

CCSVI: What We Need to Know Now and in the Future

Multidisciplinary collaboration is a necessary step toward answering the many questions about the relationship between MS and extracranial venous obstruction.

BY MICHAEL D. DAKE, MD

Over the last 2 years, most interventionists have become familiar with the term CCSVI (chronic cerebrospinal venous insufficiency). They share in common a passing exposure to the postulated concept of an association between venous obstruction to drainage of the brain and spinal cord and multiple sclerosis (MS), but most lack firsthand experience evaluating or treating CCSVI. Many are aware of the frequently contentious and inflamed public discussions among groups of interested parties, including neurologists, MS patients and their families, interventionists, federal officials, etc., and thus have decided to observe the drama rather than join the heated fray.

In discussions around the world in cath labs, angio suites, operating rooms, neurology departments, and MS clinics on patient social networks; in feature pages of prominent newspapers and magazines and programming of mainstream media outlets; and at local, national, and international medical meetings, the proposed relationship between MS and extracranial venous obstruction is examined, questioned, but always debated. Everyone wants to learn more.

Everyone wants to understand: What do we know and what don't we know about CCSVI?

WHAT WE NEED TO KNOW

As all involved focus on these two unknowns, it may prove pragmatically more relevant at this early stage of our fundamental knowledge to consider: What do we need to know? Or posed in another way: What is necessary to establish before it is reasonable to embark on large-scale controlled, multi-institution, randomized trials of CCSVI treatment capable of demonstrating or disproving a link between MS and venous obstruction?

When considering the inability over the last 150 years to definitively grasp the underlying cause of MS, the conceptual difficulties that persistently challenge our understanding of the interplay between anatomical and physiological factors that contribute to symptomatic venous obstruction of

other vascular territories, and the difficult-to-comprehend roles of a variety of conditions that apparently portend a predisposition to developing MS, it is unlikely that the CCSVI theory will lend itself to easy pathophysiological examination. Paradoxically, it may prove easier to move forward with CCSVI treatment studies that incorporate established objective endpoints accepted by MS neurologists rather than pursue unproven evaluations of specific but possibly irrelevant physiological consequences of venous flow disturbances.

SKEPTICISM AND CRITICISM

It is understandable that the vast majority of neurologists who deal with MS patients are highly skeptical of CCSVI. Most neurologists have lived through a series of unproven and even dangerous pseudotherapies that prey on the vulnerability and hope-seeking nature of patients with an incurable, progressively disabling disease. From snake venom, to bee stings, and hyperbaric oxygen, etc., neurologists are especially sensitive to potential scams that have plagued the MS landscape, while at the same time consciously aware that many patients are marginally satisfied by their response to the "effective" approved pharmacological therapies.

Despite the current criticism of CCSVI and the recognition that most conversations on the subject between neurologists and interventionists don't always go well, there is experience that is providing data and evidence to support future randomized controlled treatment trials. Undoubtedly, one of the foremost issues to be addressed is the risk to patients of any CCSVI treatment procedure. Fortunately, the safety of currently practiced endovascular therapy—predominantly percutaneous balloon angioplasty (PTA), is the one area where a substantial fund of data is available from the estimated 13,000 to 15,000 patients treated to date worldwide.

Multiple large patient series published in the medical literature document that any serious complications from PTA

QUESTIONS CONCERNING DIAGNOSIS AND TREATMENT

Diagnosis

- Is CCSVI something we are born with, acquire, or both?
- What percentage of MS patients and healthy controls have CCSVI?
- Is CCSVI a consequence of MS or part of the disease pathogenesis?
- How do we reliably best diagnose CCSVI and know if it is physiologically relevant?
- How does CCSVI fit into the current immune concept of MS, or does it not?
- Are extracranial cervical collaterals simply a normal variant or do they portend some physiological and clinical relevance?

Treatment

- Is PTA the best possible treatment? What about oversized balloons or cutting balloons?
- When are stents warranted, if at all?
- What percentage of lesions respond to PTA? How do you judge?
- Are any jugular lesions outside the valves important? Do you address extrinsic narrowing?
- Is it good or bad to disrupt the valves in CCSVI? Does this increase reflux, and is this bad?
- How do you know intraprocedurally if CCSVI is adequately treated? Is it necessary to successfully treat all lesions?
- What are the risks and complications of the procedure? Do individuals ever get worse after treatment?

of jugular and azygous veins are exceedingly rare.¹⁻⁵ Untoward effects that are encountered are not dissimilar from adverse events known to accompany balloon dilation of lesions in other venous territories. Establishment of a safety profile for endovascular treatment of CCSVI that is consistent in these reports is a very important step forward and the demonstration of only mild side effects in a minority of patients is critical to advancing further study.

THE FUTURE OF CCSVI

So, as we are poised at this snapshot in time, ready to advance to the next chapter of the CCSVI story—one that will hopefully include genuinely collaborative, multidisciplinary controlled treatment trials with randomized designs and meaningful objective efficacy endpoints—it is important to think about the future and what we would like to know. From this perspective, we can focus on the long list of questions that we hope future trials will bring us closer to answering. In terms of CCSVI diagnosis, treatment, and follow-up, some of the interesting unresolved issues are noted

QUESTIONS CONCERNING POSTTREATMENT AND FOLLOW-UP

- After PTA or stent placement, what is the ideal pharmacological regimen to prevent thrombus formation and for how long is it used?
- How do we know if there is any real benefit from treating CCSVI (ie, that it is not a placebo effect)?
- What percentage of patients notice improvement? In what percentage of responders do symptoms return?
- Do any objective measurements improve after treatment, such as cerebral perfusion, tissue oxygenation, jugular flow measurements, etc.?
- What typically reverses after treatment? What doesn't improve, or is there simply no typical response?
- How should patients be followed? What evaluations should be monitored? If symptoms return, what is the anticipated timeframe? Why do symptoms return and what should be done if they return?

in the *Questions Concerning Diagnosis and Treatment* and *Questions Concerning Posttreatment and Follow-Up* sidebars.

In addition to this abridged list of questions are three of the most fundamental issues yet to be understood: What is the endovascular treatment of venous obstruction really affecting—is it flow or something else? Is there any evidence that the trajectory of disease progression is altered after CCSVI treatment? Finally, how can interventionists engage MS neurologists in a nonthreatening, meaningful collaboration to study a concept they regard as total lunacy?

Addressing these and other concerns will sternly test the resolve, patience, and willingness of all concerned individuals to engage in multidisciplinary collaborations to better understand the nature of CCSVI and potentially benefit the lives of MS patients. ■

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