The chronic cerebrospinal venous insufficiency syndrome

P Zamboni and R Galeotti
Vascular Disease Centre, Interventional Radiology Unit, University of Ferrara, Italy

Abstract
Chronic cerebrospinal venous insufficiency (CCSVI) is a syndrome characterized by stenoses of the internal jugular and/or azygous veins (IJVs-AZ) with opening of collaterals and insufficient drainage proved by reduced cerebral blood flow and increased mean transit time in cerebral MRI perfusional study. The present review is aimed to give a comprehensive overview of the actual status of the art of the diagnosis and treatment of this condition. As far as the origin of venous narrowing is concerned, phlebographic studies of the IJVs and AZ systems demonstrated that venous stenoses were likely to be truncular venous malformations; mostly, they are intraluminal defects such as malformed valve, septa webs. CCSVI condition has been found to be strongly associated with multiple sclerosis (MS), a disabling neurodegenerative and demyelinating disease considered autoimmune in nature. In several epidemiological observations performed at different latitudes on patients with different genetic backgrounds, the prevalence of CCSVI in MS ranges from 56% to 100%. To the contrary, by using venous MR and/or different Doppler protocols, CCSVI was not detected with the same prevalence. Two pilot studies demonstrated the safety and feasibility in Day Surgery of the endovascular treatment of CCSVI by means of balloon angioplasty (PTA). It determines a significant reduction of postoperative venous pressure. Restenosis rate was found out elevated in the IJVs, but negligible in the AZ. However, PTA seems to positively influence clinical and QoL parameters of the associated MS and warrants further randomized control trials.

Keywords: chronic cerebrospinal venous insufficiency; multiple sclerosis; echoDoppler; venous PTA

Anatomy of the cerebrospinal venous system
The cerebrospinal venous system is a three-dimensional structure that is often asymmetric and considerably represents a more variable pattern than the arterial anatomy.1,2

The intracranial venous system is mainly composed of parenchymal veins draining into the dural sinuses. The former can be subdivided into two systems:1,2

- The superficial (cortical) system reaches dural sinuses by cortical veins and drains blood mainly from cortex and subcortical white matter;
- The deep cerebral venous system (DCVs) is composed by the internal cerebral veins, the basal vein of Rosenthal and the great cerebral vein of Galen and their tributaries, and drains the deep white and gray matter surrounding the lateral and third ventricles.

The cerebral veins collect blood into the dural sinuses and in turn redirected toward the main extracranial venous outflow routes: the internal jugular veins (IJVs) and the vertebral veins (VVs) system (Figure 1). The anatomical pathways of jugular drainage are well established. The main jugular blood drainage pathway leads from the
transverse sinuses via the sigmoid sinuses into the IJVs, which meet the superior cava vein via the brachiocephalic vein. Valve fractioning of the blood column is possible only at the distal portion of the IJVs, where valves were found in 93% of post-mortem studies, and in 87% of Bmode investigations, mainly on the right side.\(^3\)

The VVs system is a freely communicating, valve-less system present throughout the entire spinal column and may be divided into an internal intraspinal part, the epidural veins and an extraspinal para-vertebral part.\(^1,2\) The system communicates with deep thoracic and lumbar veins, intercostal veins, the azygous vein (AZ) and hemiazygous veins. The AZ represents the final collector of such an enormous plexus, and in turn drains into the superior vena cava, as well as into the inferior vena cava, via the anastomosis of the hemiazygous veins with the left renal vein (Figure 1).

**Physiology of cerebral venous return**

The blood leaves the brain by using the back propulsion of the residual arterial pressure (*vis a tergo*), complemented by anterograde respiratory mechanisms (*vis a fronte*).\(^1,2,4–7\)

The latter consists of the thoracic pump increased venous outflow during inspiration, thanks to increased thoracic negative pressure, which improves the aspiration of blood toward the right atrium. In addition to *vis a tergo* and *vis a fronte*, postural mechanisms play a main role in ensuring a correct cerebral venous return. Several ultrasound studies of healthy volunteers demonstrated that the pattern of cerebral venous drainage changes, even under physiological conditions, depending on the body position.\(^1,2,4–7\)

In the prone position, the outflow through the IJVs is favoured; this assumption was based on angiographic studies and cerebral blood flow analyses with nitrous oxide, labelled erythrocytes and thermodilution techniques.\(^3\) Moreover, the supine posture favours cerebral venous outflow through the IJVs, whereas passing to the upright position transfers most of the encephalic drainage to the VVs.\(^4–7\)

**Echo-colour Doppler as a tool for assessing the physiology of cerebral venous return**

The echo-colour Doppler (ECD) is an ideal tool for assessing cerebral venous return. Given the influence of posture on venous outflow, ECD permits to turn rapidly the subject with the help of a tilt chair. It is intuitive that this cannot be easily done by the means of MR. The different significance of the gravitational gradient in ensuring venous return requires investigating the subject with the head, respectively, either at 90° or at 0°. Moreover, ECD permits assessing the flow direction by activating the thoracic pump. The detection of five parameters related to the above described physiology of cerebral venous return have been proposed.\(^6,8\)

1. **Flow direction in the cervical veins:** It has been reported that flow is monodirectional in the IJVs/VVs. Flow is always increased by the activation of the pump asking the subject to breath. Flow direction is usually assessed during the apnoea phase;

2. **Flow direction in the intracranial veins:** The cerebral veins are not easy to be insonated. By using the temporal window the basal vein of Rosenthal is one of the more constant segments to be detected, in consequence of the anatomical relationship with the P2 segment posterior cerebral artery. The normal flow is expected in the opposite direction to the transducer position.\(^9\) Below the classical temporal window, the intracranial venous compartment can also be studied in the supra-condylar projection. Such a window permits assessing the direction of flow in the inferior petrosus

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*Figure 1* Schematic of the cerebrospinal venous system with the location and relative prevalence of extracranial and extravertebral venous stenosis. DMCVs, deep middle cerebral veins; TS, transversal sinus; CV, condylar veins; VV, vertebral veins; IJV, internal jugular vein; VP, vertebral plexus; SVC, superior vena cava; AZY, azygous vein

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sinus and/or sphenoparietal sinus. In both, the normal flow is elicited by inspiration and directed backward. These are the more easily accessible venous segments by the means of the trancranial ECD technique.\(^9\)–\(^11\)

(3) **B-mode anomalies/stenosis of the IJVs:** Out of the valves of the distal portion of the internal jugular, usually open, in normal cases there are no other intraluminal leaflets. Valves are closed whenever central venous pressure rises. Ultrasonography easily demonstrated the valve leaflets in 87% of patients.\(^3\) Finally, it is frequent that the observation of some asymmetry comparing the cross-sectional area (CSA) of the two IJVs; however, in normal volunteers the smallest CSA measured in the IJVs was never less than 0.4 cm\(^2\);

(4) **Blocked outflow in the cervical veins:** Blood flow velocity in the cervical veins is increased by activation of the thoracic pump. Temporary outflow block can be seen in the cervical veins in healthy subjects, but never reported in all the postural and respiratory conditions;

(5) **CSA in the IJV:** As reported above, under normal physiological conditions, the CSA of the IJV is wider in supine position. This parameter can be assessed in B-mode in transversal access, giving the elliptical shape of the cervical veins.

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**The chronic cerebrospinal venous insufficiency syndrome**

Chronic cerebrospinal venous insufficiency (CCSVI) is a syndrome characterized by stenoses of the IJVs and AZ venous system with opening of collaterals\(^2\)–\(^7\) and insufficient drainage proved by increased mean transit time in a cerebral magnetic resonance imaging (MRI) perfusional study.\(^12\)

Phlebographic studies of the IJVs and AZ systems demonstrated that venous stenoses were truncular venous malformations (Figures 7 and 8), and quite recently were inserted in the Consensus Document of the UIP on venous malformations.\(^13\)

The CCSVI syndrome showed four main patterns of distribution of the venous stenosis:\(^7\)

(1) **Type A pattern (30%)** is characterized by significant stenosis either of the proximal azygous or of one of the two IJVs, with a compensatory contralateral IJV that appears with an ample cross-sectional area;

(2) **Type B pattern (38%)** is characterized by significant stenoses of both IJVs and the proximal azygous;

(3) **Type C pattern (14%)** is characterized by bilateral stenosis in both IJVs, with a normal azygous system;

(4) **Type D pattern (18%)** is characterized by the multilevel involvement of the azygous and lumbar systems. Association with the IJVs was observed in approximately 50% of cases, causing an additional obstruction in these patients.

As far as the collaterals or substitute circles is concerned when venous flow is deviated into collaterals to bypass an obstacle, there exists an anatomic bypass called a vicarious shunt.\(^2\)\(^,\)\(^6\)\(^,\)\(^14\)

This type of shunt is desirable because it bypasses blocked veins and thereby reduces resistance to drainage. Blood flows regularly in the substitute circle under the effects of distal cardiac residual pressure and proximal thoracoabdominal aspiration. The main collateral pathways activated in the course of CCSVI are the condylar venous system, the pterygoid plexus and the thyroid veins.\(^2\)\(^,\)\(^6\) Additionally, the suboccipital cavernous sinus and the hemiazygous-lumbar venous anastomosis with the left renal vein may also become prominent substitute circles. Collateral circulation prevents brain oedema and intracranial hypertension,\(^2\)\(^,\)\(^4\) and ensures a correct but slower, and thus insufficient, venous drainage.\(^12\)\(^,\)\(^14\)

**CCSVI a paradigm shift in the physiology of cerebral venous return**

Extracranial and extravertebral venous narrowing characterizing the CCSVI syndrome deeply modifies the physiology of cerebral venous return. This can be assessed by investigating the five ECD parameters related to cerebral venous return described above:

(1) **Flow direction in the cervical veins:** CCSVI can be characterized by the detection of reflux in the cervical veins. This is usually a long-lasting reflux expressing a reverse flow in order to permit a drainage through collateral circle.\(^14\) The parameter is positive when reflux in one of the IJVs and/or in one of the VVs is assessed in both sitting and supine posture, through activation of the thoracic pump, without the need of Valsalva.\(^7\)\(^,\)\(^8\) These findings suggest stenoses in the IJV and/or in the AZ, respectively (Figure 2, right);

(2) **Flow direction in the intracranial veins:** The parameter is positive when reflux, indicating a flow in the direction opposite to the physiological...
one, is detected in the vein of Rosenthal and in other deep cerebral veins, and/or in the dural sinusis. Flow direction in the cranial veins is not often simple to be identified. Multi-angle Doppler, like QDP system (MyLab Vinco, Esaote Biosound, Genoa, Italy) may facilitate the detection of B-directional flow (Figure 3). This finding suggests the waste of cerebral venous return, in consequence of the hampered outflow.7,8,15

(3) **B-mode anomalies\stenosis of the IJVs**: The parameter is positive when the B-mode detects stenoses in the IJVs in the form of hypoplasia, annulus, webs, septum or malformed valves (Figure 4);7,16

(4) **Blocked outflow in the cervical veins**: The parameter is positive when the absence of Doppler signal is detected in the IJV and/or in the VV, even after forced inspiration, in both sitting and supine posture; or alternatively,
in one posture but with reflux detection in the other position. Blocked outflow is related to stenosis distal to the point of assessment (Figure 5, right); CSA in the IJV:

The CSA of the IJV is measured both in supine and sitting posture. Thus, the parameter is assigned if the CSA in sitting posture should be greater. This happens frequently in CCSVI MS; alternatively, often the CSA in the IJV appears almost flat despite the change in posture (Figure 6, left).

Operationally, a subject is considered affected by CCSVI if two or more of the proposed physiological parameters should be positive and, nowadays, ECD can be considered a screening device.

The inter-observer variability rate between trained and not trained ECD operators, assessed using the same equipment (MyLab Vinco, Esaote Biomedica, Genoa, Italy), was 0.47 (95% CI 0.27–0.68), whereas the inter-observer agreement between trained operators was 0.80 (95% CI 0.59–1.01). Finally, the intra-observer variability rate in trained operators was 0.93 (95% CI 0.80–1.06). The conclusion is that ECD diagnostic accuracy is largely dependent on specific training.

Recently, for each of the five ECD parameters a ‘contribution score’ was assigned. These scores, combined, gave an overall severity measure, the venous haemodynamics insufficiency severity score or VHISS, ranging from 0 to 16.

**Truncular venous malformations of the CCSVI syndrome**

Patients fulfilling the Doppler screening criteria for CCSVI underwent selective venography of the lumbar veins, left renal vein, AZ and IJVs via catheterization of the left iliac femoral venous axis. As far as the morphology is concerned, we considered the following malformations:

- Annulus refers to significant circumferential stenosis of the whole venous wall;
- Septum-valve malformation refers to anomalous valve apparatus causing significant flow obstacles at the level of the junction of the IJVs with the brachiocephalic/anonymous trunk;
- Hypoplasia refers to under-developed long venous segments;
- Twisting refers to severe stenoses in consequence of a twisted venous segment;
Membranous obstruction refers to a membrane almost occluding a vein; Agenesis refers to the complete anatomical absence of a venous segment.

Annulus, septum, membranous obstruction, hypoplasia and agenesis are truncular malformations previously described in other venous segments (cava, iliac, deep veins of the lower limbs). In Figure 7 there are some examples of venous stenosing lesions morphologically quite similar to those described in the IJVs/AZ in course of CCSVI. In contrast, twisting of the AZ is a truncular malformation never been described so far (Figure 8). In Table 1 the distribution of the different truncular lesions in the extracranial and extravertebral cerebrospinal veins are given, and the more typical malformations are shown in the figures.

Association of the CCSVI syndrome with neurological disorders

Blocked extracranial venous blood outflow causes a high rate of cerebral venous reflux in multiple sclerosis (MS) patients, as demonstrated in previous studies. This detected reflux, propagated from the chest and neck veins into the parenchymal veins of the brain, was found strongly associated to the more common cause of disability in young patients.

Figure 6 Left: increased cross-sectional area (CSA) measured in the IJVs of healthy controls passing from the sitting to the supine posture. Right: flat or even negative CSA variation measured in the majority of CCSVI-MS patients. IJV, internal jugular vein; CCSVI-MS, chronic cerebrospinal venous insufficiency multiple sclerosis

Figure 7 Left: annulus of the IJV between the venous valve (VV) and the brachio cephalic trunk (BCT). Right: twisting of the AZY just below the arch with dilation and reflux toward the spine. AZY, azygous vein; IJV, internal jugular vein
people, namely to MS. It has been demonstrated that extracranial reflux was also transmitted up to the DCV system in 50% of MS cases. Extracranial blockages and haemodynamic disturbances of the cerebral veins are particularly associated to MS. CCSVI was not found in patients affected by other neurodegenerative diseases, such as Alzheimer, Parkinson and amyotrophic lateral sclerosis, but was detected in a miscellaneous of other neurological disorders.

Cerebral vein haemodynamics in healthy subjects are characterized by a laminar, mono-directional flow with low velocity, and it has been established that steady laminar shear stress promotes a release of factors from endothelial cells that inhibit migration of leukocytes. In contrast, altered haemodynamics have been documented by transcranial ECD in veins anatomically related to MS lesions, characterized by a high rate of reverse flow with a chaotic displacement of blood at the activation of the thoracic pump. Refluxing oscillatory flow favours the expression of adhesion molecules on endothelial cells, becoming a previously overlooked inflammatory mechanism in MS. Finally, the score of severity of anomalous venous haemodynamics (VHISS) is strongly correlated to a significant reduction of the cerebrospinal fluid flow dynamics in consequence of increased transmural pressure in CCSVI.

The CCSVI prevalence in MS

Duplex scanning, despite the need of a formal training, is the perfect tool for screening for CCSVI. It provides information on the prevalence of CCSVI in MS, and in healthy people at different geographical regions and among populations with different genetic backgrounds. For instance the prevalence in MS ranges between 56% and 100%, indicating that CCSVI is one of the major risk factors for the development of MS. Particularly, in the USA a prevalence of 56% versus 22% was found in the normal population; in Middle Orient of 84% versus 0%; and in Central/Eastern Europe of 90% without data on healthy controls.

To the contrary, by using MR venography and/or different from the above echo-colour-Doppler protocols, some authors did not find evidence of different prevalence of CCSVI in MS patients respective

### Table 1

| Morphology, location and relative rate of the stenosing venous truncular malformations found out in 65 consecutive patients |
|---|---|---|---|---|---|---|
| Annulus (%) | Septum/valve malformation (%) | Hypoplasia † (%) | Twisting (%) | Membranous obstruction (%) | Agenesis (%) |
| AZ | 0 | 14 | 9 | 0 | 48 | 0 |
| Distal AZ | 0 | 0 | 5 | 18 | 0 | 0 |
| Lumbar | 0 | 0 | 2 | 0 | 0 | 8 |
| IJVr | 28 | 46 | 6 | 0 | 0 | 0 |
| IJVl | 52 | 43 | 6 | 0 | 0 | 0 |

AZ, azygous vein; IJV, internal jugular vein
†Hypoplasia can be combined with other malformations in the AZ and in the IJVl
to controls. Particularly, the Doppler methodology proposed by Doepp et al. seems to be inadequate because measures more than 40% differences in cerebral venous outflow among healthy controls.

Given that both the autoimmune model and the CCSVI model have robust data and theory to back them up, it may well be that both CCSVI and externally driven, central nervous system (CNS) autoimmunity are important contributors to MS. The above recently released data from ongoing CCSVI studies seem to favour an MS disease model which integrates both CCSVI and CNS autoimmunity.

**Histology of MS plaques related to CCSVI**

In chronic venous disorders (CVDs) of the leg, it is well established that the same altered venous haemodynamic conditions negatively affect tissue drainage, with development of chronic inflammation, iron deposition and various degrees of tissue injury. At the microcirculatory level, erythrocyte sludge facilitates the transmigration of these cells and subsequent extravascular haemolysis, leading to increased pericapillary iron deposition. Histological studies demonstrate the peculiar disposition of the iron stores in MS constantly encircling the venous wall. Iron stores are arranged in hemosiderin deposits as well as in ferritin-like structures inside the macrophage, curiously resembling perivenous iron stores commonly observed in peripheral venous disease. Starting from histology, an impressive parallel has been delineated between the inflammatory process activated in course of CVD, and that profoundly studied in MS. Interestingly, pericapillary fibrin cuffs, a well-known marker of venous hypertension, have also been demonstrated in CCSVI associated with MS. Pressure in the AZ and in the IJVs measured significantly higher in CCSVI-MS respect to controls, testifying the haemodynamic significance of venous obstruction. These findings are consistent with a role of venous hypertension in the complex pathogenesis of MS, only hypothesized to date. Raised venous pressure can stretch vein walls sufficiently to separate the tight junctions between endothelial cells forming the blood–brain barrier. Colloids and erythrocytes could then pass through the exposed porous basement membranes participating to the inflammatory process.

In addition, VHISS is strongly associated to a parallel impairment of the cerebro-spinal fluid (CSF) dynamics measured by the means of advanced MR techniques. The CCSVI-MS patients showed a significantly lower net CSF flow (P = 0.038), which was highly associated with the VHISS (r = 0.77, r^2 = 0.60, P < 0.0007). This finding is consisting with increased venous pressure in the superior sagittal sinus. This study demonstrates that venous outflow disturbances in the form of CCSVI significantly impact on CSF pathophysiology in patients with MS.

**Neurological outcome measures in MS**

Several validated outcome measures are currently used to assess treatment effect in MS. Clinical measures are the Kurtzke Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC).

(i) EDSS is a method of quantifying disability in MS. The EDSS categorizes a person’s level of disability. EDSS scores range from 0 to 10, with higher scores indicating more severe disability. It is an important tool in clinical practice, because it is widely used and photographs the clinical situation. The EDSS score is based upon neurological testing and examination of functional systems, which are areas of the CNS which control bodily functions. The functional systems are:

- Pyramidal (ability to walk);
- Cerebellar (coordination);
- Brain stem (speech and swallowing);
- Sensory (touch and pain);
- Bowel and bladder functions;
- Visual;
- Mental;
- Other (includes any other neurological findings due to MS).

(ii) MSFC is more sophisticated and less utilized in clinical practice, but preferable in clinical trials. MSFC is a multidimensional clinical outcome measure consisting of quantitative timed tests of leg function/ambulation (Timed 25-Foot Walk – T25FW), arm function (Nine-Hole Peg Test – 9HPT) and cognitive function (Paced Auditory Serial Addition Test – PASAT) expressed as a single score along a continuous scale. Tests were administered using a standardized protocol according to MSFC guidelines.

The MSFC score was derived from three components: (1) the average scores from the four trials on the 9HPT (the two trials for each hand are averaged, converted to the reciprocals of the mean times for each hand and then the two reciprocals are
averaged); (2) the average scores of two 25FW trials; and (3) the number correct from the PASAT-3. For each component a \( z \)-score was then created using test results from the baseline visit. A \( z \)-score is a standardized score obtained by subtracting the baseline mean from the test result then dividing by the baseline SD. The composite score was calculated by adding the \( z \)-scores obtained and dividing the sum by 3, as described in the following formula: MSFC score = \( (z_{\text{arm, average}} - z_{\text{leg, average}} + z_{\text{cognitive}}) / 3.0 \). The negative value of the 25FW \( z \)-score was used to make the direction of change the same as the other components.

A decrease or an increase in the MSFC score represents, respectively, deterioration or improvement in neurological functions.

MS quality-of-life (QoL) questionnaire is another validated tool to assess not only physical performances but also disabilitating symptoms such as chronic fatigue and mental status as well. It was specifically projected taking into account disabilities and disease course of MS.37

There are also neurophysiological measurements, such as motor-evoked potentials. The pyramidal pathway is frequently affected early on in MS and impaired motor performance is a major cause of disability. Pyramidal tract function can be assessed using transcranial magnetic stimulation (TMS). TMS supports the diagnosis of MS, detecting corticospinal tract involvement and monitoring its course with or without treatment.38

Finally, the MRI measures are considered very important. Although it is unlikely that one single outcome measure can capture all aspects of the MS disease process, there is potential for MR imaging outcomes to evaluate inflammatory and degenerative components within clinical trials. They include the number of active plaques in the brain and in the spinal cord, corresponding to the number of lesions assessed in T1 enhanced gadolinium, the T2 lesions volume and the measurement of atrophy based on global brain volume and/or segmentary brain.39

**CCSVI endovascular treatment**

Endovascular treatment of CCSVI was reported to be feasible in day surgery with a minor and negligible complication rate.16,40 It consisted of percutaneous transluminal angioplasty (PTA) performed in the majority of cases (Figure 9). Stenting procedures was used in selected cases of AZ twisting.16 Postoperative venous pressure was significantly lower in the IJVs, and in the AZ as well \( (P < 0.001) \). However, the cumulative patency rate at 18 months in the IJVs was 53%, whereas in the AZ was 96%, absolutely more satisfactory.

Clinical outcome measures of the associated MS were significantly improved by PTA treatment, especially in the group characterized by a relapsing-remitting clinical course: rates of relapse-free patients passed from 27% to 50% postoperatively \( (P < 0.001) \), and that MRI Gad+ active lesions from 50% to 12% \( (P < 0.0001) \). In addition, MSFC at one year improved significantly, as well physical and mental QoL.

![Figure 9](image_url) (a) Closed stenosis of the right IJV; (b) The balloon inflated during the PTA; (c) Postoperative result

IJV, internal jugular vein; PTA, percutaneous transluminal angioplasty
The result of this open label prospective study was highly positive in the neurological outcome of MS patients. It presents several limitations, yet. The main shortcomings of this pilot study are represented by the lack of a control group, and the unblinded clinical evaluation. However, the reduction of Gad+ active lesion at the MRI is a blinded and significant measure. It seems that endovascular treatment could add further advantages with respect to current therapy, because all the patients were under the treatment Food and Drug Administration approved drugs for MS.

In a further pilot study two groups of CCSVI-MS patients were evaluated. The first group underwent to the PTA at baseline, whereas the second group had a delayed endovascular treatment six months later. This study confirmed the safety of PTA because again no major complications occurred. MS outcome measure is currently under evaluation.

Further subanalysis of the first trial demonstrated a significant reduction of chronic fatigue, one of the more debilitating symptoms in MS. Chronic fatigue is still the orphan of any effective treatment. The dramatic reduction of fatigue perception following PTA appears to be a symptom peculiar to CCSVI in the highly complex symptomatic picture of MS.

Moreover, it has been reported that treatment of the associated CCSVI made a parallel improvement in both clinical and neurophysiological TMS parameters. The demonstration of a modification of the cerebrovenous function with both clinical manifestation and via TMS suggests that the hampered cerebral venous return may contribute to the motor clinical manifestation of MS. The results of such pilot studies warrant subsequent randomized control trials.

References
