Chronic Cerebrospinal Venous Insufficiency in Multiple Sclerosis
Buffalo Experience

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Disclosures

• **Dr. Robert Zivadinov** has received personal compensation for activities with Teva Neuroscience, Biogen Idec, Questcor, and EMG Serono as a speaker and consultant. Dr. Zivadinov has received research support from National Institute of Health, National Multiple Sclerosis Society, National Science Foundation, Biogen Idec, Teva Neuroscience, Genzyme Corporation, Aspreva, Bracco, Questcor, and EMD Serono.

• The Buffalo CCSVI studies received financial support from the Direct MS Foundation, the Jacquemin Foundation, Hillarescere Foundation and from smaller donors.
Potential Triggers for Multiple Sclerosis

- Infectious agent
- Abnormal immunologic response
- Genetic predisposition
- Environmental factors
- MS (multiple sclerosis)

MS = multiple sclerosis
MS a Vascular Disease?

• A vascular pathogenesis for MS was suggested long ago

• The extent of microvascular abnormalities and their relationship to lesions has been difficult to assess until the recent advancements in MRI

• Ultra-high field MRI has become a tool for assessing vascular involvement in MS lesions

• Recent studies show perivenous association of MS lesions on high-contrast 7T susceptibility-sensitive MRI in MS patients
Susceptibility Weighted Imaging *

- 3D gradient echo with magnitude and phase image
- High resolution to reduce conventional spin dephasing
- Fully flow compensated in 3 dimension
- Modifying the contrast in the magnitude image using phase mask
- mIPping the images to create an angiographic effect (venography)

* Haacke EM 2004, MRM
Phase Imaging of MS at 7T

Chronic Cerebrospinal Venous Insufficiency (CCSVI) and Multiple Sclerosis

Zamboni et al. JNNP, 2009
Zamboni et al. JNS, 2009

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Selectie Venography

- Annulus
- Septum/valve malformation
- Membrane obstruction
- Twisting
- Hypoplasia
- Agenesis
- Compression

Pathogenesis of Iron Deposition in MS

• The source of iron deposition in MS has not been completely elucidated
• Primary or secondary to chronic inflammation in MS
• May derive from:
  – myelin/oligodendrocyte debris
  – destroyed macrophages
  – product of hemorrhages from damaged brain vessels
• May be related to oxidative stress and the generation of toxic free radicals
• Recently proposed CCSVI theory
  – may be a powerful chemotactic stimulus that attracts macrophages and contributes to or causes initial activation of T-cell autoimmunity
Hypothesis of Pathogenesis of CCSVI and MS

- Reflux of the venous blood from the periphery to the CNS
- Deposition of iron in the brain
- Toxic reaction
- Multiple Sclerosis
- Diapedesis of the erythrocytes in the brain parenchyma
- T cell activation
Potential Triggers for Multiple Sclerosis

- Environmental factors
- Abnormal immunologic response and neurodegeneration
- Genetic predisposition
- Infectious agent

CCSVI

Iron deposition

Environment factors

MS = multiple sclerosis

Diagnosis of CCSVI

“Vascular picture characterized by combined stenoses of the principal pathways of extracranial and extravertebral venous drainage”
COMPLIANCE of the jugular system

Courtesy of Zamboni P.
PROXIMAL VENOUS BLOCK Impairs the Aspirating Effect

Flow velocity cm/sec

DCVs Sinuses IJV-AZY

Velocity Lateral Pressure

Courtesy of Zamboni P.
Venous Hemodynamic (VH) Criteria for CCSVI in MS

- **Criterion 1**: Reflux in the IJVs and/or in the vertebral veins (VVs) assessed in both sitting and supine posture
- **Criterion 2**: Reflux in the deep cerebral veins (DCVs)
- **Criterion 3**: B-mode detection of stenosis in the IJVs in the form of annulus, webs, septum, or malformed valves
- **Criterion 4**: Absence of Doppler signal in the IJV and/or in the VVs
- **Criterion 5**: The presence of a negative difference in the cross sectional area (CSA) of the IJV
  - VH (0-5; ≥2 is considered pathologic)

- **VHISS** (Venous Hemodynamic Insufficiency Severity Score 0-16)

  Zamboni et al. JNNP, 2009
  Zamboni et al. Funct Neurol, 2009
Criteria 1
Reflux in the IJV in both positions
Criteria 2
Reflux in the Deep Cerebral Veins
Criteria 3
Septum
Criteria 4

No flow noted in the IJV collateral vein noted (blue)
CCSVI Patterns in MS

Zamboni et al. JNNP, 2009

Zamboni et al. JNS, 2009
3D Time Resolved Imaging of Contrast Kinetics (TRICKS) and enhanced and unenhanced 2D Time of Flight (TOF) on 3T scanner

• Jugular vein flow morphology is assessed into two segments:
  – Inferior and superior
  – Flow is classified for each segment as absent, pinpoint, flattened, crescentic and ellipsoidal (only, the absent and pinpoint flow is considered as pathologic)

• The vertebral vein flow is classified as absent/present

• The prominence:
  – Is defined as diameter of the veins >5mm or >7mm in the inferior segments) of vertebral, deep cervical, thyroid, external and anterior jugular and facial veins, and of jugular arch was evaluated. Left and right asymmetries were compared

• All MRI scans are examined in a fully blinded manner by 2 independent neuroradiologists

Hojnacki et al. Int Angiolog, 2010
Good overlap between narrowing of left internal jugular veins on axial 2D-TOF (a), axial (b) and volumetrically reconstructed (c) 3D-TRICKS and Doppler sonography (d) in multiple sclerosis patient. All three techniques showed similar findings in left internal jugular vein.

Hojnacki et al. Int Angiolog, 2010
Healthy control showing right internal jugular vein pinpoint/absent flow on axial 2D-TOF (a) and absent flow on axial (b) and volumetrically reconstructed (c) 3D-TRICKS. No Doppler sonography (d) abnormalities were detected in the right internal jugular vein.

Hojnacki et al. Int Angiolog, 2010
Variability between the baseline (a and c, 2D-TOF and 3D-TRICKS respectively) and follow-up (b and d, 2D-TOF and 3D-TRICKS respectively) exams in a healthy control. Absent segment of the right internal jugular vein at the baseline exam and normal right internal jugular vein at follow-up. Prominent bilateral external jugular veins (thick arrows). DS (e) showed normal right internal jugular vein at baseline.

Lopez et al. (submitted)
3D-TRICKS showed changes in the morphology of both internal jugular veins in a patient with MS. Comparison between pre-treatment (a) and 1 month post-treatment (b) and after 3, 6 and 9 months of the treatment respectively (c,d,e). Prominent left anterior jugular vein and jugular arch (thick arrows). SV showed abnormal right and left internal jugular veins.

Lopez et al. (submitted)
Sensitivity, specificity, accuracy, PPV and NPV value of Doppler sonography and MRV in relation to selective venography (gold standard) for detection of internal jugular vein abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>Accuracy % (95% CI)</th>
<th>PPV % (95% CI)</th>
<th>NPV % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS</td>
<td>100 (80.6-100)</td>
<td>75 (30.0-95.4)</td>
<td>95 (76.3-99.1)</td>
<td>94 (73.0-98.9)</td>
<td>100 (43.8-100)</td>
</tr>
<tr>
<td>2D-TOF</td>
<td>25 (10.1-49.5)</td>
<td>100 (51.0-100)</td>
<td>40 (21.8-61.3)</td>
<td>100 (51.0-100)</td>
<td>25 (10.1-49.5)</td>
</tr>
<tr>
<td>3D-TRICKS</td>
<td>31 (14.1-55.6)</td>
<td>100 (51.0-100)</td>
<td>45 (25.8-65.7)</td>
<td>100 (56.5-100)</td>
<td>26 (10.9-51.9)</td>
</tr>
</tbody>
</table>


Hojnacki et al. Int Angiolog, 2010
Conclusions

• MRV has limited value for diagnosis of CCSVI
• The reasons for this limitation are mainly due to:
  – lack of MRV dynamism in real-time
  – lower resolution than DS and SV
  – nature of the veins themselves, which are prone to morphological and haemodynamic changes under various circumstances:
    – MRV techniques do not have enough resolution to show vessel wall or intraluminal abnormalities such as annulus, webs, flaps, webs, etc., in contrast to high-resolution DS and SV
    – MRV for assessment of the AZY vein needs further technical improvement

Zivadinov et al. ISMRM, 2010
Causality vs. Association
Epidemiology and Biostatistics
Evaluating Outcomes: Association and Causality

• Strength of association
  • Measured by RR
• Dose response association
• Consistency of association
  • Correlation studies: replication of findings by multiple methods, multiple testing
  • Many lines of converging evidence
• Temporal association
• Specificity of association
  • How does RR predicts outcome
  • Ideally 1:1
• Plausibility
  • Conference with scientific knowledge

2005, Stanton H, Wolfe
Combined Transcranial and Extracranial Venous Doppler Evaluation in Multiple Sclerosis and Related Diseases (CTEVD Study)

This study received financial support from the Direct MS Foundation, the Jacquemin Foundation and from smaller donors.

Zivadinov et al. Neurology, AAN 2010, P06.144
Study Population (1700 subjects)

- **900 Adult CDMS**
  - 500 RRMS
  - 300 SPMS
  - 50 PPMS
  - 50 NMO

- **50 Pediatric MS**

- **50 CIS**

- **50 RIS**

- **300 Adult Healthy and Familial Controls**

- **50 Pediatric Healthy and Familial Controls**

- **150 CNS Autoimmune-Vascular Disorders**
  - SLE
  - PALP
  - Vascular

- **150 CNS Neurodegenerative Disorders**
  - AD
  - PD
  - Epilepsy

Zivadinov et al. Neurology, AAN 2010, P06.144
Progress of the Study

Unblinding originally planned in 3 different time frames:
- 500 subjects (CTEVD phase I)
- 1000 subjects (CTEVD phase II)
- 1700 subjects (CTEVD phase III, if necessary, and based on statistical interim analyses)

Current status as of April 1, 2010:
- 500 subjects underwent examinations until Dec 2009 in the CTEVD phase I study; results presented at this meeting
- CTEVD phase II – awaiting for funding
- In late 2009, the recruitment was extended nation-wide
# Demographic and Clinical Characteristics of the Enrolled Disease Groups and MS Subtypes

<table>
<thead>
<tr>
<th></th>
<th>HC (n = 163)</th>
<th>CIS (n = 21)</th>
<th>OND (n = 26)</th>
<th>All MS (n = 289)</th>
<th>NMO (n = 6)</th>
<th>PP (n = 11)</th>
<th>PR (n = 1)</th>
<th>RR (n = 191)</th>
<th>Relapsing SP (n = 19)</th>
<th>Non-relapsing SP (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Median (IQR)</td>
<td>47 (18.5)</td>
<td>38 (11)</td>
<td>50 (21.5)</td>
<td>48 (16)</td>
<td>48.5 (10.8)</td>
<td>54 (10.5)</td>
<td>46 (16.5)</td>
<td>44 (16.5)</td>
<td>55 (12)</td>
</tr>
<tr>
<td><strong>Sex (%)</strong></td>
<td>Male Male/Female</td>
<td>46.0% 75&lt;sup&gt;b&lt;/sup&gt; / 88</td>
<td>33.3% 7/14</td>
<td>26.9% 68 / 221</td>
<td>23.5% 16.7% / 5</td>
<td>16.7% 45.5% / 5/6</td>
<td>0% 0 / 1</td>
<td>23.6% 45 / 146</td>
<td>5.3% 1/18</td>
<td>26.2% 16 / 45</td>
</tr>
<tr>
<td><strong>EDSS</strong></td>
<td>Median (IQR)</td>
<td>1.5 (1)</td>
<td>3 (4)</td>
<td>5 (2.3)</td>
<td>6 (2)</td>
<td>3.5 (2)</td>
<td>2 (1.5)</td>
<td>5.5 (2)</td>
<td>6 (1.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Disease duration (years)</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Median (IQR)</td>
<td>4 (6)</td>
<td>5 (9.5)</td>
<td>12 (13)</td>
<td>10.5 (3.8)</td>
<td>15 (9.5)</td>
<td>13 (11)</td>
<td>18 (23)</td>
<td>20 (16)</td>
<td></td>
</tr>
</tbody>
</table>

HC – healthy controls; CIS – clinically isolated syndrome; OND – other neurologic diseases; MS – multiple sclerosis; NMO – neuromyelitis optica, PP – primary-progressive, PR – progressive-relapsing; RR – relapsing-remitting; SP – secondary-progressive; EDSS – expanded disability status scale; IQR – interquartile range

<sup>a</sup> Defined as age at Doppler visit; <sup>b</sup> Includes one transgender male; <sup>c</sup> Defined as the difference between age at Doppler visit and age at onset

Zivadinov et al. Neurology, AAN 2010, P06.011
CCSVI Classification by Disease Group in the CTEVD phase I study

• 499 of the 500 enrolled subjects were eligible for statistical analysis

• 374 subjects were assessed on the five CCSVI “Zamboni criteria”; the remaining 125 subjects were assessed on only VH criteria 1, 3, 4, and 5

• ≥ 2 abnormal CCSVI criteria – “CCSVI Diagnosis”

• 42 subjects not assessed on VH criterion 2 (technical difficulty) - did not fulfill any of the other 4 criteria – “No CCSVI group”

• 31 subjects not assessed on VH criterion 2 - fulfilled at least 2 of the other 4 criteria – “CCSVI group”

• 52 subjects - fulfilled exactly one of the other 4 criteria – “CCSVI Borderline group”

HC – healthy controls; CIS – clinically isolated syndrome; OND – other neurologic diseases; MS – multiple sclerosis; CCSVI classification was significantly related to disease group (p< .001 from Fisher’s exact test)

Zivadinov et al. Neurology, AAN 2010, P06.144
<table>
<thead>
<tr>
<th>Criterion</th>
<th>HC</th>
<th>CIS</th>
<th>OND</th>
<th>MS</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</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%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Criterion 2</td>
<td>15 / 118 (12.7%)</td>
<td>6 / 14 (42.9%)</td>
<td>7 / 20 (35%)</td>
<td>104 / 222 (46.8%)</td>
<td>&lt; .001</td>
</tr>
<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%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Criterion 4</td>
<td>12 / 163 (7.4%)</td>
<td>0 / 21 (0%)</td>
<td>7 / 26 (26.9%)</td>
<td>30 / 289 (10.4%)</td>
<td>0.014</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>0.449</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>
</tr>
<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>

HC – healthy controls; CIS – clinically isolated syndrome; OND – other neurologic diseases; MS – multiple sclerosis; <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.
### By Age Group for MS Patients

No significant relationship between CCSVI classification and age group \((p = .894\) from Fisher’s exact test).

### By MS Subtype

Significantly related to MS subtype \((p = .033\)).

### By Familial Status

Not significantly related to familial status \((p = .627\)).
### Comparison Between Multiple Sclerosis Patients and Healthy Controls

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Odds Ratio</th>
<th>(^{a})p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criterion 1</strong></td>
<td>45.0% ((39.3, 50.8))</td>
<td>79.9% ((72.9, 85.2))</td>
<td>79.8% ((72.9, 85.2))</td>
<td>45% ((39.3, 50.8))</td>
<td>3.21</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>Criterion 2</strong></td>
<td>46.8% ((40.4, 53.4))</td>
<td>87.3% ((80.1, 92.1))</td>
<td>87.4% ((80.2, 92.2))</td>
<td>46.6% ((40.1, 53.2))</td>
<td>6.02</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>Criterion 3</strong></td>
<td>64% ((58.3, 69.3))</td>
<td>61.3% ((53.7, 68.5))</td>
<td>74.6% ((68.8, 79.6))</td>
<td>49% ((42.2, 55.8))</td>
<td>2.82</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>Criterion 4</strong></td>
<td>10.4% ((7.4, 14.4))</td>
<td>92.6% ((87.6, 95.7))</td>
<td>71.4% ((56.3, 82.8))</td>
<td>36.8% ((32.3, 41.6))</td>
<td>1.46</td>
<td>0.316</td>
</tr>
<tr>
<td><strong>Criterion 5</strong></td>
<td>11.4% ((8.3, 15.6))</td>
<td>93.3% ((88.3, 96.2))</td>
<td>75% ((60.5, 85.4))</td>
<td>37.3% ((32.7, 42.0))</td>
<td>1.78</td>
<td>0.137</td>
</tr>
<tr>
<td><strong>CCSVI(^{b})</strong></td>
<td>62.5% ((56.5, 68.2))</td>
<td>74.5% ((66.8, 80.9))</td>
<td>81.4% ((75.4, 86.2))</td>
<td>52.7% ((45.9, 59.4))</td>
<td>4.85</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>CCSVI(^{c})</strong></td>
<td>56.1% ((50.3, 61.7))</td>
<td>77.3% ((70.3, 83.1))</td>
<td>81.4% ((75.4, 86.2))</td>
<td>49.8% ((43.7, 55.9))</td>
<td>4.33</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>(\geq 1) VH Positive Criterion</td>
<td>81.3% ((76.4, 85.4))</td>
<td>44.8% ((37.4, 52.5))</td>
<td>72.3% ((67.2, 76.9))</td>
<td>57.5% ((48.8, 65.7))</td>
<td>3.52</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

**Notes:**
- HC = healthy controls; CIS = clinically isolated syndrome; OND = other neurologic diseases; MS = multiple sclerosis;
- \(^{a}\)p-value for Fisher’s exact test for independence;
- \(^{b}\)Borderlines excluded;
- \(^{c}\)Borderlines included in “No CCSVI” group

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**Zivadinov et al. Neurology, AAN 2010, P06.011**
CCSVI and MRI Outcomes
SWI in Multiple Sclerosis and Healthy Controls

- ↓ oxygen utilization due to tissue destruction → less deoxyhemoglobin in the venous blood?
- Occlusion of vessels?

Schirda et al. AAN, 2009
A Three-Dimensional Multi-Scale Line Filter Algorithm for Segmentation of Vein Vessels in SWI

Normal Control

Multiple Sclerosis

Poloni et al. ISMRM 2010
### Quantitative Venous Vasculature Assessment on SWI Reflects Presence of Severe Chronic Venous Insufficiency in the Brain Parenchyma of MS Patients. A Case-Control Study

<table>
<thead>
<tr>
<th></th>
<th>Multiple Sclerosis (N=62)</th>
<th>Healthy Controls (n=33)</th>
<th>% difference</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total venous volume pre-GAD</td>
<td>(67.5 ± 19.8)ml</td>
<td>(82.7 ± 17.1)ml</td>
<td>-18.4%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Venous volume with diameter &lt;0.3mm pre-GAD</td>
<td>(45.3 ± 10.7)ml</td>
<td>(53.3 ± 10.1)ml</td>
<td>-15.0%</td>
<td>.001</td>
</tr>
<tr>
<td>VIF pre-GAD</td>
<td>0.048 ± 0.013</td>
<td>0.058 ± 0.011</td>
<td>-17.2%</td>
<td>.001</td>
</tr>
<tr>
<td>VIF of venous volume with diameter &lt;0.3mm pre-GAD</td>
<td>0.032 ± 0.007</td>
<td>0.037 ± 0.006</td>
<td>-13.5%</td>
<td>.003</td>
</tr>
<tr>
<td>Average distance from veins pre-GAD</td>
<td>(1.20 ± 0.23)mm</td>
<td>(1.04 ± 0.13)mm</td>
<td>+15.4%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total venous volume post-GAD</td>
<td>(70.3 ± 19.0)ml</td>
<td>(87.1 ± 18.0)ml</td>
<td>-19.3%</td>
<td>.011</td>
</tr>
<tr>
<td>Venous volume with diameter &lt;0.3mm post-GAD</td>
<td>(49.0 ± 10.3)ml</td>
<td>(58.3 ± 0.76)ml</td>
<td>-16.0%</td>
<td>.018</td>
</tr>
<tr>
<td>VIF post-GAD</td>
<td>0.049 ± 0.015</td>
<td>0.061 ± 0.009</td>
<td>-19.7%</td>
<td>.039</td>
</tr>
<tr>
<td>VIF of venous volume with diameter &lt;0.3mm post-GAD</td>
<td>0.034 ± 0.009</td>
<td>0.041 ± 0.0056</td>
<td>-17.0%</td>
<td>.046</td>
</tr>
<tr>
<td>Average distance from veins post-GAD</td>
<td>(1.17 ± 0.34)mm</td>
<td>(0.94 ± 0.16)mm</td>
<td>24.5%</td>
<td>.104</td>
</tr>
</tbody>
</table>

Quantitative venous vasculature differences between multiple sclerosis patients and normal controls. VIF-venous intracranial fraction; ICV-Intracranial volume

Poloni et al. AAN 2010, ISMRM 2010
Phase Imaging of MS at 7T

The basal ganglia in MS patients was more paramagnetic (P<0.05) than in controls, suggesting increased iron deposition:

<table>
<thead>
<tr>
<th>Region</th>
<th>Patients Mean ± SD</th>
<th>Controls Mean ± SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen</td>
<td>4.29 ± 1.13</td>
<td>2.82 ± 0.52</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(N = 14)</td>
<td>(N = 14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>6.35 ± 1.67</td>
<td>4.71 ± 1.24</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(N = 12)</td>
<td>(N = 14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td>3.03 ± 0.98</td>
<td>2.49 ± 0.64</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(N = 13)</td>
<td>(N = 14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head of caudate</td>
<td>5.85 ± 1.40</td>
<td>4.84 ± 1.09</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(N = 14)</td>
<td>(N = 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenium of corpus callosum</td>
<td>0.66 ± 0.15</td>
<td>1.02 ± 0.43</td>
<td>0.77</td>
</tr>
<tr>
<td>(N = 14)</td>
<td>(N = 15)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Putamen / Globus Pallidus / Caudate

High iron

Low iron

Normal Control

Multiple Sclerosis

Zivadinov et al. Int Angiolog, 2010
Thresholded high-iron tissue mean iron concentration (HITMIC) and iron volume fraction (IVF)

Healthy Control

Multiple Sclerosis

Zivadinov et al. Int Angiolog, 2010
CCSVI is Related to Iron Deposition on SWI

- Higher number of VH and VHISS criteria was related to HITMIC and IVF in different DGM structures (pulvinar nucleus of thalamus, thalamus, globus pallidus, and hippocampus and in T2-LV, T1-LV)

- HITMIC in DGM structures was predictive of higher disability status (EDSS) in almost all examined regions. The highest correlations were detected for thalamus and red nucleus

The findings from this pilot study suggest that CCSVI may be an important mechanism related to iron deposition in brain parenchyma of MS patients. In turn, iron deposition, as measured by SWI, is a strong predictor of disability progression in patients with MS

Zivadinov et al. Int Angiolog, 2010
Thank you.

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