Chronic Cerebrospinal Venous Insufficiency (CCSVI) for Multiple Sclerosis

TCT: Plenary Session IX. Endovascular Horizons
Interventional Hot Topics II
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    - REVA Medical
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  - Cytograft Tissue Engineering
- Officer, Director, Board Member or other Fiduciary Role
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- Speaker’s Bureau
  - None
CCSVI Presentation Outline

• History of multiple sclerosis
• Venocentric lesions
• Blood-brain barrier considerations
• CCSVI hypothesis
• Extracranial venous lesions
• Diagnosis of CCSVI
• Treatment of CCSVI
• The Future
Georg Eduard von Rindfleisch (1836-1908)

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." (8)
Figure 1. Plaque formation (arrows) in the lateral ventricular wall in MS. Note the close relationship to the terminal veins.
Hand-rendered Depictions of MS Plaques in Illuminated Brain Sections
Chronic MS; large periventricular demyelinated plaque with perivenous extension into adjacent WM

Congested Vessels Surrounded by Demyleination
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.”

Chronic cerebrospinal venous insufficiency and multiple sclerosis

What do we know about Multiple Sclerosis?

- Clinical manifestations: Motor, Somatosensory, Cognitive
- Differential diagnosis: Inflammatory, Infectious, Metabolic, Neoplastic
- No cure
- Treatments: Immunosuppression
Degeneration Versus Autoimmunity In Multiple Sclerosis

The most widely accepted hypothesis for the cause of MS is that a CD4 T-cell-mediated autoimmune reaction is directed against myelin-related proteins; in addition myelin-specific T- and B-cell responses are memorized as a permanent adaptive immunity, perpetuating the disease.
Multiple Sclerosis
Distribution of Inflammatory Cells in Newly Forming Lesions

Andrew P. D. Henderson, MBBS,1 Michael H. Barnett, MBBS, PhD,1,2 John D. E. Parratt, MBBS, PhD,1 and John W. Prineas, MBBS1

Objective: CD4 T-cell–dependent macrophage activation directed against a myelin or oligodendrocyte antigen is generally thought to be the mechanism causing myelin destruction in multiple sclerosis (MS). However, areas within expanding MS lesions may exhibit prominent oligodendrocyte loss and apoptosis in the absence of infiltrating lymphocytes. The present study was designed to further investigate the inflammatory profile of different regions within rapidly expanding MS lesions.

Methods: Twenty-six active lesions from 11 patients with early MS were serially sectioned and immunostained for T and B cells, plasma cells, ramified microglia, macrophages, monocytes, and CD209-positive dendritic cells. Cell counts were compared in prephagocytic, phagocytic, and immediately postphagocytic areas.

Results: Parenchymal T and B cells were largely absent in areas of initial oligodendrocyte loss and in areas of degenerate and dead myelin infiltrated by myelin phagocytes. In contrast, trailing areas of complete demyelination packed with lipid macrophages, and, in some lesions, regenerating oligodendrocytes, showed large numbers of T cells, B cells, and immunoglobulin G (IgG)-positive plasma cells. Lesions in 2 exceptionally early cases contained relatively few T and B cells, and no IgG-positive plasma cells.

Interpretation: Early loss of oligodendrocytes is a prominent feature in tissue bordering rapidly expanding MS lesions. Macrophage activity is largely an innate scavenging response to the presence of degenerate and dead myelin. Adaptive immune activity involving T and B cells is conspicuous chiefly in recently demyelinated tissue, which may show signs of oligodendrocyte regeneration. The findings suggest that plaque formation has some basis other than destructive cell-mediated immunity directed against a myelin or oligodendrocyte antigen.

Ann Neurol 2009;66:739–753
Multiple Sclerosis
Distribution of Inflammatory Cells in Newly Forming Lesions

Andrew P. D. Henderson, MBBS, Michael H. Barnett, MBBS, PhD, John D. E. Parratt, MBBS, PhD, and John W. Prineas, MBBS

In this issue of *Annals of Neurology*, Prineas and colleagues provide histopathological evidence supporting the concept that MS may be primarily a degenerative disorder rather than an autoimmune disease. These authors focused on early lesions from human autopsy material, examining inflammatory cell infiltration in different parts of expanding MS lesions. They found loss of oligodendrocytes in even the earliest lesions, then infiltrating macrophages appeared to scavenge the degenerated/dead oligodendrocytes and myelin. Most importantly, and quite surprisingly, relatively little T- or B-cell infiltration (especially CD4+ T-cell infiltration, which is an important mediator in adaptive immunity) was noted in the earliest lesions, where oligodendrocytic pathology and dropout were clearly evident, and where myelin degeneration was already well established.
Fig 17. Most of the lesions in this patient with early multiple sclerosis were of this size, lymphocytes were present in relatively small numbers, and there was no evidence of endogenous production of immunoglobulin G (IgG) within the lesions, that is, IgG-positive plasma cells were absent. Magnification, ×1.75.
These observations raise questions about the long-held premise that MS is primarily an auto-immune disease.

Their findings strongly suggest that the early loss of oligodendrocytes/demyelination is not by adaptive immune attack; taken together, their results are consistent with autoimmunity/inflammation being a secondary reaction to some unidentified process triggering death of oligodendrocytes and degeneration of myelin that is independent of a primary cell-mediated or humorally-mediated immune reaction.
To Begin – What Is CCSVI?

Chronic Cerebrospinal Venous Insufficiency (CCSVI) has been hypothesized by Paolo Zamboni and others to explain the pathogenesis of Multiple Sclerosis (MS) and/or many of its associated symptoms. CCSVI has its basis in the observed relationship between the cerebral veins and lesions of MS. It proposes that extracranial venous obstruction interferes with the venous drainage from the CNS, leads to changes in the normal intra- and extracranial hemodynamics, and contributes to the development and progression of MS.
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)
Inflammation surrounding vessels (yellow) in very early lesions.
Detection of Small Parenchymal Veins within MS Lesions Using T2-weighted 3T and 7T Imaging

Investigative Radiology 2009 44:491-494
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
Laminar Flow Promotes Factors that Reduce Inflammation
Disturbed or Reversed Flow Promotes Inflammatory and Thrombotic Phenotype

Figure 4. Contrasting Effects of Steady, Laminar Shear Stress (Panel A) and Turbulent or Reversing Shear Stress (Panel B) on Vessel Walls.
NO denotes nitric oxide, MCP-1 monocyte chemoattractant protein 1, and VCAM-1 vascular-cell adhesion molecule. (Reproduced from Traub and Berk with the permission of the publisher.)

Adhesion molecule (VCAM-1) and cytokine expression
Oxidative stress, nFKB activation, reduced NOS activity
Leukocyte rolling and adhesion
Immune cell infiltration of vein wall
VSMC hyperplasia
Microhemorrhage and parenchymal cell death

From studies of vein pathology after experimental AV fistula, venous occlusion, or vein grafts
Active Lesions of Multiple Sclerosis

Blood vessel with RBCs in the lumen is ringed by small lymphocytes.

Small lymphocyte adherent to vascular endothelium, and another has almost traversed into the peri-vascular space through a gap (arrow).

Human Tissue

Mouse Spinal Cord

How Is CCSVI Diagnosed?

- Doppler ultrasound
- MR venography (CT venography)
- Conventional catheter venography
What is the imaging data from ultrasound, venography and MR in support of the association between venous obstruction and multiple sclerosis?
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)
Color doppler reveals abnormal venous outflow in majority of MS patients

Zamboni et al, JNNP 2009
Detection of CCSVI by color doppler

Zamboni et al, JNNP 2009
Association between chronic cerebrospinal venous insufficiency and multiple sclerosis: a meta-analysis

Andreas Laupacis MD MSc, Erin Lillie MSc, Andrew Dueck MD MSc, Sharon Straus MD MSc, Laure Perrier Med MLIS, Jodie M. Burton MD MSc, Richard Aviv MBChB, Kevin Thorpe MMath, Thomas Feasby MD, Julian Spears MD SM

Abstract

Background: It has been proposed by Zamboni and colleagues that multiple sclerosis is caused by chronic cerebrospinal venous insufficiency, a term used to describe ultrasound-detectable abnormalities in the anatomy and flow of intra- and extracerebral veins. We conducted a meta-analysis of studies that reported the frequency of chronic cerebrospinal venous insufficiency among patients with and those without multiple sclerosis.

Methods: We searched MEDLINE and EMBASE as well as bibliographies of relevant articles for eligible studies. We included studies if they used ultrasound to diagnose chronic cerebrospinal venous insufficiency and compared the frequency of the venous abnormalities among patients with and those without multiple sclerosis.

Results: We identified eight eligible studies: all included healthy controls, and four of them also included a control group of patients with neurologic diseases other than multiple sclerosis. Chronic cerebrospinal venous insufficiency was more frequent among patients with multiple sclerosis than among the healthy controls (odds ratio [OR] 13.5, 95% confidence interval [CI] 2.6–71.4), but there was extensive unexplained heterogeneity among the studies. The association remained significant in the most conservative sensitivity analysis (OR 3.7, 95% CI 1.2–11.0), in which we removed the initial study by Zamboni and colleagues and added a study that did not find chronic cerebrospinal venous insufficiency in any patient. Although chronic cerebrospinal venous insufficiency was also more frequent among patients with multiple sclerosis than among controls with other neurologic diseases (OR 32.5, 95% CI 0.6–1775.7), the association was not statistically significant, the 95% CI was wide, and the OR was less extreme after removal of the study by Zamboni and colleagues (OR 3.5, 95% 0.8–15.8).

Interpretation: Our findings showed a positive association between chronic cerebrospinal venous insufficiency and multiple sclerosis. However, poor reporting of the success of blinding and marked heterogeneity among the studies included in our review precluded definitive conclusions.

Competing interests: Andreas Laupacis receives honoraria as a member of a data safety monitoring board for studies of two drugs for multiple sclerosis funded by Novartis Pharmaceuticals. Jodie Burton has received unrestricted educational support and honoraria for speaking and educational engagements from Teva Neuroscience Canada, EMD Serono and Biogen Idec Canada. No competing interests declared by the other authors.

Disclaimer: Andreas Laupacis is a member of CMAJ’s Editorial Board, and Sharon Straus is an associate editor for CMAJ. Neither was involved in the editorial decision-making process for this article.

This article has been peer reviewed.

Correspondence to: Dr. Andreas Laupacis, laupacisa@smh.ca
### MS patients v. healthy controls

<table>
<thead>
<tr>
<th>Study</th>
<th>MS patients</th>
<th>Controls</th>
<th>OR (95% CI)</th>
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<tr>
<td>Al-Omari et al.</td>
<td>21/25</td>
<td>0/25</td>
<td>243.7 (12.4–4785.6)</td>
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<tr>
<td>Baracchini et al.</td>
<td>8/50</td>
<td>0/110</td>
<td>44.2 (2.5–782.7)</td>
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<tr>
<td>Centonze et al.</td>
<td>42/84</td>
<td>20/56</td>
<td>1.8 (0.9–3.6)</td>
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<tr>
<td>Doeppe et al.</td>
<td>0/56</td>
<td>0/20</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Krogius et al.</td>
<td>2/10</td>
<td>0/2</td>
<td>1.5 (0.05–41.8)</td>
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<td>Mayer et al.</td>
<td>0/20</td>
<td>1/20</td>
<td>0.3 (0.01–8.3)</td>
</tr>
<tr>
<td>Zamboni et al.</td>
<td>109/109</td>
<td>0/132</td>
<td>58035.0 (1.142.2–2.948.755.8)</td>
</tr>
<tr>
<td>Zivadinov et al.</td>
<td>170/278</td>
<td>37/145</td>
<td>4.6 (3.0–7.2)</td>
</tr>
<tr>
<td>Overall</td>
<td>352/632</td>
<td>58/510</td>
<td>13.5 (2.6–71.4)</td>
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<td>Heterogeneity: $P = 89%$</td>
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### MS patients v. controls with other neurologic diseases

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<th>MS patients</th>
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<td>Krogius et al.</td>
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<td>0/5</td>
<td>3.2 (0.1–81.0)</td>
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<td>0/45</td>
<td>19929.0 (389.5–1019755.6)</td>
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<td>Zivadinov et al.</td>
<td>170/278</td>
<td>11/24</td>
<td>1.9 (0.8–4.3)</td>
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<td>Overall</td>
<td>289/447</td>
<td>11/134</td>
<td>32.5 (0.6–1775.7)</td>
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<td>Heterogeneity: $P = 90%$</td>
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Figure 2: Meta-analysis of diagnosis of chronic cerebrospinal venous insufficiency (presence of at least two parameters) in patients with multiple sclerosis (MS) versus healthy controls (top panel) and controls with other neurologic diseases (bottom panel). An odds ratio greater than 1.0 indicates an increased likelihood of a diagnosis of chronic cerebrospinal venous insufficiency in MS patients versus controls. CI = confidence interval, OR = odds ratio.
Association between chronic cerebrospinal venous insufficiency and multiple sclerosis: a meta-analysis

Andreas Laupacis MD MSc, Erin Lillie MSc, Andrew Dueck MD MSc, Sharon Straus MD MSc, Laure Perrier MEd MLIS, Jodie M. Burton MD MSc, Richard Aviv MBChB, Kevin Thorpe MMath, Thomas Feasby MD, Julian Spears MD SM

Interpretation
We found a strong and statistically significant association between chronic cerebrospinal venous insufficiency and multiple sclerosis. However, the large amount of heterogeneity among the study results prevents a definitive conclusion. The source of the heterogeneity is not clear. It is not obviously caused by differences in the definition of chronic cerebrospinal venous insufficiency, patient characteristics or the methodologic quality of the studies.

We also could not identify any factor that accounted for the large and problematic difference between the studies in the frequency of chronic cerebrospinal venous insufficiency among patients with multiple sclerosis. Although small samples may be partly responsible, the magnitude of the difference strongly suggests that other factors are important. One obvious possibility is differences in ultrasound technique. It is crucial that ultrasonographers agree upon the technique to be used to diagnose chronic cerebrospinal venous insufficiency, and on a method to ensure quality control.
How Is CCSVI Diagnosed?

• Doppler ultrasound
• MR venography (CT venography)
• Conventional catheter venography
Prominent valve cusps (R>L)
Narrowed valve orifice
Candy wrapper twisted appearance of azygous with collateral flow
Where does the extra-cranial venous obstruction occur and what causes the flow disturbance?
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)
In 38% of the 36 specimens examined, the transverse process indents the posterior wall of the vein; in 8% a more severe kink is noted.
But, the overwhelming majority are

Low Jugular Lesions
INVERTED OR MALFORMED JUGULAR VALVE MECHANISM

HEALTHY CONTROL

CCSVI-MS
Anatomical and histological analysis of venous structures associated with chronic cerebro-spinal venous insufficiency

C. Diaconu, S. Staugaitis, J. McBride, C. Schwanger, A. Rae-Grant, R. Fox (Cleveland, US)

Background: Chronic cerebro-spinal venous insufficiency (CCSVI) is a new theory for MS pathogenesis. CCSVI includes alterations in cerebral venous outflow and is often assessed by ultrasound or magnetic resonance venography (MRV). No gross anatomical description of venous outflow in MS has been reported to date.

Methods: We harvested bilateral internal jugular (IJV), subclavian, brachiocephalic, and azygous (AZY) veins from 7 deceased MS patients and 6 non-MS controls. Veins were injected with silicone, dissected en bloc, incised longitudinally to expose the luminal surface, and fixed. All valves and structural abnormalities were characterized and photographed using a stereomicroscope. Vein wall stenosis was defined as a >= 50% reduction in cross-sectional area, defined from vein wall circumference and compared to a normal appearing region in the same vein.

Results: A variety of vein abnormalities were identified. The incidence of vein wall stenoses was similar in MS and controls: eight stenoses in 4 of 7 MS patients and five in 3 of 6 controls. Marked valvular and other intraluminal abnormalities with potential hemodynamic consequences were identified in 5 of 7 MS patients (7 abnormalities) and in 1 of 6 controls (1 abnormality). These abnormalities included circumferential membranous structures (1 MS and 1 control), longitudinally-oriented membranous structures (3 MS), single valve flap replacing IJV valve (2 MS), and enlarged and malpositioned valve leaflets (1 MS). In addition, minor anatomic variations without expected hemodynamic consequences were observed similarly in both MS and controls. These included valves with >2 leaflets, the presence of valves in the AZY, additional (duplicate) normal-appearing IJV valves, and small membranous septa.
What about endovascular treatment of patients with CCSVI?
Low Jugular Lesions
LIJ valve with restricted opening
LIJ post PTA of valve
Internal jugular vein stenosis and reflux
Internal jugular vein stenosis and reflux
Right internal jugular vein post PTA
Azygous
Pre/Post stenting of twisted descending azygous vein
What are the anticipated short and long-term clinical outcomes of endovascular management of extra-cranial venous insufficiency?
Venous Obstruction (CCSVI) and MS

- *Initial Observations Recorded after Endovascular Treatment of Venous Stenotic Lesions*
  
  - Global symptoms attributable to MS, but not referrable to a specific neuro-anatomic loci (i.e., fatigue, headache, heat sensitivity, “brain fog“, urinary urgency, etc.), show short-term improvement and in some cases (low EDSS) completely resolve. This suggests that these particular “MS“ symptoms may be more accurately categorized as related to venous obstruction.
  
  - Early-term follow-up of functional mobility (high EDSS) is not conspicuously changed from pre-procedure.
Liberation Study

Longitudinal Arm (100 patient)

62% Female, 38% Male
Mean age: 47 years
Multiple Sclerosis Type
   Relapsing Remitting: 54%
   Secondary Progressive: 34%
   Primary Progressive: 12%

Mehta et al. Presented SVS 2011, In press JVS
Liberation Study

Longitudinal Arm (100 patient)

Total # lesions: 174
Location of lesion
  Right IJV: 41%
  Left IJV: 49%

Mehta et al. Presented SVS 2011, In press JVS
Liberation Study

Longitudinal Arm (100 patient)

Total # lesions: 174

Location of lesion
  Right IJV: 41%
  Left IJV: 49%
  Azygous Vein: 10%

Mehta et al. Presented SVS 2011, In press JVS
Liberation Study

Longitudinal Arm (100 patient)
Mean stenosis: 78% (range 50-100%)
Number of lesions/ patient:

1: 22%
2: 52%
3: 20%
4: 6%

1.7 lesion/ pt. (mean)

Mehta et al. Presented SVS 2011, In press JVS
Liberation Study

Longitudinal Arm (100 patient)
Anticoagulation during procedure
Antiplatelet post-procedure
Immediate success <30% residual stenosis: 82%

Mehta et al. Presented SVS 2011, In press JVS
Liberation Study

Longitudinal Arm (100 patient)
Anticoagulation during procedure
Antiplatelet post-procedure
Immediate success <20% residual stenosis: 82%
Mean follow-up 4.5 months (N=79)
Restenosis >50%: 8%
Occlusion: 2%
Other complications: 0.8% (new onset A-fib)
Major complications: 0%
Death: 0%

Mehta et al. Presented SVS 2011, In press JVS
Liberation Study: timed 25-Foot walk

Follow-up 4.5 months

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<td>11.47</td>
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Mehta et al. Presented SVS 2011, In press JVS
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### Liberation Study: timed 25-Foot walk

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Mehta et al. Presented SVS 2011, In press JVS
## Liberation Study

mean follow-up 4.5 months

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<td>59.2</td>
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# Liberation Study

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<tr>
<td><strong>MS QOL – Mental Health Composite Score (Mean)</strong></td>
<td>52.7</td>
<td>70.5</td>
<td>0.006</td>
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*Mehta et al. Presented SVS 2011, In press JVS*
**Liberation Study**

mean follow-up 4.5 months

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<td><strong>Modified Fatigue Impact Score (Mean)</strong></td>
<td>15.8</td>
<td>12.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Mehta et al. Presented SVS 2011, In press JVS
Liberation Study  
mean follow-up 4.5 months

<table>
<thead>
<tr>
<th>Patients Reporting Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MS QOL – Physical Health Composite Score (Mean)</strong></td>
</tr>
<tr>
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</tr>
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### MS Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Pre Procedure</th>
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<tbody>
<tr>
<td>Loss of Balance</td>
<td>89%</td>
</tr>
<tr>
<td>Lower Extremity Weakness</td>
<td>84%</td>
</tr>
<tr>
<td>Bladder incontinence</td>
<td>71%</td>
</tr>
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**Liberation Study**

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<table>
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<th>P-value</th>
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<tbody>
<tr>
<td>Loss of Balance</td>
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<td>&lt;0.05</td>
</tr>
<tr>
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<td>79%</td>
<td>21%</td>
<td>&lt;0.05</td>
</tr>
<tr>
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<td>67%</td>
<td>33%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Decreased Coordination</td>
<td>74%</td>
<td>61%</td>
<td>39%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Vertigo</td>
<td>47%</td>
<td>71%</td>
<td>29%</td>
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## Liberation Study

**Mean follow-up 4.5 months**

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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?
What is the evidence for CCSVI?

2009–2011: 53 reports on CCSVI

Confusion & Controversy!

- < 20% of published studies: Evaluate evidence for or against CCSVI
- > 80% of published reports: Commentaries, interpretations, opinions, diatribes, rants, HIPA violations
Current Thoughts and Ruminations Regarding CCSVI and MS

- **Exploring leads to the pathogenesis of MS**
  - It is like a detective story. New evidence surfaces; clues are investigated; research may produce conflicting, supporting and refuting observations that confound, bolster, or dispel prior notions; pieces of the puzzle are ultimately put in place. Each step may only illuminate the next step to take as we progress along a path toward understanding the multi-dimensional interplay that triggers disease.
Harvard Business Review

Build a culture of trust and innovation.

COLLABORATE

SPOTLIGHT PAGE 67
Conclusions

• There has been a growing understanding of CCSVI in MS as studies are performed all over the world.

• It is helpful to understand what we know and we don’t know for obvious reasons:
  – To help effectively communicate with potential patients.
  – To make sure that discussions with neurology are balanced.
  – To be certain that research is directed towards answering the unanswered questions.
2nd Annual
ISNVD Scientific Meeting
February 18-22, 2012

Orlando, Florida 2012

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