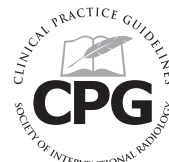


Interventional Endovascular Management of Chronic Cerebrospinal Venous Insufficiency in Patients with Multiple Sclerosis: A Position Statement by the Society of Interventional Radiology, Endorsed by the Canadian Interventional Radiology Association



Suresh Vedantham, MD, FSIR, James F. Benenati, MD, FSIR, Sanjoy Kundu, MD, FSIR, Carl M. Black, MD, Kieran J. Murphy, MD, FSIR, and John F. Cardella, MD, FSIR

J Vasc Interv Radiol 2010; 21:1335–1337

Abbreviations: CCSVI = chronic cerebrospinal venous insufficiency, MS = multiple sclerosis

IT has been recently hypothesized that a phenomenon known as chronic cerebrospinal venous insufficiency (CCSVI) may play a significant role in the etiology, pathogenesis, and/or disease progression of multiple sclerosis (MS) (1,2). Preliminary studies suggest that anatomical and physiological abnormalities of venous blood flow are significantly more common in patients with clinical MS than in healthy control subjects or patients with other neurologic disorders (3–6). Of particular interest has been the documentation of stenotic and occlusive lesions in the azygos and internal jugu-

lar veins on duplex ultrasound and contrast venography of patients with clinical MS. One group (1,7,8) has reported improvement in clinical outcomes including quality of life in two small prospective uncontrolled cohorts of patients with MS in whom such lesions were treated with balloon angioplasty. Although additional clinical studies have not yet been published, the potential for image-guided, catheter-based procedures to evolve into a standard treatment option for MS has engendered great interest and major controversy among interventional radiologists, vascular surgeons, neurologists, patients with MS, and their advocates.

The prevalence in the United States of MS is estimated to range from 250,000 to 500,000 persons (9,10). Despite the use of current therapies that aim to reduce inflammation, interrupt specific components of the immune system, or prevent neurodegeneration, most patients with MS exhibit a disease course that includes periodic acute relapses that initially resolve but eventually lead to significant clinical deterioration and disability (11–14). Existing MS therapies can also cause disabling side effects that can lead to additional morbidity, precluding the use of such therapies in many patients (14). Therefore, new innovative therapies for MS are urgently required.

2. SIR recognizes that patients with MS constitute a particularly vulnerable population, whose safety must be protected as new therapeutic approaches are evaluated.

MS can have devastating consequences in affected patients and their family members, who are often very aware of its progressive course and the relative lack of available treatments that are consistently effective in preventing long-term neurologic degeneration. Patients with MS and their families are anxious for any

From the Mallinckrodt Institute of Radiology (S.V.), 510 S. Kingshighway Blvd., Box 8131, St. Louis, MO 63110-1076; Peripheral Vascular Laboratory (J.F.B.), Baptist Cardiac and Vascular Institute, Miami, Florida; Department of Medical Imaging (S.K.), Scarborough General Hospital; Department of Medical Imaging (K.J.M.), University of Toronto, Toronto, Ontario, Canada; Department of Radiology (C.M.B.), Utah Valley Regional Medical Center, Provo, Utah; and Department of Radiology (J.F.C.), Geisinger Health System, Danville, Pennsylvania. Received and accepted July 15, 2010. Address correspondence to S.V.; E-mail: vedanthams@mir.wustl.edu

S.V. has received support for a NIH trial from Covidien and MEDRAD Interventional. None of the other authors have identified a conflict of interest.

© SIR, 2010

DOI: 10.1016/j.jvir.2010.07.004

SOCIETY OF INTERVENTIONAL RADIOLOGY POSITION STATEMENT

Outlined below is the current position of the Society of Interventional Radiology (SIR) on the use of image-guided interventional endovascular treatment of MS:

1. SIR recognizes the urgent need for more effective treatments for MS patients and the public's interest in rapidly making such therapies available to this patient group.

glimmer of hope from the scientific community, and some are willing to assume the risks and uncertainties of promising new therapies even when they are relatively untested. SIR understands and respects their concerns and also agrees with MS advocates, physicians, and other caregivers that the use of any treatment (antiinflammatory, immunomodulatory, interventional, or other) in patients with MS should be based on an individualized assessment of the patient's disease status, his/her tolerance of previous therapies, the particular treatment's scientific plausibility, and the strength and methodologic quality of its supporting clinical evidence. When conclusive evidence is lacking, SIR believes that these often difficult decisions are best made by individual patients, their families, and their physicians.

3. At present, SIR considers the published literature to be inconclusive on whether CCSVI is a clinically important factor in the development and/or progression of MS, and on whether balloon angioplasty and/or stent placement are clinically effective in patients with MS.

A compelling body of published research indicates that MS is a disorder with predominantly autoimmune features and an unknown primary etiology. The hypothesis that CCSVI may be a primary factor in the pathogenesis of MS or an aggravating factor in its clinical progression, if firmly established, would represent a major paradigm shift in the general scientific understanding of this disorder. The discovery of extracranial venous stenoses in patients with MS certainly merits serious study, but it is unclear whether they truly represent a cause of MS versus a secondary effect of the pathologic process arising from the disease, an effect of MS treatments, or an unrelated finding. Although promising, the pilot studies that suggest a clinical benefit for patients with MS with the use of balloon angioplasty had important methodologic limitations: (i) small sample size ($N = 96$ patients combined); (ii) single-center performance; (iii) lack of blinding of clinical outcome assessors; and (iv) nonrandomized design with lack of a placebo control group (particularly lim-

iting as a robust placebo effect would be expected in patients with MS) (7,8). In addition, although balloon angioplasty and stent placement of central thoracic veins have been performed safely for many years in other clinical scenarios, the procedures are invasive and carry a risk of complications. Also, the durability of clinical response has not been established. Hence, the current body of literature is insufficient to judge (i) whether an interventional treatment approach for MS is effective; if so, (ii) for how long and (iii) whether its clinical benefits outweigh the associated risks and costs; and (iv) which patients with MS, if any, should be treated and at what stage in the disease process.

4. Interventional radiologists possess the ideal skill set to provide interventional MS therapy with maximum safety and effectiveness when clinically appropriate.

If interventional MS therapy proves to be effective, patients with MS must be treated by physicians with specialized expertise in delivering image-guided venous treatments. Interventional radiology is a recognized subspecialty requiring dedicated training that encompasses clinical patient evaluation and management, noninvasive venous imaging, catheter venography and hemodynamic assessment, and the delivery of targeted, image-guided, minimally invasive treatments to patients (15). Interventional radiologists perform balloon angioplasty and stent placements on a daily basis in thousands of patients with diverse venous conditions including acute deep vein thrombosis, postthrombotic syndrome, superior vena cava syndrome, and portal hypertension; they also perform procedures to maintain hemodialysis access. SIR has a stated mission to improve public health by pioneering advances in image-guided therapies. SIR and its members are committed to developing and maintaining the highest standards of excellence in patient care, integrating disease management, proficiency with a wide range of imaging technologies, and specialized technical expertise in providing image-guided therapies. SIR and its members adhere to the highest standards of ethical behavior, placing the interests of patients first.

5. SIR strongly supports the urgent performance of high-quality clinical research to determine the safety and efficacy of interventional MS therapies, and is actively working to promote and expedite the completion of the needed studies.

SIR believes that the completion of high-quality studies on CCSVI and interventional MS therapies should be considered an urgent research priority by investigators, funding agencies, and MS community advocates. SIR, through its Neurovascular and Venous Service Lines, is moving rapidly to catalyze the development of the needed studies by bringing together expert researchers in image-guided venous interventions, neurology, central nervous system imaging, MS outcomes assessment, and clinical trial methodology.

CONCLUSION

SIR recognizes the challenge and the potential opportunity presented by promising early studies of an interventional approach to the treatment of MS. SIR is pleased that public advocacy groups have pushed the medical community forward to meet this challenge and is committed to assuming a national leadership role in launching the needed efforts.

References

1. Zamboni P, Galeotti R, Menegatti E, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2009; 80:392-399.
2. Embry AF. Integrating CCSVI and CNS autoimmunity in a disease model for MS. *Int Angiol* 2010; 29:93-94.
3. Singh AV, Zamboni P. Anomalous venous blood flow and iron deposition in multiple sclerosis. *J Cereb Blood Flow Metab* 2009; 29:1867-1878.
4. Zamboni P, Menegatti E, Weinstock-Guttman B, et al. CSF dynamics and brain volume in multiple sclerosis are associated with extracranial venous flow anomalies: a pilot study. *Int Angiol* 2010; 29:140-148.
5. Al-Omari MH, Rousan LA. Internal jugular vein morphology and hemodynamics in patients with multiple sclerosis. *Int Angiol* 2010; 29:115-120.
6. Simka M, Kostecki J, Zaniewski M, Majewski E, Hartel M. Extracranial Doppler sonographic criteria of chronic cerebrospinal venous insufficiency in the patients with multiple sclerosis. *Int Angiol* 2010; 29:109-114.

7. 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; 50:1348–1358.
8. Malagoni AM, Galeotti R, Menegatti E, et al. Is chronic fatigue the symptom of venous insufficiency associated with multiple sclerosis? A longitudinal pilot study. *Int Angiol* 2010; 29:176–182.
9. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the “common” neurologic disorders? *Neurology* 2007; 68:326–337.
10. Mayr WT, Pittock SJ, McClelland RL, Jorgensen NW, Noseworthy MD, Rodriguez M. Incidence and prevalence of multiple sclerosis in Olmsted County, Minnesota, 1985–2000. *Neurology* 2003; 61:1373–1377.
11. Tremlett H, Zhao Y, Rieckmann P, Hutchinson M. New perspectives in the natural history of multiple sclerosis. *Neurology* 2010; 74:2004–2015.
12. Jones JL, Coles AJ. New treatment strategies in multiple sclerosis. *Exp Neurol* 2010; doi:10.1015/j.expneurol.2010.06.003. Accessed June 12, 2010.
13. Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Am J Neurol* 2002; 58:169–178.
14. Marriott JJ, Miyasaki JM, Gronseth G, O'Connor PW. Evidence Report: The efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Am J Neurol* 2010; 74:1463–1470.
15. Society of Interventional Radiology. Global statement defining interventional radiology. *J Vasc Interv Radiol* 2010; 21:1147–1149.