Chronic Cerebrospinal Venous Insufficiency

CCSVI: Update
Research: Why

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MRI
Doppler

Specializing in Neurological Conditions
Multiple Sclerosis
Alzheimer’s
Parkinson’s
Multiple Sclerosis (MS)

- Inflammatory demyelinating neurodegenerative disease
- Myelin sheath around the axons are attacked
- Myelin sheath protects the axon transmission
- Affects the ability of the nerve cells to communicate with each other effectively
- May progress to physical and cognitive disability
  - Bladder
  - Walking
  - Small motor control
  - Memory

- No known cure

MS Prevalence

- Canadian population: ~ 240/100,000
  - 75,000 MS patients diagnosed
  - Atlantic & Prairie provinces highest rate

- United States: 400,000 diagnosed
  - 10,000 new cases diagnosed annually

- 2.5 million patients worldwide

  - 1st degree relative: ~1/50 (2%)
  - Dizygotic twin: ~1/25 (4%)
  - Monozygotic twin: ~1/3 (30%)
MS Disease Patterns

- RELAPSING-REMITTING (RR)
- SECONDARY PROGRESSIVE (SP)
- PRIMARY PROGRESSIVE (PP)
- PROGRESSIVE RELAPSING (PR)
Potential Triggers for MS

- Genetic predisposition
- Infectious agent
- Environmental factors
- Abnormal immunologic response
- MS
FDA Approved Disease Modifying Agents:

Interferon β
- Interferon β-1b 250 mcg qod
- Interferon β-1a 44 mcg SC tiw
- Interferon β-1a 30 mcg IM weekly

Glatiramer Acetate
- 20 mg SC qd

Mitoxantrone
- 12 mg/m² every 3 mths: lifetime max-144 mg/m²

Natalizumab
- 300mg IV mthly infusion

Fingolimod
- First oral treatment
Limitations of Current Therapies

- difficulty predicting therapeutic response
- injection or IV
- all only partially effective
- have side effects
- risks versus benefits
- expensive
- not a cure – disease modifying treatments
Published a working hypothesis

“Multiple Sclerosis is caused by venous outflow obstruction” specifically the internal jugular veins, vertebral veins and azygous vein.
• A vascular pathogenesis for MS was suggested in the late 1860’s by Charcot
• Due to inability to assess the microvascular abnormalities Charcot’s discovery went undeveloped
• Putman, Schlesinger and Dow in the 1930’s and 1940’s noted a relationship between the location of MS lesions and veins
• 1975 Adams published a paper stating early plaque shows infiltration with monocytes, lymphocytes and plasma cells around its central vein.
• 1980’s Schelling described venous reflux into the skull and/or spine in relation to MS
• From Schelling’s reports – iron deposit, endothelial cell activation and vasculitis
Dr. Zamboni theorized:

• venous reflux increased transmural pressure
• resulting in blood brain barrier opening
• allowing perfusion across the blood brain barrier
• causing inflammatory reaction and iron overload
• iron overload leads to perivenous iron deposits demonstrated in histological MS lesions

Dr. Zamboni proposed 5 ultrasound criterion to determine a condition he termed ‘Chronic Cerebrospinal Venous Insufficiency’ - CCSVI

Two or more positive criterion indicate CCSVI
Doppler Criteria for CCSVI in MS

- **Criterion 1**: Reflux in the IJV and/or VVs in sitting and supine posture
- **Criterion 2**: Reflux in the DCVs
- **Criterion 3**: High resolution B-mode evidence of proximal IJV stenoses
- **Criterion 4**: Flow not Doppler detectable in the IJVs and/or in the VVs
- **Criterion 5**: Reverted postural control of the main cerebral venous outflow pathway

≥2 positive criterion is considered pathologic

2008
100% of MS patients tested positive for CCSVI

0.5% of Control subjects tested positive for CCSVI

The location of venous obstructions plays a key role in determining the clinical course of the disease.

Zamboni P et al; Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis, JNNP.2008.157164V1
Dr. Zamboni - Treatment Study

2007-2008 MS Patients
Treated with balloon angioplasty
Angioplasty of IJV’s and Azygous
2 patients received stents in their azygous
Due to re-stenosis

Zamboni P, Galeotti R ...... Salvi F; Rationale and preliminary results of endovascular treatment of multiple sclerosis , the liberation procedure; Jan 2009
Neurological and Medical Community

Too simple

Nothing 100%

Questioned Research Ethics
BNAC
CTEVD Phase 1 Study

March 2009 to December 2009

Largest single research study to date on CCSVI
500 Subjects

Objective – to replicate Dr. Zamboni’s findings
<table>
<thead>
<tr>
<th></th>
<th>HC yes/no</th>
<th>CIS yes/no</th>
<th>OND yes/no</th>
<th>MS yes/no</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Criterion 1</td>
<td>33/163 (20.2%)</td>
<td>7/21 (33.3%)</td>
<td>4/26 (15.4%)</td>
<td>130/289 (45.0%)</td>
<td>&lt;.001</td>
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<tr>
<td>Criterion 2</td>
<td>15/118 (12.7%)</td>
<td>6/14 (42.9%)</td>
<td>7/20 (35.0%)</td>
<td>104/222 (46.8%)</td>
<td>&lt;.001</td>
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<tr>
<td>Criterion 3</td>
<td>63/163 (38.7%)</td>
<td>12/21 (57.1%)</td>
<td>12/26 (46.2%)</td>
<td>185/289 (64.0%)</td>
<td>&lt;.001</td>
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<tr>
<td>Criterion 4</td>
<td>12/163 (7.4%)</td>
<td>0/21 (0.0%)</td>
<td>7/26 (26.9%)</td>
<td>30/289 (10.4%)</td>
<td>.014</td>
</tr>
<tr>
<td>Criterion 5</td>
<td>11/163 (6.7%)</td>
<td>2/21 (9.5%)</td>
<td>2/26 (7.7%)</td>
<td>33/289 (11.4%)</td>
<td>.449</td>
</tr>
<tr>
<td>CCSVI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>37/145 (25.5%)</td>
<td>8/19 (42.1%)</td>
<td>11/24 (45.8%)</td>
<td>162/259 (62.5%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CCSVI&lt;sup&gt;c&lt;/sup&gt;</td>
<td>37/163 (22.7%)</td>
<td>8/21 (38.1%)</td>
<td>11/26 (42.3%)</td>
<td>162/289 (56.1%)</td>
<td>&lt;.001</td>
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<tr>
<td>≥1 VH Positive Criterion</td>
<td>90/163 (55.2%)</td>
<td>16/21 (76.2%)</td>
<td>17/26 (65.4%)</td>
<td>235/289 (81.3%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>p-value for Fisher’s exact test for independence

<sup>b</sup>borderlines excluded

<sup>c</sup>borderlines included in the “No CCSVI” group

Zivadinov et al. Neurology, 2011
### MS Subtype

<table>
<thead>
<tr>
<th></th>
<th>NMO</th>
<th>PP</th>
<th>PR</th>
<th>RR</th>
<th>Relapsing SP</th>
<th>Non-relapsing SP</th>
<th>Total</th>
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<tbody>
<tr>
<td>CCSVI</td>
<td>4 (66.7%)</td>
<td>6 (54.5%)</td>
<td>0</td>
<td>94 (49.2%)</td>
<td><strong>17 (89.5%)</strong></td>
<td><strong>41 (67.2%)</strong></td>
<td><strong>162 (56.1%)</strong></td>
</tr>
<tr>
<td>No CCSVI</td>
<td>2 (33.3%)</td>
<td>4 (36.4%)</td>
<td>1 (100%)</td>
<td>74 (38.7%)</td>
<td>2 (10.5%)</td>
<td>14 (23%)</td>
<td><strong>97 (33.5%)</strong></td>
</tr>
<tr>
<td>Borderline</td>
<td>0</td>
<td>1 (9.1%)</td>
<td>0</td>
<td>23 (12.1%)</td>
<td>0</td>
<td>6 (9.8%)</td>
<td><strong>30 (10.4%)</strong></td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>11</td>
<td>1</td>
<td>191</td>
<td>19</td>
<td>61</td>
<td><strong>289</strong></td>
</tr>
</tbody>
</table>

- Trend for MS subtype ($p = .033$)
- Significantly different in non-progressive vs. progressive MS ($p = .004$)

Zivadinov et al. Neurology, 2011
Our findings were consistent with increased prevalence of CCSVI in MS, but substantially lower than the originally reported sensitivity/specificity rates in MS.

There were differences between the groups studied, with MS patients showing the highest CCSVI prevalence compared to HC, CIS or OND patients.

CCSVI prevalence was significantly higher in progressive MS than in non-progressive MS or CIS patients.

Our findings point against CCSVI having a primary causative role in the development of MS.

Data findings indicate an association between CCSVI and MS.

Zivadinov et al. Neurology, 2011
Other Center’s Treatment
2008-2010

Stenting of the internal jugular veins
  • 1 patient death
  • 1 obtained open heart surgery due to stent movement

Many other countries (Poland, Jordan, Bulgaria, Scotland, Mexico) conduct stent treatment

Two deaths from treatment side effects

Estimated that between 20,000 – 30,000 patients received vein treatment worldwide
~20,000 – 30,000 treated patients

Approximately 2000 patient info for research

Patients:

- Felt Improvement
- Improvement for different time periods – 3 to 12 months
- Felt no improvement
- Felt improvement in some symptoms but not others
BNAC
CTEVD Phase II Study

February 2010 – March 2012
550 subjects
Continue Phase I protocol
with quantitative doppler data
Presently undergoing data analysis
International Society of Neurovascular Disease
ISNVD

First Conference held March 2011 in Bologna, Italy

Majority of CCSVI players attended

Study data presented

Ultrasound Consensus established
General Considerations from ISNVD

A major limitation of all studies of diagnostic accuracy is the necessity to refer to a gold standard.

Standardized interpretation guidelines for reader/operator training need to be developed.

Hemodynamic nature of the type of pathology cannot be neglected.

Power of the sample size should be considered.

Genetic, immunologic, viral, environment, clinical, conventional and non-conventional MRI associations need to be established.

Open-label vascular surgical interventions are promoted against a yet-to-be-proven relevance of CCSVI to MS pathogenesis.

Safety and preliminary efficacy studies need to be conducted in a pilot, placebo-controlled manner.
Research

Positive Studies

**Zamboni et al. JNNP, 2009**
**Zamboni et al. J NeurolSci, 2009**
**Zamboni et al. J VascSurg, 2009**
**Hojnacki et al. Int Angiol, 2010**
Simka et al. Int Angiolog, 2010
Ludyga et al. Phlebology, 2010
**Zivadinov et al. AJNR, 2011**
Zivadinov et al. Neurology 2011
*Zaharchuk et al AJNR, 2011*
Bavera et al ACTA Phlebol, 2011
Bastianello, BMC Neurol, 2011
Petrov et al. J Endovasc Ther, 2011
Radak et al. Phlebology, 2011
Radak et al. BMC Neurol, 2011

Negative Studies

Doepp et al. Ann Neurol, 2010
Sundstrum et al. Ann Neurol, 2010
Wattjes et al JNNP, 2010
#Baracchini et al. Ann Neurol, 2011
Zivadinov et al. Radiology, 2011
Mayer et al. JNNP, 2011
Tsivgoulis et al. Neurol, 2011
Marder et al, Arch Neurol, 2011
#Barrachini et al. Neurol, 2011
Doepp et al. Neurol, 2011

* Multimodal non-invasive imaging
** Multimodal non-invasive and invasive imaging
# Multimodal invasive imaging performed only on CCSVI positive subjects
A meta-analysis of these studies published last fall in the Canadian Medical Association Journal reported a strong and statistically significant association between MS and CCSVI, although researchers said they could not reach a definite conclusion about the role of CSSVI in MS.

This lead the CIHR to approve a CCSVI clinical study which is presently under protocol review.
BNAC & University of Buffalo Neurosurgery
Prospective Randomized Endovascular therapy in Multiple Sclerosis (PREMISE) study
Phase II Study

Sham procedure

20 subjects

Difficulty in recruiting volunteers

Results 6 months from last procedure

January 2011 – October 2011

January 2011 – September 2012
Intra-luminal (inside) and Extra-luminal (outside) Structural and Functional Venous Abnormalities

**Intra-luminal structural:**
- Web
- Flap
- Septum
- Membrane
- Malformed valve

**Extra-luminal structural:**
- Stenosis
- Annulus

**Results**
Significant MS subjects tested positive for intra-luminal structures (74%)
Significant MS subjects tested positive for functional anomalies (54.7%)
Intra-luminal structural:
- Web
- Flap
- Septum
- Membrane
- Malformed valve

Extra-luminal structural:
- Stenosis
- Annulus

Functional:
- Reflux/bidirectional flow
- Non-compliant
- No flow

Collateral circulation:
- Presence of collaterals
- Number of collaterals

Dolic et al. AJNR, January 2012
Diaconu et al
Anatomical and Histological Analysis of Venous Structures Associated with CCSVI
ECTRIMS 2011

Harvested bilateral internal jugular, subclavian, brachiocephalic and azygous veins
7 deceased MS patients
6 deceased non-MS patients
Histological Analysis of Venous Structures

Vein wall stenosis defined as >50% reduction in CSA as compared with normal appearing CSA in region of same vein.

Intra-luminal defect defined as marked valvular and intra-luminal abnormalities with potential hemodynamic consequences.

<table>
<thead>
<tr>
<th></th>
<th>MS (n=7)</th>
<th>C (n=6)</th>
<th>p value</th>
<th>* p value not provided by authors</th>
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</thead>
<tbody>
<tr>
<td>Stenosis, n</td>
<td>4 of 7</td>
<td>3 of 6</td>
<td>.799</td>
<td></td>
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<tr>
<td>Intra-luminal defects, n</td>
<td>5 of 7</td>
<td>1 of 6</td>
<td>.048</td>
<td></td>
</tr>
</tbody>
</table>

Comparison between number of MS subjects and Control subjects. Difference between number of subjects were tested using Chi-square.
International Society of Neurovascular Diseases
ISNVD

2nd Annual Conference held in Orlando, Florida, February 2012

Form a consensus document on
• Doppler update protocol
• MR/MRV protocol
• Venography protocol
• IVUS protocol
• Follow-up care to interventional treatment
Research
Stemming from CCSVI Hypothesis

Hemodynamic effect on endothelial lining
Jugular venous reflux in aging
Flow effects and brain function
Iron gene variants
Metal-induced hypersensitivity
Post treatment physiotherapy
Diet regimes
Autonomic dysfunction: A unifying multiple sclerosis theory, linking chronic cerebrospinal venous insufficiency, vitamin D(3), and Epstein-Barr virus

Z. Sternberg reviewed CCSVI articles
Narrowing of cerebral veins arises from autonomic nervous system dysfunction

“The absence of CCSVI specificity for MS, observed in recent clinical studies, may stem from a high prevalence of autonomic nervous system dysfunction in control groups which were recruited to these studies. Future studies should investigate CCSVI in relation to cardiovascular autonomic function.”

Sternberg Zohara, Autonomic dysfunction: A unifying multiple sclerosis theory, linking chronic cerebrospinal venous insufficiency, vitamin D3, AND Epstein-Barr virus; Autoimmunity Reviews, 2012
Additional research is required.
We need to learn more about CCSVI

Is CCSVI the cause for the shift from RR MS to SP MS?
Does the venoplasty subside all MS symptoms?
Does venoplasty cure all MS patients?
Is venoplasty a longevity cure?
Is CCSVI present in other neurological diseases?
We need to learn more about CCSVI/venous anomalies.

Multimodal approach is needed to determine to what extent CCSVI is present in various disease groups and MS subtypes.

Spectrum of venous anomalies needs to be defined.

Standardized diagnostic and research interpretation guidelines need to be developed and validated.

Further studies into SWI/fMRI role in diagnosis of CCSVI.

Further collaborative studies of:

- Biochemistry
- Genetic
- Molecular
- Nutritional
- Cytology
- Histology
- Pathology
- Environmental
- Endocrinology
- Immunology
- Physiology
- Physiotherapy
FDA Warns About Dangers of 'Liberation Therapy' for MS

May 10, 2012 — A controversial treatment for multiple sclerosis (MS) called "liberation therapy" comes with serious risks and unproven benefits, the US Food and Drug Administration (FDA) warned today.

The FDA also said that physicians and clinical investigators who plan to conduct clinical trials to treat CCSVI with vein-widening devices must first obtain an investigational device exemption from the agency because of the significant risks involved.

Robert Lowes. Medscape Medical News Neurology, 5/10/12
Potential Triggers for MS

Infectious agent

Genetic predisposition

Environmental factors

Interaction with multiple mechanisms

Abnormal immunologic response and neurodegeneration

CCSVI

MS = multiple sclerosis
Thank You for Your Attention

http://www.bnac.net

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