Conflict of Interest Statement

I am affiliated with:
Wayne State University
McMaster University
The MRI Institute for Biomedical Research
and have an interest in
MR Innovations, Inc
and have support from
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Sean Sethi, MS
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Why perform MR imaging before and after treatment?

We need to:
- monitor lesions and iron content quantitatively
- monitor arterial, venous and CSF flow changes
- use the 3D vascular data to plan the intervention, (and if appropriate avoid the intervention)
- categorize different types of MS populations
- serve as a baseline pre-treatment
- make meaningful correlations between post treatment clinical status and current vascular hemodynamics
- track anatomic changes, assess effects of other treatments, and assess the need for reintervention in a noninvasive manner.
## Conventional MS MRI Protocol

**Conventional Neuro MS: Tier I**

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Time (approx.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial T2 Head</td>
<td>4:30</td>
</tr>
<tr>
<td>Saggital FLAIR Head</td>
<td>5:22</td>
</tr>
<tr>
<td>Axial T1 Head (prefer 3D)</td>
<td>4:30</td>
</tr>
<tr>
<td>Saggital T2/PD Cspine</td>
<td>3:40</td>
</tr>
<tr>
<td>Saggital T1 Cspine</td>
<td>3:30</td>
</tr>
<tr>
<td>Select Axial T2 Cspine through lesions</td>
<td>4:00 est</td>
</tr>
<tr>
<td>Inject Gadolinium</td>
<td>5:00</td>
</tr>
<tr>
<td>Axial T1 Head post Gad</td>
<td>4:30</td>
</tr>
<tr>
<td>Cspine T1 FS post Gad</td>
<td>3:40</td>
</tr>
<tr>
<td><strong>Total Time</strong></td>
<td><strong>38:42</strong></td>
</tr>
</tbody>
</table>
NEURO-ANATOMICAL INFORMATION:
Multiple white matter lesions from high resolution 3D FLAIR including diffuse WM hyper-intensities.
## CCSVI MS MRI Protocol: Tier II(a)

### Head and Neck without Contrast

<table>
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</tr>
<tr>
<td>Axial T1 Head (prefer 3D)</td>
<td>4:30</td>
</tr>
<tr>
<td>Sagittal T2/PD Cspine</td>
<td>3:40</td>
</tr>
<tr>
<td>Sagittal T1 Cspine</td>
<td>3:30</td>
</tr>
<tr>
<td>Select Axial T2 Cspine through lesions</td>
<td>4:00*</td>
</tr>
<tr>
<td>2D TOF MRV Neck</td>
<td>7:00</td>
</tr>
<tr>
<td>Flow Quantification at C2/C3 and C6/C7 with Venc = 50cm/s</td>
<td>6:00</td>
</tr>
<tr>
<td><strong>Total Time</strong></td>
<td><strong>34:40</strong> <em>(38:40)</em></td>
</tr>
</tbody>
</table>
Blood Brain Barrier Breakdown: T1 WI Post-Contrast Enhancement of Lesions

Data from a secondary progressive MS patient.

Pre-contrast T1 weighted images show hypo-intense lesions which enhance post contrast injection presumably representing acute lesions associated with a breakdown of the blood brain barrier.
CCSVI MS MRI Protocol: Tier II(b)
Head and Neck with Contrast and without 2D TOF MRV

<table>
<thead>
<tr>
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</tr>
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<tr>
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<tr>
<td>Sagittal FLAIR Head</td>
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<td>Sagittal T2/PD Cspine</td>
<td>3:40</td>
</tr>
<tr>
<td>Sagittal T1 Cspine</td>
<td>3:30</td>
</tr>
<tr>
<td>Select Axial T2 Cspine through lesions</td>
<td>4:00*</td>
</tr>
<tr>
<td>3D CE MRAV Neck</td>
<td>2:30</td>
</tr>
<tr>
<td>Flow Quantification at C2/C3 and C6/C7 with Venc = 50cm/s</td>
<td>6:00</td>
</tr>
<tr>
<td>Axial T1 Head post Gad</td>
<td>4:30</td>
</tr>
<tr>
<td>Cspine T1 FS post Gad</td>
<td>3:40</td>
</tr>
<tr>
<td><strong>Total Time</strong></td>
<td><strong>38:20</strong></td>
</tr>
<tr>
<td><em>(42:20)</em></td>
<td></td>
</tr>
</tbody>
</table>
Major Arteries of the Neck

- Right internal carotid artery
- Right external carotid artery
- Right common carotid artery
- Right vertebral artery
- Right subclavian artery
- Left common carotid artery
- Thyrocervical artery
- Left subclavian artery
- Innominate artery (brachiocephalic truck)
- Internal thoracic artery
Major Extracranial Veins of the Neck: Critical to also gain experience in visualizing collaterals

Coronal MIP: Time resolved 3D MRAV of the early venous phase (0.6x0.6x2.0mm³)
Dural Sinus by 3D High Resolution

Superior Sagittal Sinus

Straight Sinus

Sigmoid sinus

Transverse Sinus (Right: Blue, Left: Red)

Sagittal MIP: CE 3D VIBE, Axial MIP: CE T1WI with Fat Signals Saturated
ABNORMAL VENOUS STRUCTURE:
Upper level stenosis and string stenosis. Notice the presence of collaterals.
Venous abnormalities, including stenosis and atresia, observed in dynamic contrast-enhanced 3D MR venography.

Coronal MIP: Time resolved 3D MRV of the early venous phase
Phase Contrast Flow Quantification at 2 Levels in the Neck

C2/C3 CORE

C5/C6/C7 CORE
Flow at the cross sectional cut at C6/C7

High in-plane resolution of 0.5mm x 0.5mm is used.
Flow quantification with PC-MRI

- Vessel contours (red-arteries, blue-veins) were drawn on both magnitude and phase images
- Only phase image was used for flow quantification
Flow analysis at C2-C3 Level

The LIJV has a reflux in its flow pattern which likely extends back to the inferior petrosal sinus.
The goal of early MR imaging flow studies

To examine the extracranial flow characteristics using MR imaging methods (especially IJV flow) in order to identify risk factors or potential biomarkers associated with venous flow in the MS population.
Study design

Subjects:
300 MS Patients
recruited at Applied fMRI in San Diego
22 were excluded due to degraded image quality,

The data from the remaining 278 MS patients will be reported here.
MR imaging protocol (CCSVI protocol): Data collected on a 3T Siemens TRIO

<table>
<thead>
<tr>
<th>Sequence</th>
<th>CE-MRA</th>
<th>TOF-MRV*</th>
<th>PC-MRI**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation</td>
<td>Coronal</td>
<td>Transverse</td>
<td>↓ IJV@C6</td>
</tr>
<tr>
<td>TR (ms)</td>
<td>3.06</td>
<td>21</td>
<td>14.4</td>
</tr>
<tr>
<td>TE (ms)</td>
<td>1.25</td>
<td>4.78</td>
<td>4.41</td>
</tr>
<tr>
<td>Flip Angle</td>
<td>19°</td>
<td>60°</td>
<td>25°</td>
</tr>
<tr>
<td>Field-of-View (mm x mm)</td>
<td>340 x 255</td>
<td>320 x 255</td>
<td>256 x 256</td>
</tr>
<tr>
<td>Resolution (mm x mm x mm)</td>
<td>0.9 x 0.9</td>
<td>0.63 x 0.63</td>
<td>0.57 x 0.57</td>
</tr>
<tr>
<td>Bandwidth (Hz/pixel)</td>
<td>590</td>
<td>215</td>
<td>530</td>
</tr>
</tbody>
</table>

* arterial saturation band = 40mm, separation from slice = 10mm
** VENC = 50cm/sec; retrospective gating; 25 phases/R-R interval
Stenoses identification with CE-MRA and TOF-MRV

Stenosis threshold = 25 mm² (C6) / 12.5 mm² (C2).
1/3 of a normal IJV cross-sectional area with a diameter of 1cm \(^{(1,2)}\) at C6.

A threshold of 30cm² was used by Mayer\(^3\) (US, supine position).

1. Tartiere et al., Crit Care, 2009; 2. Furukawa et al., Romanian J Legal Med, 2010
## Results - Anatomical assessment with CE-MRA + TOF-MRV

<table>
<thead>
<tr>
<th>Stenotic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral C6 stenosis</td>
<td>51 (36%)</td>
</tr>
<tr>
<td>Unilateral C2 stenosis</td>
<td>50 (35%)</td>
</tr>
<tr>
<td>Bilateral C6 stenosis</td>
<td>27 (19%)</td>
</tr>
<tr>
<td>Bilateral C2 stenosis</td>
<td>15 (10%)</td>
</tr>
<tr>
<td>Diffuse stenosis</td>
<td>16 (11%)</td>
</tr>
<tr>
<td>Atresia</td>
<td>26 (18%)</td>
</tr>
<tr>
<td>Aplasia</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>143</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Stenotic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>135</td>
</tr>
</tbody>
</table>
Pre-post treatment of a young Canadian with severe MS

Using MRI and angiography, it is clear that MS patients HAVE venous abnormalities
Total internal jugular flow as a biomarker for a sub-population of MS patients

Type 1

Type 2

Type 3
LIJV is stenosed at UL and truncated at LL
RIJV is stenosed at LL
LEJV is stenosed at LL
Note the flow is carried mostly by only one internal jugular vein.
Flows for all major veins can be determined and for all major arteries to study the cardiovascular input/output to the brain. This will complement the PWI data nicely.
Parkinson’s study: CCSVI look alike

LIJV is stenosed at UL and truncated at LL
RIJV is stenosed at LL
LEJV is stenosed at LL
Lesions are seen in 2005 scans-red arrows; the lesions are at the same level as seen in the 2010 scans.

The 2010 scans shows multiple new lesions: yellow arrows.
Data collected at Wuhan Hospital under the auspices of Haibo Xu

- Total: 29 cases processed
- Age range 36 - 76 years
  - age mean: 61.3 years
  - age SD: 9.5 years
- 16 males and 13 females processed

- Symptoms included: hand shaking, leg shaking, bilateral pain in legs, swelling of limbs, weakness of limbs, etc.

- UPDRS scores ranged from 8 to 56

- 24 have FLAIR data of which 12 have white matter lesions
Normal vessels and normal flow
CCSVI and Parkinson’s Disease

• Of 29 cases, 18 of them have potentially missing left transverse sinus or slow flow in the left transverse sinus.

• These 18 have abnormal flow in the left internal jugular vein.

• Of 50 normal controls, only 10 show this type of behavior.
WM hyperintensities seen in FLAIR
The distribution of PD patients with white matter lesions

![Graph showing the distribution of PD patients with white matter lesions.](image)
F(sdj) vs F(dj): 229 MS patients at C2
F(sdj) vs F(dj): normal controls

The diagram shows a scatter plot with data points representing Type I, Type II, and Type III in relation to normal controls. The plot compares two variables, $F_{sdj}$ (TAF) and $F_{dj}$ (TAF), with a 4:1 ratio line and a shaded area indicating the normal controls range.
Conclusions and future directions

- Quantitative flow imaging provides the potential to sub-characterize the MS population into:
  - low flow and high flow groups and
  - those dominated by one jugular

Future work
- Many more normal controls are needed to validate these biomarkers
Conclusions: CCSVI and Neurodegenerative Disease

CCSVI may be a very broad vascular problem associated with a number of different diseases:

- Multiple sclerosis
- Parkinson’s
- Optic neuritis
- Exertional headache
- Transient global amnesia