Multiple Sclerosis with Iron and Chronic Cerebral Spinal Vascular Insufficiency (CCSVI)

E. Mark Haacke
Wayne State University, Detroit, MI
The MRI Institute for Biomedical Research, Detroit, MI
Outline

• Susceptibility Weighted Imaging (SWI) is an MRI technique to image veins and tissue iron
• Multiple Sclerosis shows venous involvement and iron build up
• Possible cause of this is Chronic Cerebral Spinal Vascular Insufficiency (CCSVI)
• MRI is uniquely suited to test these hypotheses
  ▫ SWI to measure tissue iron
  ▫ SWI to visualize small veins
  ▫ MR Venography (contrast enhanced or time of flight) to check for venous insufficiency
  ▫ Flow measurements (phase contrast) to quantify flow and check for retrograde flow
Putative iron seen with SWI correlates with the vasculature

- Synchrotron Radiation X-Ray Fluorescence (SR-XRF) validates phase and iron association
- Capillary density in the basal ganglia
- Expected increase of iron with age

- In multiple sclerosis:
  - MS lesions
  - The thalamostriate venous drainage system
Validating Iron Content: SWI phase contrast correlates to iron seen with XRF scanning

Susceptibility Weighted Imaging: 500μ resolution
X-Ray Fluorescence Imaging: 50μ resolution

Images courtesy of: Helen Nichol and Richard McCrea, University of Saskatchewan.
SWI Phase contrast correlates to vascular India ink injection (by Henri M. Duvernoy)
Tissue Iron as Measured with SWI

- Studies have shown the tissue iron seen with SWI is not predominately venous blood
Caudate veins and the thalamostriate venous drainage system as seen with SWI at 7T
Iron in Multiple Sclerosis
Iron deposition in MS follows the thalamostriate venous system

Figure A is from 10-10-2006
Figure B is from 3-25-2008
Increases in the basal ganglia and thalamus iron content in multiple sclerosis

SWI putative iron content as measured with SWI phase data shows that iron in younger MS patients is much higher than that compared to age matched normals.
Perhaps the iron seen with SWI in MS is hemosiderin present in and around the damaged venous wall?

Panel A, intra and extra-cellular iron deposits (ID) encircle a dilated vein (V) in a cerebral MS plaque, Perls’ method 150 x.

Panel B, intra and extra-cellular iron deposits (ID) encircle a dilated vein (V) in venous ulcer bed, Perls’ method 80 x.


J. Royal Society of Medicine, V99, Nov 2006 pages 589-593.
What came first?

- Is MS first an inflammatory demyelinating process followed by a disturbance of the venous system or is it first a perivenular disease followed by an inflammatory demyelinating process.

- Could it be that MS is in fact a cardiovascular disease?

- What if the veins were stenosed outside the brain? The brave pioneer who tackled this work, Paolo Zamboni ventured not only to guess what it was but to operate on the patients to treat them, and with some success.
Reverse chronology of this idea

• Zamboni discusses the major problem of reflux of blood which disrupts the body’s expected normal flow hemodynamics and can lead to inflammation and destruction of the vessel wall in a mechanism similar to that seen in atherosclerosis. With prolonged pressure, induced inflammation, valve remodeling and reflux occur.


Reverse chronology of this idea


“The early event in the demyelination plaque formation is the homing of lymphocytes, macrophages and plasma cells on the post-capillary venules of the white matter. The observations that put the cerebral vessels and change in BBB at the center stage of the earliest events in multiple sclerosis are widely supported.”


- Putnam and Adler, Arch Neurol Psychiat 38: 1, 1937. “MS plaques spread along the periventricular veins.”
Paolo Zamboni and his team’s proof of concept via DSA and balloon therapy.
The second MS case from Juergen Reichenbach, Jena, Germany: September 24, 2009 collected with the MS NICE protocol, processed at the MRI Institute for BMR

Coronal view

Sagittal view
MS patient

Normal control
Cerebral venous system
We have proposed a simple first pass protocol to include the following three tests:

- **Post contrast time resolved MRA: to find the stenoses**
- **SWI: to find the iron and venous damage**
- **Flow quantification: to find the abnormal fluid dynamics**

Please visit our site [www.nice-mri.com](http://www.nice-mri.com) to review the database concept we are proposing and more importantly for MS updates visit [www.ms-mri.com](http://www.ms-mri.com)
Short term future directions:

We are trying to collect as many cases as we can in the next few weeks in an open study so that I can take a proposal to some MS groups around the world to join us in this venture and share their data for a fixed protocol. *This work will be continued for the next few months to collect as many cases as possible.*

Long term goals:

Create a continuing database with a single international protocol for a blinded study in MS for patients with 10 years or less MS indications. Collect hundreds of cases from sites around the world.

Research protocols could easily be tacked on to this such as 4D flow measurements, higher resolution SWI, etc but the baselines should stay the same for now. This would make all the work we do far more valuable to the medical community at large.
Website contact and information

Please visit our site www.nice-mri.com to review the database concept we are proposing and more importantly for MS updates visit www.ms-mri.com