Venous angioplasty for "CCSVI" in multiple sclerosis

Ending a therapeutic misadventure

Dennis N. Bourdette, MD, FAAN, FANA
Jeffrey A. Cohen, MD

Correspondence to Dr. Bourdette: bourdett@ohsu.edu

Neurology® 2014;83:388–389

In 1889, Charcot described the results of "suspension therapy" for tabes dorsalis and other diseases.[1] The procedure entailed suspending patients from a harness attached to their chin and occiput for several minutes. The goal was to stretch the spinal cord, presumably to improve circulation. Charcot described several patients with tabes dorsalis whose symptoms improved following the treatment. However, the therapy was often painful, one patient with multiple sclerosis (MS) developed paraplegia after 2 treatments, and there were other serious side effects, including death by strangulation. Despite his initial enthusiasm for the treatment, Charcot eventually abandoned suspension therapy, displaying the wisdom to recognize a treatment that did not result in sustained benefit and carried serious risks.

In this issue of *Neurology*®, Siddiqui et al.[2] describe the results of a randomized trial of venous angioplasty for MS. Prior to 2009, this clinical trial would have seemed as sensible as an investigation of suspension therapy for MS. However, in 2009, Zamboni et al.[3] described venous flow abnormalities detected by color Doppler ultrasound in most of 65 patients with MS and in none of 235 controls. They called this phenomenon chronic cerebrospinal venous insufficiency (CCSVI) and suggested that it contributed to the pathogenesis of MS by causing venous congestion. Also in 2009, Zamboni et al. described the results of an open-label, unblinded trial of venous angioplasty in 65 patients with MS. They reported clinical improvement primarily among the 35 subjects who had relapsing-remitting MS in whom there was an increased proportion of participants who were relapse-free and a reduction in proportion of participants with brain MRI gadolinium-enhancing lesions following transluminal angioplasty.[4] Despite the lack of adequate controls and blinding, word of these results spread rapidly through lay print, electronic, and social media and raised the hopes of many people with MS, leading some to advocate vigorously for provision of this seemingly effective treatment for MS.[5] In response, the US and Canadian MS Societies jointly committed over $2.4 million for research to determine whether people with MS had cerebrospinal venous abnormalities. Concurrently, some interventional radiologists in the United States, Canada, and elsewhere began to treat patients with MS ad libitum with venous angioplasty with and without stenting, occasionally with tragic consequences.[6]

Now Siddiqui et al. report on a randomized, double-blind trial comparing venous angioplasty with sham angioplasty in 19 participants with MS who met the Zamboni Doppler flow criteria for CCSVI. These patients were randomized to undergo balloon angioplasty (n = 9) or sham angioplasty (n = 10). Participants and personnel evaluating responses remained blinded to the treatment participants received. While there were no notable complications from the venous angioplasty, there was no evidence of clinical improvement in participants undergoing venous angioplasty compared with those receiving sham angioplasty. However, 5 of 9 participants receiving venous angioplasty had evidence of increased disease activity by brain MRI compared with 2 of 10 participants undergoing sham treatment. Importantly, improvements occurred in some subjective outcome measures in the sham-treated participants, such as measures of fatigue and quality of life, suggesting that the subjective positive outcomes reported by participants in unblinded, open-label studies might represent placebo effects. Siddiqui et al. concluded that venous angioplasty did not result in clinical improvement and increased venous flow might increase disease activity in some patients with MS. While this study was small, it is the first double-blind sham angioplasty-controlled trial of venous angioplasty in MS and the results do not support a larger trial of this treatment.

Multiple research groups have failed to find evidence of cerebrospinal venous flow or anatomic abnormalities in MS.[7–9] This has cast serious doubts on the validity of CCSVI as a pathologic entity in MS. Thus, the rationale for venous angioplasty as a treatment for MS is flawed. Of course a therapy can be beneficial even if the theory about how it works is wrong. A Cochrane review of reports of clinical trials for percutaneous transluminal angioplasty for CCSVI in people with MS found major methodologic problems with all trials published prior to

See page 441

From the Department of Neurology (D.N.B.), Oregon Health & Science University and Multiple Sclerosis Center of Excellence West, Veterans Affairs Medical Center, Portland; and the Mellen Center for MS Treatment and Research (J.A.C.), Cleveland Clinic, OH.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

June 2012.[10] The authors emphasized that randomized, double-blind, controlled clinical trials with objective outcomes needed to be conducted before any conclusions about the effectiveness of this procedure could be made. The clinical trial that Siddiqui et al. conducted met these requirements and failed to show any benefit to the procedure. So the theory of CCSVI is wrong and, when an appropriately blinded and controlled trial of venous angioplasty was performed, there was no evidence of benefit.

What happens now with CCSVI and venous angioplasty for MS? Interventional radiologists should cease subjecting people with MS to venous angioplasty and charging patients and private and governmental insurance programs for this ineffective treatment that is based on an incorrect theory. We also question the ethics of continuing to conduct clinical trials of venous angioplasty for CCSVI. Clinical equipoise requires that uncertainty exists about the efficacy of an intervention being studied in a clinical trial. Since there is substantial evidence indicating that CCSVI is not a disorder and there is now a well-controlled double-blind clinical trial showing no benefit to venous angioplasty, there is no longer equipoise. Clinical trials of venous angioplasty for MS are placing participants at risk of complications without a reasonable hope of benefit.

Despite initial encouraging results from an uncontrolled and unblinded trial, Charcot was wise enough to eventually abandon the use of suspension therapy. The treatment was founded on a faulty theory of pathogenesis, did not result in sustained benefits, and carried risks. The same can be said of CCSVI and venous angioplasty for MS. It is time for us to show the same wisdom that Charcot displayed.

AUTHOR CONTRIBUTIONS

Dennis Bourdette: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Jeffrey Cohen: drafting/revising the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

D. Bourdette has received honoraria for consulting and speaking from BiogenIdec, Teva Neurosciences, and Genzyme and has had research support from the Department of Veterans Affairs, NIH, and National MS Society. Dr. Cohen reports personal compensation for consulting from EMD Serono, Genzyme, Innate Immunotherapeutics, and Novartis. J.A. Cohen received research support paid to his institution from Biogen Idec, Consortium of MS Centers, Department of Defense, Genzyme, NIH, National MS Society, Novartis, Receptos, Synthon, Teva, and Vaccinex. Go to Neurology.org for full disclosures.

REFERENCES

1. Lanska DJ, Edmonson JM. The suspension therapy for tabes dorsalis: a case history of a therapeutic fad. Arch Neurol 1990;47:701–704.
2. Siddiqui AH, Zivadinov R, Benedict RHB, et al. Prospective randomized trial of venous angioplasty in MS (PREMiSe). Neurology 2014;83:441–449.
3. 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.
4. 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.
5. Pullman D, Zareczny A, Picard A. Media, politics and science policy: MS and evidence from the CCSVI trenches. BMC Med Ethics 2013;14:6.
6. Samson K. Experimental multiple sclerosis vascular shunting procedure halted at Stanford. Ann Neurol 2010;67:A13–A15.
7. Valdueza JM, Doepp F, Schreiber SJ, et al. What went wrong? The flawed concept of cerebrospinal venous insufficiency. J Cereb Blood Flow Metab 2013;33:657–668.
8. Comi G, Battaglia MA, Bertolotto A, et al. Observational case-control study of the prevalence of chronic cerebrospinal venous insufficiency in multiple sclerosis: results from the CoSMo study. Mult Scler 2013;19:1508–1517.
9. Barkhof F, Wattjes MP. CCSVI deconstructed and discarded. Nat Rev Neurol 2013;9:661–662.
10. van Zuuren EJ, Fedorowicz Z, Pucci E, Jagannath V, Robak EX. Percutaneous transluminal angioplasty for treatment of chronic cerebrospinal venous insufficiency in people with multiple sclerosis: a summary of a Cochrane systematic review. J Neurol Neurosurg Psychiatry 2014;85:405–410.