CHRONIC CEREBROSPINAL VENOUS INSUFFICIENCY:
A CSI APPROACH—CSI OF CCSVI

Norah S. Linoff, MD
SUNY, School of Medicine
Buffalo, NY

LEARNING OBJECTIVES
1. To examine CCSVI in MS
2. To describe the 3 forms of vascular dysfunction proposed in MS
3. To discuss the value of venous angioplasty in MS
4. To describe the valuable new information/outcomes of the studies on CCSVI

CME QUESTIONS
1. What is CCSVI?
   a) Cerebral venous insufficiency secondary to outflow obstruction
   b) Chronic cavernous sinus vestibular input syndrome
   c) A new show on ABC family
2. What are the 3 forms of vascular dysfunction suspected in MS?
   a) Patients with MS are at higher risk of cerebrovascular disease
   b) CCSVI
   c) Global CNS hypoperfusion seen in patients with MS
   d) Multiple recurrent aneurysms in patients with MS
   e) a, b and c
3. What are the venous abnormalities found in CCSVI?
   a) Flaps
   b) Webs/membranes
   c) Annuli
   d) Stenosis
   e) All of the above
4. What are complications associated with venous angioplasty?
   a) Restenosis at site of venoplasty
   b) Post-procedural bruising or hemorrhaging at the point where the catheter enters the vein
   c) Short-term (1-2 hours) post-procedure dizziness or headache
   d) Migration/slippage of inserted devices (e.g. when stents used)
   e) Serious complications such as abrupt deterioration of neurological status, stroke, or death
   f) All of the above

KEYWORDS
1. Cerebral Venous Insufficiency
2. Multiple Sclerosis
3. Venous Angioplasty

INTRODUCTION
Multiple Sclerosis is an autoimmune degenerative disorder still of unknown etiology. CCSVI is one of the newer suggested etiologies in the literature. Venous angioplasty (venoplasty) has therefore been introduced as a treatment option in Multiple Sclerosis. In the past 3 years over 20 papers have been published about it, with about half supporting it and half refuting it. The consensus for 2011 is in.

HYPOTHESIS OF THE PROPOSED CCSVI TREATMENT
Can iron deposition in the CNS cause MS to develop and if it can are the veins in the brain the cause? Are they functionally and anatomically abnormal and causing poor venous outflow to leave iron behind in the tissues to incite the neuronal/venular inflammation?

As far back as Charcot (1868) venous obstruction in MS was described. Putnam (1933) described the vascular architecture of the lesions of multiple sclerosis and furthered this theory. In 2009 this long put to rest theory was brought to the forefront again as a cause of MS, despite the numerous other theories proposed since Charcot including immunologic factors, other vascular factors, environmental factors, genetic factors, HLA DR 1501, vitamin D deficiency, EBV, and smoking.

The new theory suggests that the impaired brain’s venous drainage is due to outflow obstruction in the extracranial venous system. Internal venular changes as well as external venular changes of the internal jugular, azygous and vertebral veins are felt to be the biggest culprits. Doppler sonography and transcranial doppler reportedly have shown abnormal flaps, annuli, septae, valves, membranes, webs and stenoses, while MRI has show abnormal iron deposition around veins that are known to be the site of MS inflammation. CNS damage is possibly further enhanced by reflux of the blood in the deep cerebral veins – a form of sludging effect.
Venous angioplasty (percutaneous transluminal angioplasty (PTA)) and stenting have been used to dilate veins where obstruction has been found in hope of improving venous outflow and decreasing any further excessive iron deposition. Some reports suggest over 15,000 such procedures have been performed since 2009.

**SUMMARY OF CRITICAL DEFICIENCIES IN PRIOR STUDIES ATTEMPTING TO ASSESS ROLE OF VASCULAR DISEASE IN THE PATHOGENESIS OF MS**

- Failure in various studies to consistently show presence of CCSVI in patients with MS compared to controls
- Failure to prove that iron deposition is from CCSVI and not from damaged oligodendrocytes or iron laden macrophages
- Failure to prove that vascular insufficiency does not stem from vascular arterial hypoperfusion instead of venous obstruction
- Variable diagnostic accuracy in detecting venous abnormalities with echo-doppler and transcranial doppler technique and criteria
- Methodological limitations of the studies
- Long term follow up of treated cohorts to assess for any longterm benefit vs placebo effect of angioplasty
- Safety and efficacy of endovascular treatment still being investigated, and still no randomized, controlled, blinded trials completed as of yet.

**MS AS A VASCULAR DISEASE?**

It is known that patients with MS have a higher risk of cerebrovascular disease compared to the normal population, and since 2009 many studies have been dusted off and new ones run to clarify further the question of the vascular aspects in MS.

The three types of vascular dysfunction at the forefront include:

1. Diffuse cerebral hypoperfusion especially in focal plaques, the white and grey matter (MRI perfusion studies and PET scan studies)
2. Cerebrovascular disease has a higher incidence in patients with MS
3. Chronic state of impaired venous drainage CCSVI

A recent study investigated the association between abnormalities of the cerebral venous outflow and clinically defined MS (Zamboni et al., 2009a). This study included 65 patients with MS and 235 healthy subjects. All patients underwent screening with transcranial color-coded Doppler sonography and high-resolution echocolor Doppler (TCCS–ECD). Those patients identified to have two or more of five previously defined venous outflow abnormalities subsequently underwent catheter venography. Venography showed no abnormalities in control patients, however those patients with MS had multiple areas of venous stenoses and four distinct patterns of central nervous system venous outflow rerouting. They found a CCSVI in 100% of patients with MS.

Zivadinov and Guttman et al examined the prevalence of CCSVI in the largest blinded cohort of MS patients and found a less impressive statistic with a lower prevalence of 56% in patients with MS. They found a 22.7% prevalence in healthy controls. They tried to reconcile the inconsistent CCSVI prevalence results among different centers, some of which found a 0% prevalence rate. Doepp et al, Barracellini et al and Majer et al are a handful of scientists who found no significance difference in frequency between MS patients and controls regarding CCSVI.

Zivadinov and Guttman et al clarified that the problem is that not only are people simply born with variations in design of their cerebral, jugular and vertebral veins but different techniques are used between centers to study venous abnormalities. Another issue is that none of the noninvasive or invasive techniques of CCSVI have proven to be entirely accurate. It is also very difficult to blind the Doppler ultrasonographer regarding which patients may have MS in that many patients interested in the study are quite disabled in the first place. A third important issue was differences in interpretation of the findings since the direction of blood flow in veins connecting cortical with deep veins varies considerably. A last serious issue is that though CCSVI suggests that venous obstructive disease contributes to MS many studies suggest that arterial hypoperfusion may actually be an equal or more relevant factor in the disease and even be the cause of the venous insufficiency state.

**CONTRIBUTION THAT CAME OUT OF THIS HUGE ENDEAVOR:**

Despite the above problems it DOES appears though that venous abnormalities are higher in the MS population. What this means at this time is unclear but likely is relevant.

Additionally, those patients with relapsing–remitting and secondary progressive MS showed venous outflow rerouting patterns (collaterals) significantly different from
those with primary progressive MS which may help guide us to future investigations and help us differentiate earlier these two presenting groups with MS leading to earlier treatment intervention.

Also doppler ultrasound does appear to be the most reliable technique to study these findings in the hands of skilled and well trained technicians and fortunately is the cheapest and most available of the tests to obtain.

**CME ANSWERS**

1. a
2. e
3. e
4. f

**REFERENCES**


**First open-label study to describe benefit of endovascular treatment for CCSVI in multiple sclerosis.

* The largest study to date that determined prevalence of CCSVI in patients with multiple sclerosis, clinically isolated syndrome and other neurologic diseases, and in healthy subjects.

** The hypothesis study proposing that iron deposits in multiple sclerosis may be a consequence of chronic insufficient venous drainage.

* The first study that did not confirm the existence of CCSVI in patients with multiple sclerosis or in healthy controls; however, it found postural venous drainage differences between MS patients and controls.
null


