Current Status of Chronic Cerebrospinal Venous Insufficiency in Multiple Sclerosis

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Michael D. Dake, M.D.
Thelma and Henry Doelger Professor
Department of Cardiothoracic Surgery
Stanford University School of Medicine
Falk Cardiovascular Research Center

What is the background rationale that supports an association between MS and venous obstruction?

Michael Dake, MD
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- Research/Research Grants, Clinical Trial Support
  - W. L. Gore
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- Consulting Fees/Honoraria
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  - NovoStent
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  - Endoluminal Sciences
  - REVA Medical
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  - Cytograft Tissue Engineering
- Officer, Director, Board Member or other Fiduciary Role
  - VIVA Physicians Group
- Speaker’s Bureau
  - None

The Association of Chronic Cerebro-Spinal Venous Insufficiency (CCSVI) and Multiple Sclerosis

Background and Hypothesis

- **MS plaques venocentric**
  - Lesions extend counter-current to normal venous flow direction
  - Distribution of lesions often peri-ventricular where higher vein density
  - Peri-venous cuffs similar to appearance noted in chronic venous disease

- **BBB breakdown**
  - Vessel wall breakdown which leads to micro-bleeds
  - Iron acts as an inflammatory agent (histo and MR SWI show increased iron content in plaques developing in pattern identical to venous counter-current
  - Ischemic areas associated with shunting of blood volume and vessel atrophy

- **Extracranial venous obstruction**
  - Lesion site is non-specific (dural sinus, jugular, brachiocephalic, azygous veins alone or in combination)
  - Lesion etiology is non-specific (congenital/hereditary, osseous impingement, arterial compression, post-inflammatory, arachnoid granulation, etc., alone or in combination)
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**Georg Eduard von Rindfleisch (1836-1908)**

Von Rindfleisch wrote: "If one looks carefully at freshly altered parts of the white matter ... one perceives already with the naked eye a red point or line in the middle of each individual focus... the lumen of a small vessel engorged with blood ... All this leads us to search for the primary cause of the disease in an alteration of individual vessels and their ramifications: All vessels running inside the foci, but also those which traverse the immediately surrounding but still intact parenchyma are in a state characteristic of chronic inflammation." (3)

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**7-Tesla MRI Images of Patient with MS**

Inflammation surrounding vessels (yellow) in very early lesions

NYU Physician 2008 60:16-17

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**Detection of Small Parenchymal Veins within MS Lesions Using T2-weighted 3T and 7T Imaging**

Investigative Radiology 2009 44:491-494
Putnam proposes that the basic etiology of MS is venous obstruction

Tracey Putnam, Boston City Hospital, developed an experimental dog model of venous obstruction to study MS.

At the end of his paper, he stated:

"The similarity between such lesions and many of those seen in cases of multiple sclerosis in man is so striking that the conclusion appears almost inevitable that venular obstruction is the essential immediate antecedent to the formation of typical sclerotic plaques."


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Peri-venous Fibrin Cuff in Chronic Venous Disease and MS

Figure 1. Panel A, classic fibrin cuffs (arrow) thicken veins (v) in a venous ulcer bed, 40 x. Panel B, fibrin cuffs (arrow) encircle proliferated thick walled veins (v) in a peri-ventricular MS plaque, 30 x. Panel A is courtesy of Professor Caggati, Rome, Italy. Panel B is modified from Adams OW. A Colour Atlas of Multiple Sclerosis. London: Wolfe Med., 1980.

Laminar Flow Promotes Factors that Reduce Inflammation

Disturbed or Reversed Flow Promotes Inflammatory and Thrombotic Phenotype
The conceptual framework

• The vessel wall responds dynamically to changes in flow and pressure (pulsatile shear stress and cyclic strain)
• Alterations in venous flow and pressure may elicit inflammation, thrombosis and tissue injury

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• BBB breakdown
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• Extracranial venous obstruction
  – Lesion site is non-specific (dural sinus, jugular, brachiocephalic, azygous veins alone or in combination)
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CCSVI and MS

A new conceptual framework

- Anatomical anomalies in cerebrovenous drainage (IJ, VRT, and or AZG VV) alter cerebral venous flow patterns and pressure. These alterations cause:
  - Increased expression of endothelial adhesion molecules, chemokines, cytokines, and prothrombotic factors.
  - Increased vsmc injury response and generation of oxygen-derived free radicals.
  - Adherence of immune cells and their infiltration into the surrounding tissue.
  - Infiltrating immune cells elaborate cytokines and oxygen-derived free radicals that further increase vascular permeability, leading to insudation of plasma proteins and in some cases red blood cells.
  - Parenchymal injury due to inflammation and oxidative stress with demyelination, resolving with fibrosis and plaque formation.

How Is CCSVI Diagnosed?

- Doppler ultrasound
- MR venography (CT venography)
- Conventional catheter venography

Venous Obstruction (CCSVI) and MS

- Abnormalities noted in MS and CCSVI by Duplex Ultrasound
  - Reflux/reversal of flow in IJV irrespective of body position
  - Retrograde flow in deep cerebral veins by TCD
  - Direct detection of stenotic IJV lesion
  - Absent flow in jugular - even with increase in negative thoracic pressure
  - Loss of normal postural drainage pattern between IJV and vertebral veins
  - 2 OR MORE DUPLEX PARAMETERS IN 100% OF MS PATIENTS
  - MEAN # OF ABNORMAL PARAMETERS IN MS: 3.8 (normals: 0.12)

Detection of CCSVI by color doppler

Zamboni et al, JNNP 2009
Color doppler reveals abnormal venous outflow in majority of MS patients

Table 3. Transcranial and extracranial color-Doppler high-resolution sonography (TCD/CD) criteria of high suspicion of venous abnormality.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCD/CD</td>
<td>Valve defects in internal jugular veins</td>
<td>3/3</td>
<td>5/5</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>MR venography (CT venography)</td>
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<td>4/4</td>
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How Is CCSVI Diagnosed?

- Doppler ultrasound
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Left jugular with ? abnormality: mid segment impression, valve effacement, collaterals
Candy wrapper twisted appearance of azygous with collateral flow

Evaluations of CCSVI

In the current snapshot, there is:

- General acknowledgment that anatomical renderings alone are insufficient; limited and often inadequate indicators of venous disease
  - High false positive and high false negative rates for CTV and MRV (c/w cath venography) limit clinical utility
  - Ultrasound better at identifying intraluminal lesions, but exam is operator dependent, time intense, hard to blind, depends on multiple criteria and may be difficult to reproduce.
  - Catheter venography is invasive and experience suggests it is a tarnished gold standard for CCSVI (“lesions” vary with position, respiration, muscle contraction)
- Emerging recognition that it is critical we understand the physiological relevance of anatomic luminal imaging findings in jugular and azygous veins
  - It is apparent that a physiological parameter – venous flow, cerebral perfusion, etc. – is key to put into context and determine the import of any venous narrowing identified during an evaluation for CCSVI

How We Got Where We Are?

And where do we want to go?

- In retrospect, how this evolved is understandable from a historical perspective. We used what we had and focused on what we needed.
  - We applied the diagnostic modalities that were at our disposal; those we were familiar with for vascular applications—basic CTA, MRA and ultrasound anatomic imaging.
  - In the evaluation of arterial pathologies, our legacy was to rely heavily on this anatomic imaging without a real focus on the physiological sequelae of obstructing lesions
- In the future, the diagnostic evaluation of CCSVI will NOT be a zero sum game with one imaging modality playing a dominant role. Rather, it will be a combination of evaluations (perhaps, fusion algorithms) that will contribute the requisite anatomical AND physiological data that will determine the presence of a relevant venous lesion and permit a confident diagnosis of CCSVI.

Where does the extra-cranial venous obstruction occur?
The Association of Chronic Cerebro-Spinal Venous Insufficiency (CCSVI) and Multiple Sclerosis

Summary Analysis

- **Extracranial venous obstruction**
  - Lesion site is non-specific (dural sinus, jugular, brachiocephalic, azygous veins alone or in combination)
  - Lesion etiology is non-specific (congenital/hereditary, osseous impingement, arterial compression, post-inflammatory, arachnoid granulation, etc., alone or in combination)

But, the overwhelming majority are

**Low Jugular Lesions**

That involve some aspect of the

**Jugular Valve**

Narrowed valve orifice
LIJ valve with restricted opening

But, what are we treating and how do we know if the venous lesion is significant?
INVERTED OR MALFORMED JUGULAR VALVE MECHANISM

HEALTHY CONTROL

CCSVI-MS

No reflux

HEALTHY CONTROL

CCSVI-MS

CHEST

BRAIN

CHEST

BRAIN

CHEST

BRAIN

CHEST

BRAIN

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Currently, many unknowns and lots of uncertainty

- **CCSVI Diagnosis**
  - Is CCSVI something we are born with, acquire, or both?
  - What % of MS patients and healthy controls have CCSVI?
  - Is CCSVI a consequence of MS or part of the disease pathogenesis?
  - How do we reliably diagnose CCSVI and know if it is physiologically relevant? (Doppler ultrasound, MRV with flow, IVUS, cervical plethysmography, cerebral perfusion, etc.)
  - How does CCSVI fit into the current immune concept of MS pathogenesis or doesn’t it?
  - How can we engage neurologists in meaningful collaboration to study a concept they truly regard as total lunacy?

- **CCSVI Treatment and end-point assessment**
  - Are any lesions outside the valves important?
  - Is PTA the best possible treatment? What about oversized balloons, cutting balloons and when are stents warranted, if at all?
  - What % of lesions respond to PTA; how do you judge?
  - Is it good or bad to disrupt the valves in CCSVI? Does this increase reflux and is this bad?
  - How do we know intraproducraly 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?
  - Post-treatment (PTA or stent) what is the ideal regimen for adjunctive meds to prevent thrombus formation?

- **Potential benefits of endovascular treatment and follow-up**
  - How do we know if there is any real benefit from treating CCSVI – i.e., not a placebo?
  - What % of patients notice improvement; in what % of these do symptoms return?
  - Do cerebral perfusion, tissue oxygenation and venous flow measurements improve post treatment?
  - What reverses after treatment; what doesn’t improve?
  - How do you follow patients; what evaluations should be monitored?
  - If symptoms return, what is the typical timeframe; what do you do when they return and why do they return?
  - Is there any evidence that the trajectory of disease progression is slowed post therapy?
Commentary

The current state of CCSVI discussions in the medical literature is centered in two silos: its frequency/diagnosis/association with MS, and the results of endovascular treatment. The former is highly contentious, confusing, and still quite hypothetical – with positions often argued by those with a pre-existing agenda/bias.

Conclusions: CCSVI is a sonographic construct that is poorly reproducible and questionable in terms of known pathophysiologic factors established in MS. The neuroimaging findings reviewed here do not support the CCSVI theory in MS, but rather point to a concomitant disturbance of the brain microcirculation in patients with MS, which deserves further investigation but can be well explained by secondary vascular inflammatory changes known to occur with this disease. As a consequence, endovascular treatment of presumed vascular abnormalities in MS should be discouraged vigorously.

AJNR 2011; 32:424-427

EDITORIAL

The second category of reports is relatively free of adversarial tension, populated by interventionalists and some diagnostic imagers interested in evaluating the effects of endovascular therapy on a variety of symptoms. This approach (much like with lower extremity venous disease) may prove to be an easier and more direct road to follow.
In either case, new metrics are needed to specifically address the effects of treatments on new targets - studies that allow an acceleration of the current cycle time to determine if the desired effect of therapy is achieved. This up-tempo ability to determine treatment effect in a more immediate time frame will facilitate rapid “go or no go” decision making.

This follows the trend in other disciplines –like Oncology

The need to provide tissue characterization, function, and its response to therapy

- If CCSVI exists and if it is relieved – is there a measurable effect?
- Cerebral perfusion
- Cognitive function
- Motor performance
- Exercise/heat tolerance and recovery
- OCT – beyond nerve fiber bundle thickness
- Other yet to be identified parameters

Until a time when we reach a more sophisticated, higher plane of diagnostic acumen, not just regarding CCSVI, but all MS therapies, we will continue to experience dialogues that are polarizing, unedifying and fail to benefit patients in meaningful ways.

So, where does that leave us?

What’s next?

For now, it’s step by step focus. Personally, for starters I want to know if a patient with MS has CCSVI and if the narrowing is successfully treated, is it possible to objectively demonstrate physiological improvement in relevant parameters and an associated relief of symptoms; for now, forget sustainability, restenosis, long-term MR follow-up, or the precise nature of the relationship between CCSVI and MS.