CCSVI and MRI Outcomes in MS

Robert Zivadinov, MD, PhD
The Jacobs Neurological Institute & Baird MS Center
Director, Buffalo Neuroimaging Analysis Center
Associate Professor of Neurology
University at Buffalo, State University of New York
Potential Triggers for Multiple Sclerosis

- Infectious agent
- Environmental factors
- Abnormal immunologic response

Genetic predisposition

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
Chronic Cerebrospinal Venous Insufficiency (CCSVI) and Multiple Sclerosis


© Buffalo Neuroimaging Analysis Center
Hypothesis of Pathogenesis of CCSVI and MS

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

- Infectious agent
- Genetic predisposition
- Iron deposition
- Environmental factors

CCSVI

Abnormal immunologic response and neurodegeneration

MS = multiple sclerosis

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

Magnitude images

Phase images

**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
Diminished Visibility of Cerebral Venous Vasculature in MS by SWI at 3.0 Tesla

Ge et al. JMRI, 2009
Phase Imaging of MS at 7T

- Phase images of demyelinating lesions highlighted:
- periphery of lesions, the site of iron-rich macrophages*
- penetrating vessels in 70% of lesions
- 30% more lesions than seen in magnitude

- **Phase provides a novel MR contrast for studying neurodegeneration, one sensitive to the presence of iron.**

Focal Iron Deposition in MS and SWI

Haacke et al. JMRI, 2009
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></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<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>

Regional Brain Atrophy Measures in MS

Normal control, 26 year old female

Clinically-isolated syndrome, 27 year old female; DD=1 year; EDSS=1.0

Relapsing-remitting MS, 27 year old female; DD=7 years; EDSS=3.0

Secondary-progressive MS, 34 year old female; DD=15 years; EDSS=5.5

- SIENAX, LVV, 3VW, Freesurfer subcortical segmentation, Freesurfer cortical segmentation; Postc, Postcentral; Prec-Precentral; CC- Corpuscallosum; EN- Entorhinal; Colors: Light turquoise-Superior frontal, Violet-Rostral middle frontal, Dark brown-Caudal middle frontal, Dark green-Lateral orbitofrontal, Orange-Parstriangularis. Skin tone-Parspseudualaris, Blue-Precentral, Crimson Red-Postcentral, Parrot green-supramarginal,Dark turquoise-SuperiorParietal, Light blue-SuperiorTemporal, Light Pink-InferiorParietal, Light brown-Middle temporal, Dark Blue-Lateral Occipital, Dark pink-Inferior Temporal

Benedict et al. JNNP, 2009

Ramasamy et al. J Neurol Sci 2009
Brain Atrophy Changes over 3 Years

Dalton et al. Brain, 2004
Venous Drainage & CSF Dynamics

• CSF dynamics is dependent on the venous drainage

• It is a balance:
  – between CSF ultrafiltration from veins of the lateral ventricles and
  – the CSF re-absorption into the venous system at the level of dural sinuses
Cine CSF Flow Imaging

• CSF flow measurement in the aqueduct of Sylvius for HC (left) and MS patient (right).

• A-B. Saggital T2 scans showing positioning for the MRI Cine acquisition. Slice orientation is perpendicular on the aqueduct.

• C-D. Aqueduct and background ROIs drawn on the magnitude image.

• E-F. CSF velocity distribution within the aqueduct of Sylvius ROIs, for the 32 phases, calculated using the GE ReportCard software

Zamboni et al. Funct Neurol, 2009; Schirda et al. AAN 2010; ISMRM 2010
Chronic Venous Insufficiency in MS (CVIMS Study)

- Cross-sectional study
- 16 consecutive RRMS patients and 8 age- and sex-matched HC
- Equal numbers from Bellaria Hospital, Bologna, Italy and from the Jacobs Neurological Institute, University at Buffalo, NY, USA
- Mean age 36.1±7.3 yrs, mean disease duration 7.5 ±1.9 yrs and median EDSS 2.5
- All 16 MS patients fulfilled the diagnosis of CCSVI (median VH=4, median VHISS=9) and none of the HC

Lower Net CSF Flow and Lower Brain Volume in MS Patients is Related to CCSVI

Net CSF flow vs. total number of pathologic VHISS

Zamboni et al. Funct Neurol, 2009

Brain Atrophy vs. total number of pathologic Venous Hemodynamic Criteria

Zamboni et al. Int Angiolog (in press)
Diagnosis of CCSVI

“Vascular picture characterized by combined stenoses of the principal pathways of extracranial and extravertebral venous drainage”
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
Combined Transcranial and Extracranial Venous Doppler Evaluation in Multiple Sclerosis and Related Diseases (CTEVD study)

Zivadinov et al. AAN 2010
Study Population (1700 subjects)

- 900 Adult CDMS
  - 500 RRMS
  - 300 SPMS
  - 50 PPMS
  - 50 NMO
- 300 Adult Healthy and Familial Controls
- 50 Pediatric Healthy and Familial Controls
- 50 Pediatric MS
- 50 CIS
- 50 RIS
- 150 CNS Autoimmune-Vascular Disorders
  - SLE
  - PALP
  - Vascular
- 150 CNS Neurodegenerative Disorders
  - AD
  - PD
  - Epilepsy

Zivadinov et al. AAN 2010
Combined Transcranial and Extracranial Venous Doppler Evaluation in Multiple Sclerosis and Related Diseases (CTEVD study)

- Unblinding is planned in 3 different time frames:
  - 500 subjects - Jan 2010
  - 1000 subjects – Fall 2010
  - 1700 subjects – Spring 2011

- Current status as of Feb 1, 2010:
  - 500 subjects underwent examinations
  - Recruitment extended nation-wide (>13,000 MS pts on the waiting list)

Zivadinov et al. AAN 2010
Collaborators

• University of Buffalo
  – Bianca Weinstock-Guttman
  – David Hojnacki
  – Murali Ramanathan
  – Ralph Benedict
  – Frederick Munschauer
  – Colleen Miller
  – Kim Dressler
  – Dawn Lefevre
  – Karen Marr
  – Makki Elfadil
  – Claudiu Schirda
  – Cristopher Magnano
  – Cheryl Kennedy
  – Michelle Andrews
  – Justine Reuther
  – Christina Brooks
  – Kristin Hunt
  – Ellen Carl
  – Jennifer L. Cox
  – Michael G. Dwyer
  – Niels Bergsland
  – David Wack
  – Sara Hussein
  – Mari Heininen-Brown
  – Deepa. P. Ramasamy
  – Jackie Durfee
  – Laura Willis
  – Mariya Cherneva
  – Eve Salczynski

• University of Ferrara
  – Paolo Zamboni
  – Roberto Galleoti
  – Erica Menegatti
  – Anna M Malagoni

• University of Bologna
  – Fabrizio Salvi
  – Ilaria Bratolomei

• University of Pavia
  – Stefano Bastianello
  – Guy Poloni

• University of Alabama
  – Garry Cutter

• Wayne State University
  – Marck Haacke

• University of Barcelona
  – Alexandra Lopez
Thank You for Your Attention

http://www.bnac.net