



Michael Dake
Stanford University School of Medicine
Stanford, California, USA

Hot Topics Session: CCSVI is real, and IRs should treat it with venoplasty

Proposition: Treating MS patients with venoplasty

No matter where you stand on the recent controversy surrounding the concept of chronic cerebrospinal venous insufficiency (CCSVI) and its proposed association with multiple sclerosis (MS), it is increasingly clear that this theoretical phenomenon challenges interventionists with far more questions than there are answers readily available. Whether an unconvinced sceptic, open-minded observer, perplexed clinician, hostile critic or convinced believer, no one is dispassionate and all have to agree that nothing in recent history has rocked our field with the emotionally polarising force of CCSVI.

Currently, the themes of a myriad of big picture questions concerning CCSVI can be consolidated into three important considerations:

1. Does treatment of CCSVI cure MS?
2. Does CCSVI have a fundamental role in causing MS?
3. Does endovascular therapy produce objectively measured patient benefits beyond a placebo effect?

Certainly, other equally important and more detailed diagnostic, pathophysiologic, anatomical, technical, and safety questions challenge us, but as interested parties seek to embark on collaborative controlled trials to study the outcomes of CCSVI treatment, it is perhaps prudent and beneficial to pause and examine current snapshots of these three general issues. Based on the initial clinical experience to date and with some literary license, the following comments provide perspectives that attempt to summarise the contemporary opinions of interventionists actively involved in the treatment of CCSVI.

The present consensual view of interventionists and hopeful patients is resigned to the conclusion that treatment of CCSVI is not a cure for MS. Debates rage over what roles, if any, CCSVI may play in conjunction with the genesis, progression and symptoms associated with MS, but even the most evangelical CCSVI advocates understand that relief of extracranial venous obstruction will not magically re-myelinate compromised axons or reverse existing plaques.

The question of whether CCSVI has a function in the genesis of MS is extremely contentious. Perhaps, it looms as one of the most inflammatory issues for many neurologists because it challenges the widely held immune/auto-immune paradigm that dominates MS research models and clinical treatment concepts. The influence of the doctrine that "establishes" the immune basis for MS is profound, despite the lack of a clear understanding of how an immune mechanism is involved in the initiation of disease and subsequently, its episodic course.

Clearly, a genuine collaboration that respectfully encourages involvement of all interested

parties could lead to the most objective, efficient and conclusive scientific investigations of CCSVI, but make no mistake; this will require the successful tackling of many tough challenges. Daunting impediments include: vested interests, silos with different cultures, hidden agendas, and diverse levels of understanding, strong egos, messenger killers, entrenched dogmatists, sanctimonious pontificators, cynical nihilists, and a whole range of biases.

Obviously, no one denies that interventionists are ill-equipped to exclusively shepherd clinical treatment trials aimed at providing meaningful results informed by prior experiences that refined safety and efficacy metrics to objectively investigate new drug therapies. On the other hand, what has been learned from the initial observational phase of CCSVI treatment is informative and should not be wholesale discounted.

For example, it is now apparent that after endovascular therapy, certain constitutional or general symptoms common to MS patients, such as fatigue, heat intolerance, clouded cognition, urinary problems, cold distal extremities etc., respond in a tempo that ranges from hours to days rather than the usual weeks or months typically necessary to achieve full benefits and clinical stabilisation with pharmacological disease-modifying therapies.

It is in everyone's interest to contribute to the development of new therapeutic concepts capable of delivering improved treatments that yield greater benefits for MS patients and their families. In terms of CCSVI, this involves the performance of high-quality randomised controlled trials incorporating objective analyses of results using standard measurements of outcomes established in the MS literature while taking into account other potentially positive responses related to the endovascular management of venous obstruction.

Perhaps, there are unrealised synergistic opportunities with the combination of therapeutic modalities. It is conceivable that disease-modifying drugs, together with endovascular treatment of CCSVI, working through different mechanisms to manage the disease process, have the potential to incrementally benefit patients beyond what can be achieved with a single approach. After all, it is not far-fetched to expect that combination therapies targeting different aspects of a progressive disease process might improve upon the relatively modest therapeutic advantages realised with current therapies.

Indeed, recent publications in the medical literature have questioned the exaggerated cost/benefit ratio for patients administered current disease-modifying therapies. The wisdom and value of sustaining therapeutic approaches that cost more than \$800,000 per quality-adjusted life year (QALY) – about 10 times as

expensive as what is generally considered cost-effective – may undergo further scrutiny in the future (1). Similar studies that detail benchmarks for therapeutic effectiveness in other important diseases have informed and ultimately guided decisions by insurance organisations and government healthcare agencies responsible for healthcare payments.

Currently, the long-term results of endovascular treatment of patients with CCSVI are unknown. Although it is estimated that 15,000 patients have been treated worldwide, many have not received adequate follow-up surveillance. This is often due to the lack of local or regional opportunities for undergoing the initial procedure. In many cases, this results in patients travelling long distances to undergo therapy, but subsequently leaves them without any continuity in medical care for follow-up at home.

Without the ability to capture the important necessary data for longitudinal follow-up evaluations in a large percentage of patients, the reports to date of early treatment experience have focused on detailing the safety of the procedure and immediate responses. The initial experiences of endovascular treatment of CCSVI published in the medical literature are consistent in documenting the safety of balloon angioplasty (PTA), (and in smaller groups, stent placement following failure of PTA) and lack of associated serious adverse events (2-4). The frequencies and range of procedure-related complications is similar to those established for endovascular interventions involving other venous territories, including substantial experience in iliac veins, vena cava, and brachiocephalic veins.

Many prominent neurologists have dismissed the concept of CCSVI as totally implausible and absolute lunacy; at best, an annoying distraction that steals attention from promising new drug therapies and at worst, a simplistic farcical ruse conjured to trick susceptible patients into chasing an expensive illusion. Proponents of CCSVI contend that its relevance to the location of typical peri-venous plaque in MS is supported by the presence of documented correlates elsewhere in the body. They argue that the histological appearance of peri-venous cuffing evident in MS plaques is similar to the peri-venous tissue reaction observed in a variety of other anatomic territories where there is chronic obstruction of a venous bed – such as, leg veins in the setting of chronic deep venous thrombosis (post-phlebotic syndrome), and hepatic veins associated with an obstructive venopathy like Budd-Chiari.

When presented with this notion, many neurologists are in disbelief that such a ludicrous idea could be seriously entertained. "Prevalence studies would indicate that chronic venous insufficiency of the legs and MS are as far apart pathologically as possible."

Underappreciated in the midst of these clashing positions is one other example of a similar venous lesion with potential relevance to MS – sheathing of retinal veins. This cuffing or sheathing of veins can be appreciated on fundoscopic examination of the eyes and may be associated with retinal vein thrombosis, optic neuritis and vision loss. In the majority of cases when it is diagnosed during an evaluation of disturbed vision, it occurs in patients with MS. Studied extensively at the Mayo Clinic, it is not however singularly associated with cases of established MS. Its frequency among MS patients is estimated to range from 11% to 42%. After fluorescein dye administration, it is possible to observe leakage of dye around the retinal veins and histologically, the veins display a thickened wall similar to appearances observed in other chronically obstructed venous territories.

When contemplating the possible association between venous obstruction, blood-brain barrier leakage, myelin destruction and immune mechanisms responsible for the initiation of MS, it is interesting to note that the retinal nerve fibres are not myelinated in 99% of the population.

As CCSVI is just one of many potential considerations that may fit as single pieces in a large puzzle that ultimately influences the development of MS in a particular individual, it is not terribly troublesome at our level of disease understanding to allow that not all MS subjects possess the identical predisposing conditions. The specific contributing elements may be different among MS patients and an individual's disease severity, tempo of progression, symptoms and response to therapies may be highly dependent on his/her collection of characteristic factors.

Not unlike the case of another disease – gastric ulcers – whose aetiology was once "known" until its pathogenesis was disruptively redefined by a radical idea, not all patients with *Helicobacter pylori* develop peptic ulcer disease. Similarly, not all individuals with PSEN1, PSEN2, APP, or APOE develop Alzheimer's disease, and not all patients with MS have retinal vein sheathing. There is a lot we do not know about the pathogenesis of a great many diseases and perhaps with MS, we currently still face more questions than we have answers.

References:

1. Noyes K, Bajorska A, Chappel A, et al. Cost-effectiveness of disease-modifying therapy for multiple sclerosis: a population-based study. *Neurology*. 2011;77:355-363
2. Zamboni P, Galeotti R, Menegatti E, et al. Endovascular treatment of chronic cerebrospinal venous insufficiency, a prospective open-label study. *J Vasc Surg*. 2009;6:1348-1358
3. Ludyga T, Kazibudzki M, Simka M, et al. Endovascular treatment for chronic cerebrospinal venous insufficiency: is the procedure safe? *Phlebology*. 2010;25:286-295
4. Petrov I, Grozdinski L, Kaninski G, et al. Safety profile of endovascular treatment of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Endovasc Ther*. 2011;18:314-323



Jim Reekers
Academic Medical Centre
Amsterdam, Netherlands

Opposition: There is no evidence for CCSVI or its treatment in MS patients

Some colleagues are persuaded by the data that seem to offer a compelling rationale for the theory of MS being caused by venous insufficiency disease. They also state that we (IRs) have clearly provided many therapies in the past based on less well-developed research than exists for CCSVI. As these patients are desperate for treatment options, we must be responsive to their needs [1].

I give you this reference, because you might otherwise think that I made all this up just to provoke discussion. In actual fact, these statements ought not to be discussed by those who care for good clinical practice, evidence-based medicine and doing the best for our patients. However, the whole discussion of CCSVI has been taken out of the scientific discourse and has moved instead to what is called "emotion-based medicine". Although there is growing evidence for the non-existence of CCSVI, this does not seem to make any difference to the discussion [2]. There are even rumours that there is a lobby by neurologists and the pharmacy industry to kill the theory of CCSVI. Those who are promoting the CCSVI treatment see proof and compelling data when there is nothing there: it all shows disorganised thinking.

I vainly hoped I would be able to awaken at least some with my lecture at SIR 2011 in Chicago, showing that there is precedence for this kind of jumping-to-conclusions: 200 years ago, Dr Perkin's tractors were also believed to be curing patients, until one good study proved that it was all an illusion.

There also seems to be a strange fascination in medicine for the anatomy at both ends of the Gaussian curve. To call a normal variant an abnormality is both clever, from a selling point of view, and deceptive. This is unfortunately not unique in medicine. For decades "patients" have been treated with septoplasty for nasal septum deviation or children by tonsillectomy for large tonsils to prevent all sorts of common cold diseases. It is not that long ago that many psychological diseases were connected to being left-handed. Heilpraktiker connected poor posture to learning and concentration problems. And there are many more examples where normal anatomic variations triggered wrong-thinking to support a delusion. But as the singer-songwriter Randy Newman sings, "short people are just the same as you and I."

It is good that more and more data are now coming out. Most publications are very clear in their denial of CCSVI, but some also suggest that there might be some relationship between CCSVI and MS.

It all started in 2009 with Dr. Zamboni's hypothesis that extra-cranial venous flow abnormalities (CCSVI) are leading to a stagnant venous return, which contributes to the pathogenesis of multiple sclerosis by iron deposition. Chronic Cerebrospinal Venous Insufficiency plays a crucial role in this theory [3]. However, increased venous pressure in CCSVI has never been reported.

Radiologists who performed venous sampling for parathyroid have known for decades that the venous anatomy of the neck shows wide variation. This variation was always seen as normal. There are also many other diseases which result in increased cerebral venous pressure: venous sinus thrombosis, chronic obstructive pulmonary disease, idiopathic intracranial hypertension, and others; yet none of these conditions have any association with MS.

In his 2009 study, Zamboni investigated 109 patients with clinically definite MS and 177 control subjects with transcranial and extracranial colour Doppler Sonographic examinations. None of the control patients complied with the Zamboni criteria for CCSVI, while all of the MS patients did [3]. To date, three independent studies with a control group were unable to show the same results [4-6]. The anatomic variation called CCSVI was equally distributed among both MS patients and the control group in these independent studies. These three independent investigations into CCSVI and MS not only cast doubt on whether CCSVI is the cause of MS, they call into question whether CCSVI exists at all, and indicate that such anomalies are simply anatomical variants and not pathological. However, there are also a few independent unpublished reports which show at least some increase in venous abnormalities in MS patients, but not the 100% of the earlier Zamboni paper.

However, the other controversy – improvement of MS symptoms after PTA treatment – is only supported by the paper of Zamboni [7]. This study, without control group, is full of methodological flaws which are all very well explained in a recent paper by Bagart [8]. Until

now, no other papers on treatment success have been published, despite the fact that to date, many thousands of patients should have been treated. I have no explanation for this. However, I am fully convinced that MS patients do experience improvement after treatment, but that it is no more than a placebo effect. It is well known how strong and convincing placebo can be. MS complaints also show a huge variability, which makes interpretation even more cumbersome in a study without a control group.

All scientific opinions create complex discussion, and the blend of passion and science that CCSVI and MS bring forth require tempered deliberation that should focus on data and facts. This necessitates a balance between scepticism and openness to new ideas. Although I am absolutely sure that there is no scientific proof for the existence of CCSVI and the pathologic relation in the development of MS, it is hard to believe that some of the people I have always known as honest scientists, with important contributions to the field of IR, have now adopted the habit of spreading false information, for whatever reason. This is not the case of course: I believe their support for CCSVI and MS is sincere. There is now an unpublished presentation which does suggest a higher percentage of stenosis and collaterals around the jugular vein in patients with MS. Maybe the simple solution is that these venous abnormalities are just an epiphenomenon, which is an additional condition or symptom in the course of a disease, not necessarily connected to the aetiology of the disease. Maybe we are all looking at these data from the wrong perspective.

Inflammation of the central nervous system (CNS) (neuroinflammation) is now recognised to be a feature of all neurological disorders. In multiple sclerosis, there is prominent infiltration of various leukocyte subsets into the CNS with resultant elevation of many inflammatory mediators within the CNS. An extensive dataset describes neuroinflammation to have detrimental consequences, but results emerging largely over the past decade have indicated that aspects of the inflammatory response are beneficial for CNS outcomes. Nevertheless, these inflammations might be the cause of what is now called CCSVI. If this is true, patients with longstanding MS would be particularly affected. If you then add this to the natural dis-

Don't miss it!

Is CCSVI a real entity?

Hot Topics Symposium

Sunday, September 11, 14:30-16:15

Auditorium 1

tribution of venous variations, it might lead to the observation of something like CCSVI, which would then better be named Chronic Post-Inflammation Venous Abnormality (CPIVA). If this is true, and I am just speculating, it is not the venous abnormalities which cause MS, but vice versa: the inflammation with MS is causing the venous abnormalities. Off course, this is as much as a hypothesis as the existence of CCSVI and should first be investigated in a blinded study with a control group. We have to look at early MS and late MS, and patients with other inflammatory diseases of the CNS and control groups. CPIVA could easily explain what we are discussing today.

As I stated in my 2008 Dotter lecture, science and evidence are our only chance to survive as a specialty, and we should only treat patients based on evidence, or at least objective measurable outcome parameters, such as necrosis of uterine fibroids being used as an objective parameter after UFE in the pioneer days. Subjective outcome data, like well-being or QOL can only be studied in an RCT with a control group. In the Global Statement Defining Interventional Radiology, we stated very clearly that being a clinician is essential for our credibility as IRs [9]. By endorsing and offering treatment for CCSVI at high costs to the patient, based on very poor and debatable data, we will not be seen as clinicians who protect their patients, but as trigger-happy cowboys. This last issue is the main reason I am so involved in this topic. The CCSVI debate will eventually be resolved, but whether our loss of credibility can be restored, remains to be seen.

References:

- Murphy TP. President's column, IR news vol 24: no:3, pg 3
- Omar Khan. Cerebrospinal venous insufficiency and multiple sclerosis: investigating the truth. *Mult Scler* 2011;17: 511
- Zamboni P, Menegatti E, Galeotti R, et al. The value of cerebral Doppler venous haemodynamics in the assessment of multiple sclerosis. *J Neurol Sci*. 2009;282(1-2):21-27
- Doepff F, Paul F, Valdueza JM, Schmierer K, Schreiber SJ. No cerebrocervical venous congestion in patients with multiple sclerosis. *Ann Neurol*. 2010;68(2):173-183
- Sundstrom P, Wahlin A, Ambarki K, Birgander R, Eklund A, Malm J. Venous and cerebrospinal fluid flow in multiple sclerosis: a case-control study. *Ann Neurol*. 2010;68(2):255-259
- Wattjes MP, van Oosten BW, de Graaf WL, et al. No association of abnormal cranial venous drainage with multiple sclerosis: a magnetic resonance venography and flowquantification study. *J Neurol Neurosurg Psychiatry*. 2011;82(4):429-435
- 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(6):1348-1358, e1-e3
- Bagert BA, Marder E, Stuve O. Chronic Cerebrospinal Venous Insufficiency and Multiple Sclerosis. *Arch Neurol*. Published online 2011.179
- Kaufman JA, Reekers JA, et al. Global statement defining interventional radiology. *Cardiovasc Intervent Radiol*. 2010; 33(4):672-4