

Development of a Research Agenda for Evaluation of Interventional Therapies for Chronic Cerebrospinal Venous Insufficiency: Proceedings from a Multidisciplinary Research Consensus Panel

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ABBREVIATIONS

CCSVI = chronic cerebrospinal venous insufficiency, CNS = central nervous system, MS = multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) that results in damage

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This project was supported by the Society of Interventional Radiology (SIR) Foundation. G.P.S. is a paid consultant for Boston Scientific (Natick, Massachusetts) and CeloNova Biosciences (Newnan, Georgia) and has research funded by C.R. Bard (Murray Hill, New Jersey) and MDS Nordion (Ottawa, Ontario, Canada). E.M.H. receives a salary from Wayne State University and the MRI Institute for Biomedical Research, has a patent ownership or part ownership in Magnetic Resonance Innovations (Detroit, Michigan), and has research funded by Siemens Medical Solutions (Erlangen, Germany) and the National Institutes of Health. G.M. is a paid consultant for C.R. Bard, Cook (Bloomington, Indiana), Siemens, Medtronic (Minneapolis, Minnesota), and B. Braun (Melsungen, Germany). W.R. is a paid consultant for EMD Serono (Rockland, Massachusetts) and Biogen Idec (Weston, Massachusetts). D.H. is an owner of or shareholder in the Applied fMRI Institute (San Diego, California). S.V. has research funded by Covidien (Mansfield, Massachusetts). Z.J.H. receives royalties from Cook Medical (Bloomington, Indiana) and ElCam Medical (Hackensack, New Jersey), is a paid consultant of W.L. Gore and Associates (Flagstaff, Arizona), and receives research funding from C.R. Bard (Murray Hill, New Jersey) and W.L. Gore and Associates. None of the other authors have identified a conflict of interest.

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J Vasc Interv Radiol 2011; 22:587–593

DOI: 10.1016/j.jvir.2011.03.007

to myelin and, to a lesser extent, axons in the brain, spinal cord, and optic nerves. Presently, our understanding of the pathophysiology of MS centers on an immune-mediated attack against CNS myelin antigens (1,2). The symptoms caused by MS are variable and can range from mild to quite debilitating. When a patient presents with the typical clinical manifestations, characteristic white matter lesions are often visualized with magnetic resonance (MR) imaging, which confirms the diagnosis of MS (2,3). Significant research has been focused on different treatment strategies for MS, with attention often paid to disease-modifying drugs that seek to disable a component of the immune system or to prevent the neurodegeneration seen in progressive forms of the disease (4).

Chronic cerebrospinal venous insufficiency (CCSVI) is part of a new theory that was initially put forth to explain the pathogenesis of MS and the symptoms associated with this disease. This theory, put forth by Paolo Zamboni, has its basis in the observed anatomic distribution of inflammatory lesions along cerebral veins (5–7). It proposes that extracranial venous obstruction interferes with the venous drainage from the CNS, contributing to the development and progression of MS (8,9). Whether CCSVI is truly a precursor to MS or an independent clinical entity responsible for some of the symptoms classically attributed to MS is not yet known. However, Zamboni et al (10) described a correlation between MS and abnormal venous drainage, as well as their clinical success in treating this condition with venous angioplasty. These reports have led to significant interest among patients and physicians about the role of this treatment in MS.

On October 18, 2010, the clinical trials division of the Society of Interventional Radiology (SIR) Foundation com-

missioned and convened a multidisciplinary meeting of physicians and scientists with expertise in clinical management of MS, basic sciences, neuroradiologic imaging, and vascular and venous interventions. The purpose of the meeting was to review the existing data linking CCSVI with MS and establish a research agenda for the evaluation of imaging and interventional therapies in the treatment of patients with MS.

MEETING ORGANIZATION

An 11-member research consensus panel was created from a list of leading scientists developed by the Research Consensus Panel Lead Investigators (Z.J.H., G.P.S.). The SIR Foundation Chair (G.M.) moderated the session. The Panel included members from the fields of interventional radiology, imaging physics, surgery, and neurology. Representatives from industry and the federal government were also present as observers.

Before the meeting, the panelists were given an agenda describing the structure and objectives of the session. The meeting was divided into three parts in accordance with a modification of the standard SIR Foundation process: (i) introductory presentations to establish a baseline level of knowledge; (ii) a moderated roundtable panel discussion, which included a discussion of patient population, standardization of treatment methods, imaging protocols, and clinical assessment tools; and (iii) a summary of the discussion to generate ideas about clinical trial design, tools, and preliminary data that will be needed to construct a well designed clinical trial.

Six of the panel participants (W.R., M.D.D., S.M., E.M.H., Z.J.H., and G.P.S.) made presentations of background material before the roundtable discussion. The intent was to provide a common basis for dialogue about the current state of peer-reviewed knowledge as a basis for discussion of the next appropriate steps for research.

The panel was presented with a summary of the current knowledge from the literature regarding the treatment of MS and the presentation of CCSVI. These formal presentations included “MS Overview: Classification, Clinical Presentation, and Treatment Strategies” (W.R.); “Venous Disease and MS” (M.D.D.); “The Role of Doppler Ultrasound in the Diagnosis of CCSVI” (S.M.); “The Role of MR Venography in the Diagnosis of CCSVI” (E.M.H.); “Venous Angioplasty for CCSVI: Technique and Image Interpretation” (Z.J.H.); and “CCSVI Literature Review” (G.P.S.). The key aspects of these presentations are summarized herein.

DATA COLLECTION AND ANALYSIS

The panel began a dialogue of research priorities for evaluating CCSVI interventions. Each panelist was solicited for opinions regarding the status of current knowledge, the

tools and preliminary data needed to design an appropriately powered clinical trial, and the construct of an appropriate clinical trial to evaluate CCSVI therapies. Final recommendations of the panel were reached via consensus.

OVERVIEW OF MS

MS is a common neurologic disease whose cause has yet to be definitively determined. However, the vast majority of evidence suggests that it reflects the combined effect of genetic and environmental factors (11). Multiple genes have been associated with an increased MS risk, and for the vast majority of patients, genetics accounts for some percentage of their risk of developing the disease. Among the environmental factors that have been associated with developing MS are viral infections, particularly that caused by Epstein-Barr virus, and more recently, sunlight exposure and its effects on the production of vitamin D (12–14).

There is strong evidence for an immune basis for the development of MS. It has been suggested that T and B cells in the peripheral circulation become sensitized against nervous system antigens, and then these cells cross the blood-brain barrier and enter the CNS (15). When they have been stimulated, these cells can mount an immune attack against antigen-expressing targets or cause damage as a result of “bystander” effects of the inflammation. This process injures neurons and oligodendrocytes, the cells that form myelin in the CNS, resulting in demyelination and axonal damage. It has recently been suggested that demyelination might also result from primary oligodendrocyte degeneration, perhaps caused by a viral infection, complement deposition, or a primary cellular disturbance (16).

Optic neuritis is a common initial manifestation of MS, with symptoms that include pain during eye movement and blurred vision with reduced acuity (17,18). Other symptoms often associated with MS include diplopia, weakness, fatigue, numbness, pain, limb or gait ataxia, bladder disturbances, and cognitive impairment (18). Approximately 85% of patients present with the relapsing/remitting form of MS, which is characterized by symptomatic episodes (ie, relapses) and intermittent periods of partial or complete improvement. Before the introduction of disease modifying therapies, approximately 50% of individuals with the relapsing/remitting form of MS are likely to develop the secondary, progressive type within 10 years of diagnosis. This stage is characterized by a gradual onset of new symptoms and worsening of previously established symptoms with no discernable relapses (19). Primary progressive disease, characterized by gradual clinical worsening without discernable relapses affects 10% of patients. The remaining 5% have progressive/relapsing disease, characterized as gradual worsening with rare exacerbations during the course of the illness.

The current focus of treatment in MS, which is the use of disease-modifying drugs, is based on the modulation or suppression of the immune response believed to be central

in the progression of this disease. These strategies include the use of corticosteroids to treat acute exacerbations, β -interferon agents (ie, interferon β -1a, marketed under various brand names) and glatiramer acetate (Copaxone; Teva Neuroscience, Petah Tikva, Israel) for maintenance therapy in patients with early and relapsing/remitting MS, and natalizumab (Tysabri; Biogen Idec, Weston, Massachusetts) for patients whose disease does not respond to these therapies (20–23). Natalizumab is a humanized monoclonal antibody that binds the leukocyte adhesion molecule $\alpha 4\beta 1$ integrin, which inhibits passage of inflammatory cells into the CNS (4). The β -interferons and glatiramer acetate are effective in approximately one third of patients, whereas natalizumab has been shown to be effective in approximately 70% of patients. Their side effects range from injection site reactions (β -interferon and glatiramer acetate) to flulike symptoms (β -interferon), transient hypersensitivity reactions (glatiramer acetate), and, for natalizumab, the occurrence of progressive multifocal leukoencephalopathy in approximately one in 1,000 patients. In 2010, the Food and Drug Administration approved the use of fingolimod (Gilenya; Novartis, East Hanover, New Jersey) to reduce relapses and progression in patients with relapsing/remitting disease (24). This drug inhibits the activation of sphingosine-1-phosphate receptors, which prevents migration of lymphocytes from lymphoid tissue into the CNS. Transient bradycardia and decreased lung diffusion capacity have been reported after administration of the first dose of fingolimod, and patients may develop retinal edema at any time during the first 3 months of treatment. Mitoxantrone, an anthracenedione antineoplastic agent, is the only drug currently approved for the treatment of patients with secondary progressive disease. None of the currently approved therapies have been shown to be effective for the treatment of primary progressive MS (25). Mitoxantrone treatment has been associated with cardiac toxicity and an increased risk of acute leukemia. Continued clinical trials are under way to examine the effects of individual drug therapies for the treatment of progressive MS and combination therapies for all forms of the disease.

VENOUS DISEASE AND MS

A relationship between the brain lesions of MS and cerebral veins has been suspected since the time of Charcot (5). Postmortem studies have demonstrated that periventricular plaques appear to extend along cerebral veins (26,27), and that other plaques arise from segments of large ependymal veins and extend into the cerebral hemispheres along cerebral veins (6). In light of this relationship, Putnam (7) noted in 1935 that “the conclusion appears almost inevitable that venular obstruction is the essential antecedent to the foundation of typical sclerotic plaques.”

When significant extracranial venous disease is present, collateral vessels often develop to prevent the development of intracranial venous hypertension (28). However,

even with these collateral pathways in place, venous drainage can potentially be insufficient and the transit time prolonged, as confirmed by MR perfusion studies (29–31). This can lead to several problems. As normal cerebrospinal fluid circulation depends on efficient venous drainage from the CNS, insufficient venous drainage can lead to lower net cerebrospinal fluid flow (32); this is supported by the increases in the volume of the lateral and third ventricles in MS (33). It can also cause retrograde venous flow and chronic reflux into the CNS (28), which can ultimately increase the resistance to flow and transmural pressure (34,35). Even before the recent description of CCSVI, venous hypertension was thought to play a role in the pathogenesis of MS (36,37).

The theory of CCSVI suggests that increases in venous pressure lead to venous dilation, which can potentially increase the permeability of the blood-brain barrier (38). It is possible that alterations in venous hemodynamics could increase the expression of endothelial adhesion molecules, chemokines, and cytokines that ultimately alter endothelial adhesiveness and permeability. Such alterations in vascular homeostasis permit the infiltration of immune cells into the surrounding tissue. These cells elaborate cytokines and oxygen-derived free radicals that further increase vascular permeability, leading to insudation of plasma proteins and, in some cases, red blood cells. Red blood cell extravasation with subsequent perivenous iron deposition can result in significant inflammatory change (8,34). Iron is known to be important for CNS physiology, as it is a cofactor for neural metabolism and adenosine triphosphate production and because it is involved in myelination and oligodendrocyte development (39,40). Limited studies have supported the contribution of local iron overload to the inflammation associated with MS (41,42).

THE ROLE OF DOPPLER ULTRASOUND IN THE DIAGNOSIS OF CCSVI

Using duplex ultrasonography (US) and transcranial Doppler studies, Zamboni et al (43) reported a statistically significant association between abnormal venous hemodynamics and MS. In this study of 109 patients with MS and 177 age- and sex-matched controls (43), subjects underwent a blinded assessment of five parameters related to venous outflow hemodynamics, using transcranial and extracranial color Doppler US examinations. These parameters included the following: reflux in the internal jugular or vertebral veins with the head in any position, reflux propagated upward to the deep cerebral veins, high-resolution B-mode evidence of a proximal internal jugular vein stenosis, undetectable flow in the internal jugular or vertebral veins, and absence of the normal decrease in cross-sectional area of the internal jugular vein when moving from a supine to an upright position. In control subjects, only 2.7% of the measurements were anomalous, whereas in those with MS, 47% of measurements were abnormal. When at least two

criteria were used to define a positive examination, Zamboni et al (43) had a positive predictive value of 100% and a negative predictive value of 100%. In a subsequent study, the same authors (9) found that 40%–70% of patients with MS had US findings consistent with CCSVI; when these patients were studied with venography, 86% and 91% had obstructive disease of the azygous or internal jugular veins, respectively.

Others have had mixed results in duplicating the US findings of Zamboni et al. Menegatti et al (44) confirmed the utility of US and the reproducibility of this technique to diagnose CCSVI. Simka et al (45) studied 70 patients with MS and found that sonographic abnormalities were detected in 91.4%. Al-Omari and Rousan (46) assessed 50 patients with US (25 patients with MS and 25 control subjects) and found that 92% of patients with MS and 24% of control subjects had abnormal findings. However, 84% of patients with MS and no control subjects met the criteria for the diagnosis of CCSVI (46). In contrast, Doepp et al (47) were unable to replicate these findings and found no differences in venous flow in the internal jugular vein between patients with MS and healthy control subjects. It has been suggested that the technique used by Doepp et al (47) was different than the technique used in the previous studies, making the studies difficult to directly compare. Specialized training was suggested as necessary to optimize the diagnostic accuracy and reproducibility of this technique (44).

THE ROLE OF MR VENOGRAPHY IN THE DIAGNOSIS OF CCSVI

In the setting of CCSVI and MS, MR imaging can be used not just as a treatment planning procedure to complement information available from US, but also as a means to monitor lesions, iron content, vascular anatomy, and flow in the brain and neck. Susceptibility-weighted imaging techniques can detect iron deposits in the brain (48–50), morphology of cerebral veins (51,52), and blood volume and oxygen saturation changes in MS (53). Zivadinov et al (50) suggested that iron deposition on MR imaging is a strong predictor of disability progression, lesion volume accumulation, and atrophy development in MS.

MR venography is an effective tool for imaging the intracranial and extracranial venous system (54). However, despite the potential benefits of MR imaging and MR venography in evaluation for CCSVI in patients with MS, conflicting data have been reported. Hojnacki et al (55) reported MR venography findings in 10 patients with MS and seven healthy control subjects, stating that MR venography had limited value for the diagnosis of CCSVI compared with US and catheter venography. Sundstrom et al (56) studied 21 patients with relapsing/remitting MS and 20 healthy control subjects with MR imaging and found no differences regarding internal jugular venous outflow, cerebrospinal fluid flow, or reflux in the internal jugular veins.

Finally, Wattjes et al (57) reported a study of 3-T phase-contrast and dynamic 3D contrast-enhanced MR venography in 20 patients with MS and matched healthy control subjects: normal venous anatomy was seen in 10 patients with MS and 12 control subjects, and abnormalities were seen in 10 patients with MS and eight healthy control subjects (57).

PANEL DISCUSSION

The methodical prospective study of the effects of venous interventions in patients with MS is important, as patients actively travel to physicians to undergo procedures they believe (and have read through the Internet and social media) can improve their symptoms. After Zamboni et al (10) reported their initial success with angioplasty to improve MS-related symptoms, there has been considerable popular interest among patients seeking treatment for CCSVI despite the still-limited available scientific evidence. Although anecdotal self-reported results of successful treatments in the United States and abroad have heightened expectations, the original publication of Zamboni et al (10) currently remains the only peer-reviewed publication describing outcomes after angioplasty. This report described the prospective results of 65 patients with MS who underwent angioplasty (10), and reported statistically significant improvements in 1-year outcomes measured by the MS Functional Composite index and physical and mental quality of life examinations. The study is uncontrolled (10), and the role of concurrent medications, among other confounding variables, is unclear. Because of these uncertainties, the consensus panel viewed the original report of Zamboni et al (10) as an interesting report of initial experience that should prompt more rigorous scientific investigations to support proof of concept, validate, and replicate.

Much discussion was centered on the understanding that much work needs to be done to better define, explore, and prove the concept of venous outflow obstruction playing a role in the pathogenesis of MS. Although others have raised this idea in the past, it remains, at best, poorly understood. Therefore, much investigation is needed in this area. The panel supports the path taken by the National MS Society in recommending large studies to evaluate the prevalence of CCSVI and iron deposition in patients with MS and healthy control subjects, the correlation between venous abnormalities and markers of MS activity, and the diagnostic modalities best suited to diagnose CCSVI. In addition, work should be undertaken to explore the possibility that CCSVI may be an independent clinical entity with potential relationships with a variety of clinical conditions including, but not limited to, MS.

The panel discussed the diagnosis of CCSVI at length. It was acknowledged that both Doppler US and MR venography could play a role in the diagnosis of CCSVI. The questions surrounding the work of Zamboni et al (43) strongly suggest the need for studies designed to better

define the role of US in the diagnosis of CCSVI. Studies designed to validate the protocol put forth by Zamboni et al (43) will be necessary to establish uniform technical standards and to determine the relative contribution of the extracranial and transcranial components of this examination to the diagnosis of CCSVI. The importance of training has been stressed (44), but until this diagnostic technique has been validated and standardized, and sensitivities and specificities defined with gold-standard comparisons, a discussion of training is likely premature.

Similarly, MR imaging and MR venography show natural utility as diagnostic tools for MS and CCSVI. However, it is clear that data published to date have been inconclusive (55–57). Therefore, the panel supports further investigation into defining the role of MR imaging and MR venography in assessing patients with MS for CCSVI. These studies should define optimal and reproducible protocols for MR venography of the intra- and extracranial venous vasculature and zygous vein, correlate them with other forms of invasive and noninvasive imaging, define sensitivities and specificities, and ultimately provide correlation with treatment studies and outcomes.

In the context of CCSVI diagnosis, the panel attempted to identify a progression of needed preliminary studies. Because data on the effect of CCSVI treatment on the outcomes of patients with MS is limited, the panel discussion was focused on achieving consensus on the appropriate patient populations to study and the appropriate endpoints for primary and secondary endpoint analysis, and on identifying the data needed to potentially aid in designing an appropriately powered pivotal controlled trial(s).

There was near-universal agreement that randomized trials would be required to confirm the role of venous interventions in MS. However, it was equally clear from the discussion that several factors could be better understood before large-scale randomized trials are initiated. Among these are the aforementioned confirmatory prevalence and diagnosis data, but also the need to define the appropriate study population, the need to optimize the interventional techniques for diagnosis and treatment, and to agree on appropriate endpoints for primary and secondary endpoint analysis. The panel, therefore, encourages the performance of investigator-initiated single-center and multicenter studies so safety and outcome data can be reported. In this way, a foundation of knowledge in these areas can be gathered. This knowledge will help provide the information necessary to appropriately power a prospective randomized trial.

The panel attempted to define an appropriate study population for a randomized trial. Of the major types of MS presentations, the relapsing/remitting type represents the largest patient population and the population in whom most medications are tested. MR imaging findings of plaque count and volume are accepted as surrogate markers of response in these patients to treatment in drug trials (58). The large size of this patient population and established methods of measuring outcomes in other trials makes them a natural study group. The plethora of drug regimens avail-

able to treat relapsing/remitting MS will require careful study design to control competing drug effects. The less common forms of MS have few effective medications, so patients who undergo catheter-based interventions could be compared with those who receive no drug treatment. Although the committee believed that initial safety studies could include all forms of MS, there was strong sentiment that controlled trials, as designed, should address as homogeneous a population as possible.

A separate discussion addressed patients with clinically isolated syndrome (those with MS symptoms but no identified plaques) and patients with isolated optic neuritis. These two groups are believed to represent an early phase of the MS continuum, but it was concluded that trials of CCSVI diagnosis and intervention in these populations must be separated from those in patients with a confirmed diagnosis of MS. Further definition of the MS population to be studied would be determined by phase I peer-reviewed publications from centers with large experiences.

The panel discussion turned to the interventional procedures themselves and to their appropriate endpoints. It was acknowledged that the interventional approach to CCSVI should ultimately be standardized and reproducible, but many relevant questions still need to be answered before that is possible. Examples of these current unknowns include a validated definition of flow-limiting stenosis; optimal balloon sizes for each of the varied causes of venous stenosis; venographic, hemodynamic, or sonographic endpoints of angioplasty; the role of endovascular stents or other adjunctive tools; and the use of anticoagulation and/or antiplatelet medication after endovascular intervention. The panel asked whether currently available interventional devices were sufficient for the clinical and research needs or whether further refinements were required. It was emphasized that many of these questions may need to be answered before pivotal trials are undertaken. Appropriate endpoints for clinical outcome also need to be established. Although MR imaging of the brain (eg, lesion count, plaque regression) has been a primary endpoint in drug trials, vigorous discussion ensued regarding its role as the primary endpoint in CCSVI studies. The importance of patient-reported outcomes using validated indices was discussed, for which a number of tools are available (eg, physical function, fatigue, and quality of life in MS) (59–63). Trial designs will need to use these tools in addition to more objective findings, such as MR imaging findings of plaque count and volume, as measures of outcome.

The panel session continued with a discussion of the actual designs of pivotal randomized trials. The discussion was brief, in acknowledgment of the notable volume of information that still needs to be gathered regarding the diagnosis of CCSVI, patient selection, interventional radiologic techniques, and meaningful endpoints. However, issues concerning patient blinding and study duration were raised. Although some concern was raised over the possibility of a realistic sham arm, it was the consensus of the interventional radiologists in the room that blinding of the

patients was feasible: it was believed that a sedated patient undergoing venography would not, with certainty, know whether venoplasty was being performed concurrently. To blind the data analysis, research personnel, including examining neurologists, diagnostic radiologists, and US technologists, would need to be shielded from the procedural data (ie, sham vs intervention). Blinding was believed to be a critical component of a pivotal randomized trial because of the potential contribution of placebo effects to the outcomes seen after treatment of patients with MS (64).

Finally, the duration of an ideal study and the possibility of crossover were discussed. It was stated that, in general, patients in drug trials were followed for 6 months, so the minimum time of crossover in studies including such an option should be 6 months. However, because Zamboni et al (10) also reported a high rate of restenosis, several of the committee members believed clinical and imaging follow-up should be continued for 1 year. In this study design, crossover could not occur until after 1 year. Finally, it was mentioned that the required minimum length for a MS treatment trial to show efficacy is 2 years. This part of the discussion was preliminary in its conclusions.

SUMMARY

The committee came to the general consensus that the mechanisms for evaluating patients with MS for jugular and azygous venous compromise and the value of treating these lesions with angioplasty warrant careful, well designed additional study. The committee believed the specific parameters needed for a large-scale, pivotal multicenter trial were not necessarily available at this time, but that these types of trials are the mandatory goal for study of CCSVI. Prospective safety and efficacy trials should be conducted in well defined and potentially smaller controlled populations under institutional review board approval. In addition, it is critical to support and continue the basic science work under way to better understand the relationship between venous stenoses and hypertension and the subsequent contribution of CCSVI to patients with MS. Animal models will likely prove useful, though inflammatory mediators may be assessed with serum sampling in the context of human trials.

There will be many practitioners who will offer endovascular therapy to patients with MS in advance of the availability of definitive peer-reviewed data in support of that practice. It was the general hope of the committee that this work would lead to additional peer-reviewed studies generating data that clarify the role in MS of treating venous disease with angioplasty and possibly stent placement and the potential adverse events associated with these interventions (65). If additional studies confirm the initial reports in favor of CCSVI diagnosis and treatment, and appropriate study cohorts and standardized procedural technique and reporting are developed, it will be appropriate to pursue prospective multicenter trials. Enrollment in these

trials will require the following: (i) confirmation of the diagnosis of MS based on currently accepted criteria; (ii) assessment of disease activity with conventional MR imaging; (iii) determination of clinical and functional status; (iv) listing of previous treatment for MS or other significant medical issues; (v) noninvasive screening documentation of venous disease with US and/or MR imaging/venography; and (vi) catheter-based venographic documentation of venous stenoses. Randomization against catheter venography without angioplasty would be required, with blinding of research personnel and examining neurologists. The potential role of stents would emerge from discussions of trial design. Imaging follow-up and clinical assessments might occur at 3, 6, 9, and 12 months after treatment, with a crossover permissible after a period yet to be defined. This type of study defines an ultimate goal in determining the contributory role of CCSVI and catheter-based interventions in patients affected with MS.

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