zivadinov et al. recently reported CCSVI more likely to be a secondary phenomenon to MS. Their results showed that CCSVI was found in 50% of pediatric MS cases as well as in 38% of Clinically Isolated Syndrome cases, thus making the conclusion rash.34 A well-established explanation for this great variability in CCSVI prevalence among different groups of investigators is the amount of training and experience investigators have in echo-color Doppler imaging. Studies have shown35 that inter-operator variability decreases post-training (from k=0.47 to k=0.80) while intra-operator reproducibility in trained operators was k=0.75. Apart from experience and training, ultrasound imaging still remains an operator-dependent investigation. Studies that have been done so far show great variability because of operator dependency, lack of proper training in performing venous ultrasound, and differences in protocols used. However, despite all these obstacles, in more than 2000 investigated subjects, the prevalence of CCSVI was more than 70% in MS patients compared to prevalence of about 10% in healthy controls (Table 1). Studies claiming to be in opposition to CCSVI still show different elements of abnormality of venous outflow in MS patients compared to their healthy controls. Reproducibility can be assured by performing the investigation by an accepted protocol after training the investigator. To minimize errors and variability in study results, The International Society for Neurovascular Diseases published a protocol deriving from a Consensus Conference.49

Pathology is necessary to establish a new medical entity

The morphology seen at venography and ultrasound investigations of the CCSVI picture was considered in the 2009 UIP Consensus quite similar to those affecting other segments of the caval system, supporting the decision to insert CCSVI among truncular venous malformation.67 Autopic studies and histology actually corroborate the decision of the Consensus. The presence of wall stenosis, or of a greater prevalence of intraluminal defects in specimen of patients died with MS respect to patients without the disease has been recently described by pathologists.23-25 In addition, a molecular marker has been identified in the adventitial layer of LV in CCSVI condition where there is an inverted ratio between type I and type III collagen. The latter component, less extensible, is greatly represented-
The studies above cited demonstrate how CCSVI is characterized by peculiar pathology. More specifically: i) in a post mortem study comparing MS patients with people who dead for different reasons, valvular and other intraluminal abnormalities with potential hemodynamic consequences were identified in 72% of MS patients and in 17% of controls. These abnormalities included circumferential membranous structures, longitudinally-oriented membranous structures, single valve flap replacing UV valve, and enlarged and malpositioned valve leaflets. To the contrary, vein wall stenosis occurred at similar frequency in both groups; ii) the expression of collagen type I and III, cytoskeletal proteins, and inflammatory markers was investigated in IJVs specimens from MS patients and controls. Veins of MS patients were found with a higher expression of type III collagen, whereas control specimen exhibited a clear prevalence of type I over type III collagen. A reduced collagen type III/II ratio allegedly alters mechanical stability and reduces mechanical strength of connective tissue contributing to abnormalities described in CCSVI. Interestingly, no differences in inflammatory marker expression were observed. Particularly, no-T cells infiltration suggesting an infective and/or autoimmune vasculitis was found in the jugular venous wall. According with the authors’ conclusions, this study demonstrates that extracranial venous lesions of MS patients could be of congenital origin, and not related to a product of MS autoimmunity.23

**Chronic cerebrospinal venous insufficiency and brain pathophysiology**

There are 2 proven pathophysiologic consequences of the presence of significant narrowing in the extracranial veins. The significance of blocked outflow has been proposed to be scored with the Venous Hemodynamic Insufficiency Severity Score (VHISS). Subjects with CCSVI showed higher frequency of venous reflux, blocked flow, B-mode abnormalities, and reduced IV compliance which led to increased VHISS. The latter index was used to investigate the relationship with both CSF flow dynamics and brain perfusion, both assessed with advanced and non conventional MRI measure.

The cerebrospinal fluid (CSF) is formed in lateral ventricles and mainly flows through brain’s ventricular system, over and around cerebral hemispheres, and is absorbed by arachnoid villi into the superior sagittal sinus, connected via the transverse sinus with the jugulars. Normal circulation of the CSF desires an optimal balance between ultrafiltration of CSF and its clearance from CSF spaces into the venous system at the level of dural sinuses, which depends mainly on efficient venous drainage. In 2009 Zamboni et al. performed a blinded MR study which demonstrated venous outflow disturbance in MS patients. The study showed that impaired CSF dynamics may be a factor contributing to the increased volumes in 3rd and lateral ventricles, which was frequently observed in MS patients. This study demonstrated that CCSVI has a significant impact on brain pathophysiology, especially on intracranial fluid balance. Moreover, Zivadinoz et al. demonstrated the correctness of the correlation between venous outflow and CSF flow dynamics measuring the change in CSF flow and velocity after venous angioplasty in a randomized group of patients. At month six from the treatment, significant improvement in CSF flow (P<0.001) and velocity (P=0.013) was detected in the treated arm compared to the no treatment group. This difference persisted at month 12 of the study for both CSF flow (P=0.001) and velocity (P=0.021) measures between the 2 groups. Cerebral perfusion is

Figure 1. Left) catheter venography of the internal jugular vein in healthy control; right) stenosis (arrows) and collateral circles activated in a chronic cerebrospinal venous insufficiency case, studied by the means of catheter venography. Courtesy of Dr Roberto Galeotti.
always measured as diffusely impaired in MS patients. This aspect of MS is related to the aspect of chronic hypoxia linked with increased oxidative stress and cannot be explained, of course, with the autoimmune theory. The hypothesis that CCSVI could be a contributory factor to cerebral hyperperfusion was further investigated in a blinded MRI study. Hypoperfusion of the brain parenchyma was measured to be proportionally decreased in MS patients with higher VHSS, demonstrating how the blocked outflow in the jugular veins is related to brain perfusion and oxygen delivery.

**Chronic cerebrospinal venous insufficiency and interventional procedures**

A second reason of the controversy is the opposition to perform balloon angioplasty (PTA) of the jugulars and AZ system, for treating CCSVI especially in MS patients. Despite the endovascular procedure was considered in an opinion paper published in a major journal of clinical neurology a dangerous procedure, PTA can be definitely considered a safe procedure, whereas for stenting level of risk is slightly increased.

Moreover, from 2009 the effectiveness of PTA in eventually improving the results of current medical therapy of CCSVI was assessed with prospective open label design. Clinical and quality of life (QoL) improvements are reported in a number of prospective and case control studies following interventional procedures. Particularly, chronic fatigue, a disabling symptom of MS without any effective treatment is reported to improve practically in the procedure is attempted in early cases and/or in relapsing remitting clinical form respect to long time disease and progressive forms. The results are quite interesting and warrant an increased level of evidence to conclude that results should be biased by the placebo effect. To this aim a double blinded randomized trial is actually in course.

**Conclusions**

The controversy in the CCSVI issue is strongly linked with the ultrasonographic screening which is highly operator dependent leading to a big heterogeneity in prevalence studies. However, catheter venography data, despite the invasiveness of the diagnostic procedures, clearly indicates an amazing rate of CCSVI in people affected by MS. Pathology, either gross anatomy or histology, supports that CCSVI is a new medical entity, needing of further improvement in the diagnostic methodology. This is the only way to decrease the actual controversy. Finally, the two main consequences in brain pathophysiology linked with CCSVI are respectively the reduction of CSF flow dynamics and of brain perfusion. The vascular consequences of CCSVI at the microcircular level may help us in interpreting several unknown aspect of MS, and especially those at the blood brain barrier.

Finally, all the above evidences support move to a randomized control trial in order to assess the value of vascular treatment of CCSVI in neurodegeneration.

**References**

1. 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.
2. Zamboni P, Consorti G, Galeotti R, et al. Venous collateral circulation of the extracranial cerebrospinal outflow routes. Curr Neurol Neurosci Res 2009;9:204-12.
3. Zivadinov R, Galeotti K, Hojnacki D, et al. Value of MR Venography for Detection of Internal Jugal Vein Anomalies in Multiple Sclerosis: A Pilot Longitudinal Study. AJNR 2011;32:938-46.
4. Zamboni P. Regarding no cerebrocervical venous congestion in patients with multiple sclerosis. Int Angiol 2010: 29:115-20.
5. Lee BB, Laredo J, Neville R: Embryological background of truncural venous malformation in the extracranial venous pathways as the cause of chronic cerebrospinal venous insufficiency. Int Angiol 2010:29:105-108.
6. Lee BB, Bergan J, Gloviczki P, et al. Diagnosis and treatment of venous malformations-Consensus Document of the International Union of Phlebology (IUP)-2009. Intern Angiol 2009:28:434-51.
7. Lee BB, Laredo J, Lee TS, et al. Terminology and classification of congenital vascular malformations. Phlebology 2007;22:249-52.
8. Uflocker R. Atlas of vascular anatomy. an angiographic approach. Philadelphia, PA: Lippincott Williams & Wilkins; 1997.
9. Hamoud S, Nitecky S, Engel A, et al. Hypoplasia of the inferior vena cava with azygous continuation presenting as recurrent leg deep vein thrombosis. Am J Med Sci 2000;319:414-6.
10. Gates J, Hartnell GG. Demonstration of inferior vena cava patency by retrograde azygous venography. Cardiovasc Intervent Radiol 1995;18:419-21.
11. Lane EJ, Heitzman ER, Dinn WM. The radiology of the superior intercostals veins. Radiology 1976;120:263-7.
12. Chasen MH, Charnsangavej C. Venous chest anatomy: clinical implications. Eur J Radiol 1998;27:2-14.
13. Mannen T, Keshava SN, Eapen CE, et al. Transjugular liver biopsy: a retrospective analysis of 601 cases. J Vasc Interv Radiol 2008;19:351-8.
14. Dilenge D, Perey B, Geraud G, et al. Angiographic demonstration of the cervical venous plexus in man. J Can Assoc Radiol 1975;26:77-81.
15. Zelli GP, Messinetti S, Condorelli S. Original technic of internal jugular phlebography by puncture of the external jugular vein with retrograde emmission of the contrast media. Prog Med 1964;15:681-8.
16. Gejrot T, Lauren T. Retrograde venography of the internal jugular veins and transverse sinuses, technique and roentgen anatomy. Acta Otolar yngol 1964;57:556-70.
17. Gejrot T. Retrograde jugulography in the diagnosis of abnormalities of the superior bulb of the internal jugular vein. Acta Otolar yngol 1964;57:177-80.
18. Leriche H, Auhin ML, Aboulker J. Cavo-splanchnic phlebography in myelopathies. Stenoses of internal jugular and azigos veins, venous compressions and thromboses Acta Radiol Suppl 1976;347:415-7.
19. Tzeladze B. The selective phlebography of the large tributaries of the vena cava system in the diagnosis of venous circulatory disorders in the spinal complex. Zh Vopr Neirokirch Im N N Burdenko 1999:2-8.
20. Diaconu C, Staugaitis S, McBride J, et al. Anatomical and histological analysis of venous structures associated with chronic cerebro-splanchnic venous insufficiency. 5th ECTRIMS, Amsterdam, The Netherlands, 2011, abstract.
21. Baiocchini A, Toscano R, von Lorch W, et al. Diagnosis and treatment of venous malformations-Consensus Document of the International Union of Phlebology (IUP)-2009. Intern Angiol 2009;28:434-51.
22. Diacou C, Staugaitis S, McBride J, et al. Anatomical and histological analysis of venous structures associated with chronic cerebro-splanchnic venous insufficiency. E- letter JNPN; 2011. Available from: http://jnnp.bmj.com/content/82/4/355.extra ct/reply#jnnp_el_7244.
23. Coen M, Menegatti E, Salvi F, et al. Characterization of ccsvi lesions in multiple sclerosis patients. 4th Annual ISNVD Scientific Meeting 2011, Bologna, Italy, abstract.
of chronic cerebrospinal venous insufficiency in the patients with multiple sclerosis. Int Angiol 2010;29:109-14.
39. Menegatti E, Genova V, Tessari M, et al. The reproducibility of color doppler in chronic cerebrospinal venous insufficiency associated with multiple sclerosis. Intern Angiol 2010;29:121-6.
40. Zamboni P, Morovic S, Menegatti E, et al. Screening for chronic cerebrospinal venous insufficiency (CCSVI) using ultrasound. Recommendations for a protocol. Int Angiol 2011;30:1-2.
41. Laupacas A, Lillie E, Ducek A, et al. Association between chronic cerebrospinal venous insufficiency and multiple sclerosis: a meta-analysis. CMAJ 2011;183:E1203-12.
42. Zamboni P. Regarding no cerebrocervical venous congestion in patients with multiple sclerosis. Ann Neurol 2010;68:673-83.
43. Marder E, Gupta P, Greenberg BM, et al. No cerebrocervical venous congestion in patients with multiple sclerosis. Ann Neurol 2010;68:173-83.
44. Mayer CA, Waltraud P, Matthias WL, et al. The perfect crime? CCSVI not leaving a trace in MS. J Neurol Neurosurg Psychiatry 2011;82:436-40.
45. 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;117:955-64.
46. Mandato KD, Hegener PF, Siskin GP, et al. The hypothesis of pathophysiological correlation between chronic cerebrospinal venous insufficiency and multiple sclerosis: an observational study. J Cereb Blood Flow Metab 2008;28:2063-8.
47. Petrov I, Grozdinski L, Kaninski G, et al. Safety profile of endovascular treatment for chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Endovasc Ther 2011;18:314-23.
48. Beelen R, Maene L, Castenmiller P, et al. Evolution in quality of life and epidemiological impact after endovascular treatment of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. Phlebology 2012;27:187-9.
49. Mandato KD, Hegener PF, Siskin GP, et al. Safety of endovascular treatment of chronic cerebrospinal venous insufficiency: a report of 240 patients with multiple sclerosis. J Vasc Interv Radiol 2012;23:55-9.
50. Lugli M, Morelli M, Guerzoni S, Maleti O. The hypothesis of patho-physiological correlation between chronic cerebrospinal venous insufficiency and multiple sclerosis: rationale of treatment. Phlebology 2012;27:178-86.
51. Luduga T, Kazibudzki M, Simka M, et al. Endovascular treatment for chronic cerebrospinal venous insufficiency: is the procedure safe? Phlebology 2010;25:286-95.
52. Milic DJ. Liberation procedure in the treatment of chronic cerebrospinal venous insufficiency - is chronic cerebrospinal venous insufficiency related to brain congestive syndrome rather than multiple sclerosis. J Vasc Surg 2012;55:302-3.
53. Kosteczki J, Zaniewski M, Ziaja K, et al. An endovascular treatment of chronic cerebrospinal venous insufficiency in multiple sclerosis patients - 6 month follow-up results. Neuro Endocrinol Lett 2011;32:557-62.
54. Ludyga T, AUTHORS??? (3 names et al) et al. Early results of a prospective open-label study on endovascular treatments for chronic cerebrospinal venous insufficiency in the patients with associated multiple sclerosis. Phlebol Rev 2011;19:9-14.
55. Kipshidze N, Rukhadze I, Archvadze A, et al. Endovascular treatment of patients with chronic cerebrospinal venous insufficiency and multiple sclerosis. Georgian Med News 2011;10:29-33.
56. Simka M, Ludyga T, Latacz P, Kazibudzki M. Diagnostic accuracy of current sonographic criteria for the detection of outflow abnormalities in the internal jugular veins. Phlebology 2012. [Epub ahead of print].
57. Schaller B. Physiology of cerebral venous blood flow: from experimental data in animals to normal function in humans. Brain Res Rev 2004;46:243-60.
58. Ursino M, Lodi CA. A simple mathematical model of the interaction between intracranial pressure and cerebral hemodynamics. J Appl Physiol 1997;82:1256-69.
59. Zamboni P, Menegatti E, Weinstock-Guttman B, et al. The severity of chronic cerebrospinal insufficiency in patients with multiple sclerosis is related to altered cerebrospinal fluid dynamics. Funct Neurol 2009;24:133-8.
60. Zivadinov R, Magnano C, Galeotti R, et al. Changes of cine cerebrospinal fluid dynamics in multiple sclerosis patients treated with venous angioplasty. J Int Vasc Rad 2013;24:829-38.
61. D’haeseleer M, Cambron M, Vanopdenbosch L, De Keyser J. Vascular aspects of multiple sclerosis. Lancet Neurol 2011;10:657-66.
62. Law M, Saindane AM, Ge Y, et al. Microvascular abnormality in relapsing-remitting multiple sclerosis: perfusion MR imaging findings in normal-appearing white matter. Radiology 2004;231:645-52.
63. Brooks DJ, Leenders KL, Head G, et al. Studies on regional cerebral oxygen utilisation and cognitive function in multiple sclerosis. JNNP 1984;47:1182-91.
64. De Keyser J, Steen C, Mostert JP, et al. Hypoperfusion of the cerebral white matter in multiple sclerosis: possible mechanisms and pathophysiological significance. J Cereb Blood Flow Metab 2008;28:1645-51.
65. Zamboni P, Menegatti E, Weinstock-Guttman B, 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 Neurol 2011;9:22.
Endovascular treatment for chronic cerebrospinal venous insufficiency: is the procedure safe? Phlebology 2010;25:286-95.

64. Petrov I, Grozdinski L, Kaninski G, et al. Safety profile of endovascular treatment for chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Endovasc Ther 2011;18:314-23.

65. Mandato KD, Hegener PF, Siskin GP, et al. Safety of endovascular treatment for chronic cerebrospinal venous insufficiency: a report of 240 patients with multiple sclerosis. J Vasc Interv Radiol 2012;23:55-9.

66. 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.

67. Hubbard D, Ponec D, Gooding J, et al. Clinical improvement after extracranial venoplasty in multiple sclerosis. J Vasc Interv Radiol 2012;23:1302-8.

68. Zamboni P, Galeotti R, Weinstock-Guttman B, et al. Venous angioplasty in patients with multiple sclerosis: results of a pilot study. Eur J Vasc Endovasc Surg 2012;43:116-22.

69. Salvi F, Bartolomei I, Buccellato E, et al. Venous angioplasty in multiple sclerosis: neurological outcome at two years in a cohort of relapsing-remitting patients. Funct Neurol 2012;27:55-9.

70. Beelen R, Maene L, Castenmiller P, et al. Evolution in quality of life and epidemiological impact after endovascular treatment of chronic cerebro-spinal venous insufficiency in patients with multiple sclerosis. Phlebology 2012;27:187-9.

71. Denislic M, Milosevic Z, Zorc M, et al. Disability caused by multiple sclerosis is associated with the number of extra cranial venous stenoses: possible improvement by venous angioplasty. Results of a prospective study. Phlebology 2012. [Epub ahead of print].

72. Radak D, Kolar J, Sagic D, et al. Percutaneous angioplasty of internal jugular andazygous veins in patients with chronic cerebrospinal venous insufficiency and multiple sclerosis: early and mid-term results. Phlebology 2013. [Epub ahead of print].

73. Zamboni P, Bertolotto A, Boldrini P, et al. Efficacy and safety of venous angioplasty of the extracranial veins for multiple sclerosis. Brave dreams study (brain venous drainage exploited against multiple sclerosis): study protocol for a randomized controlled trial. Trials 2012;13:183.

74. Singh AV, Khare M, Gade WN, Zamboni P. Theranostic implications of nanotechnology in multiple sclerosis: a future perspective. Autoimmune Dis 2012;2012:160830.