“Is the Basic Etiology of Multiple Sclerosis Vascular in Origin?”

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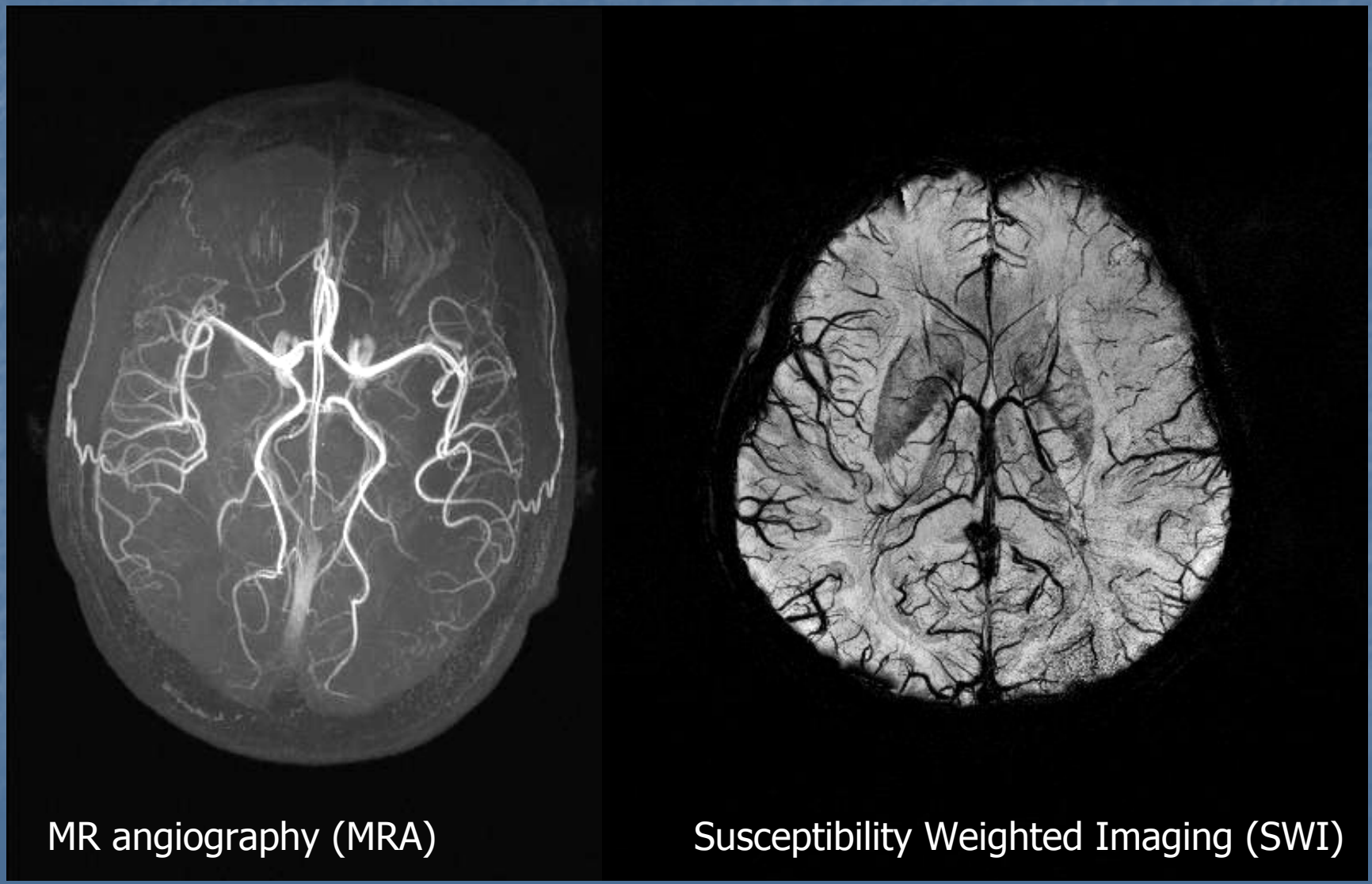
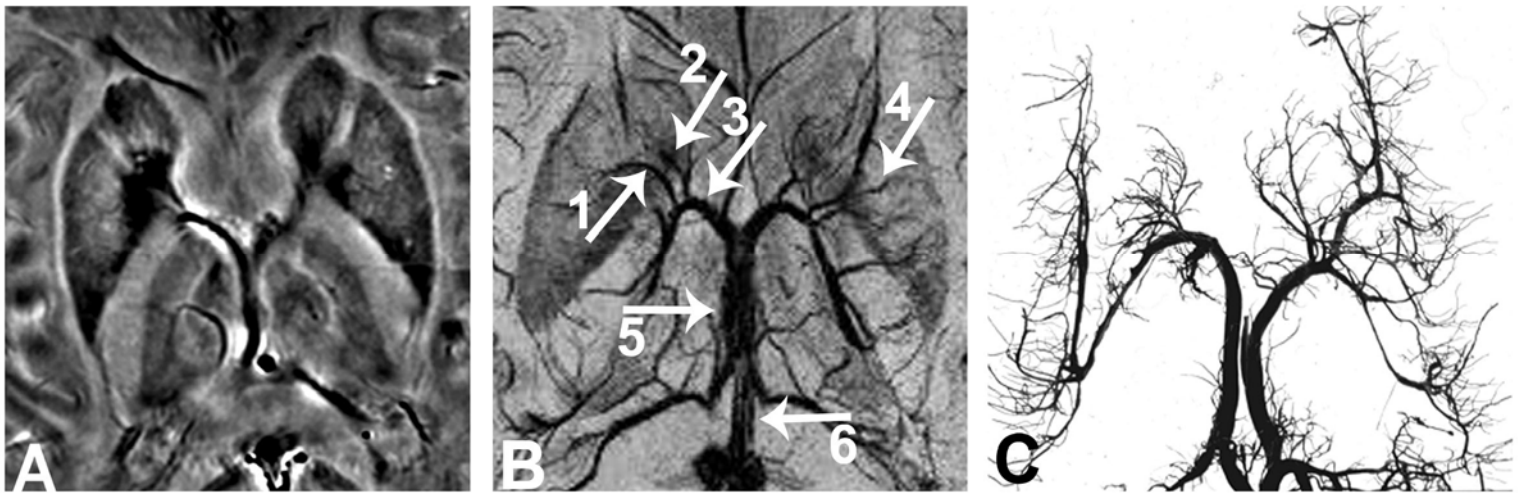
Outline

- The vasculature of the brain
- Brain iron as seen with SWI
- A short history of MS and veins
- Vitamin D considerations
- The vasculature of the neck
- MR images of the veins in the neck
- Future directions
- NICE an international database

Arteries and veins in the brain seen with MRI.



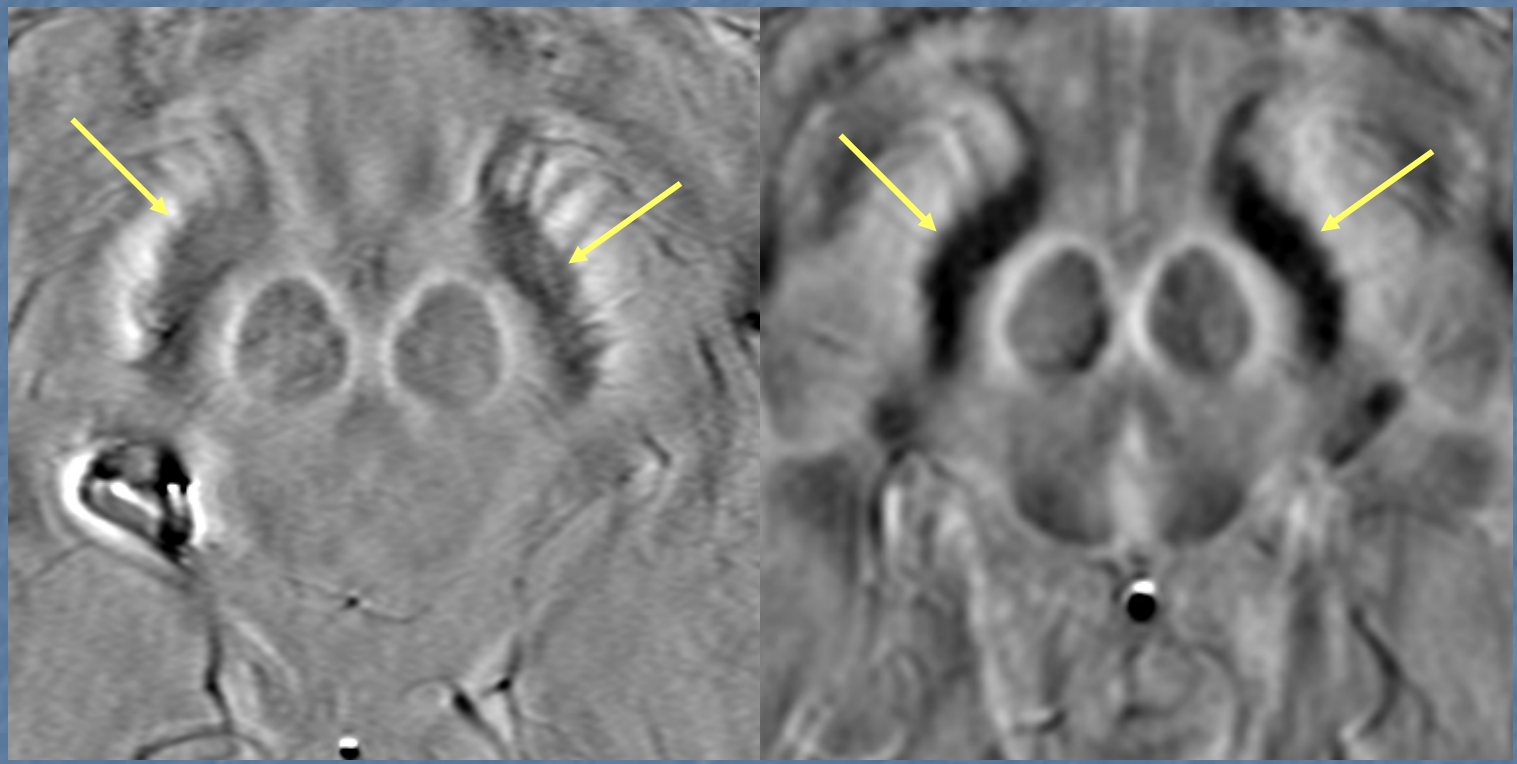
Correlating iron deposition with venous structures using SWI

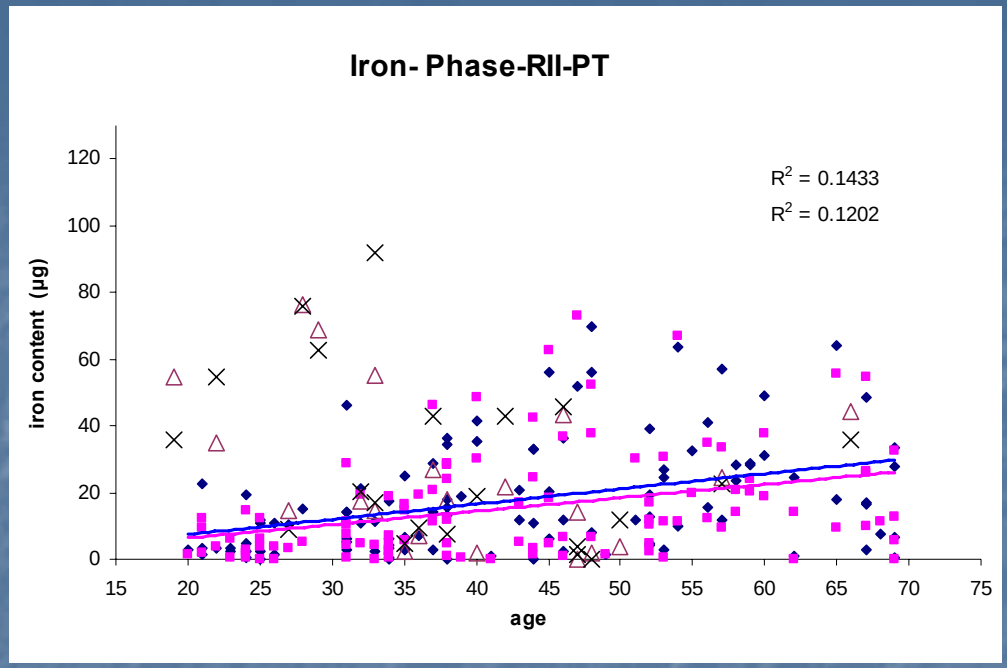


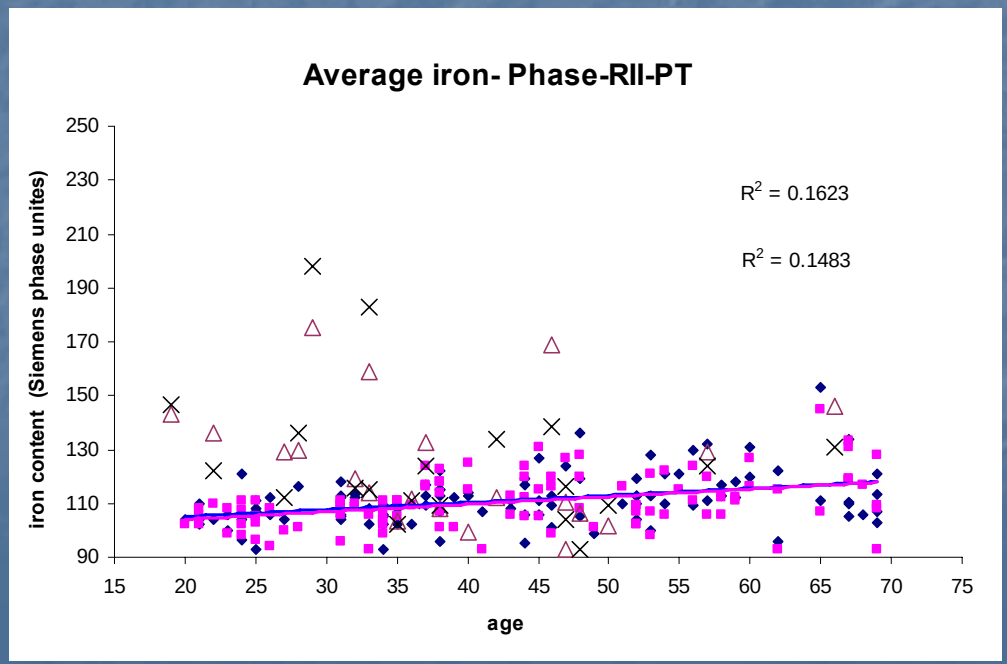
Haacke et al (2010). Evidence of an increase in basal ganglia and thalamic iron content in multiple sclerosis and its vascular implications: An initial analysis with susceptibility weighted imaging.

Submitted to Intern. Angiology.

Midbrain iron increases in the substantia nigra

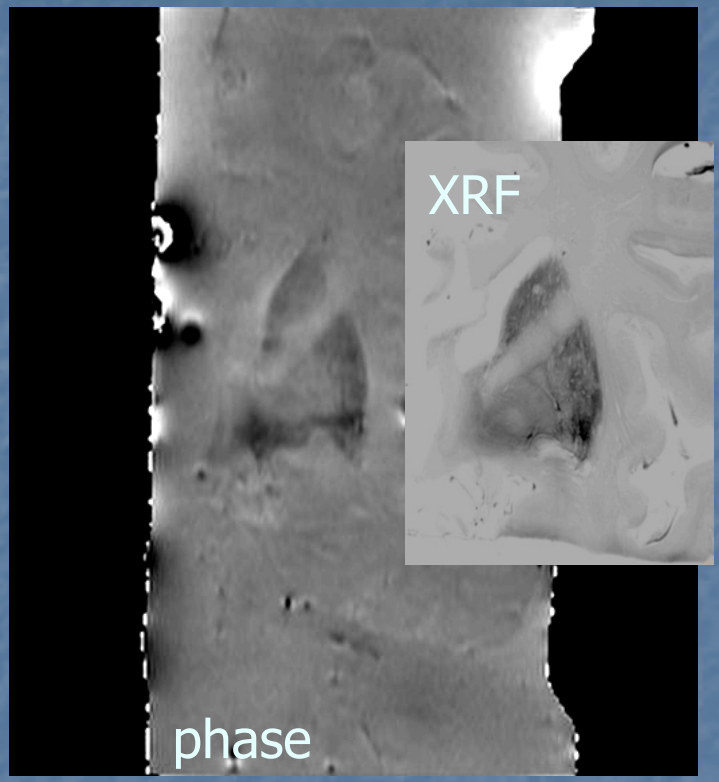






SWI putative iron content as measured with high pass filtered phase data shows a clear iron increase in younger subjects compared to age matched normals.

SWI and XRF scanning

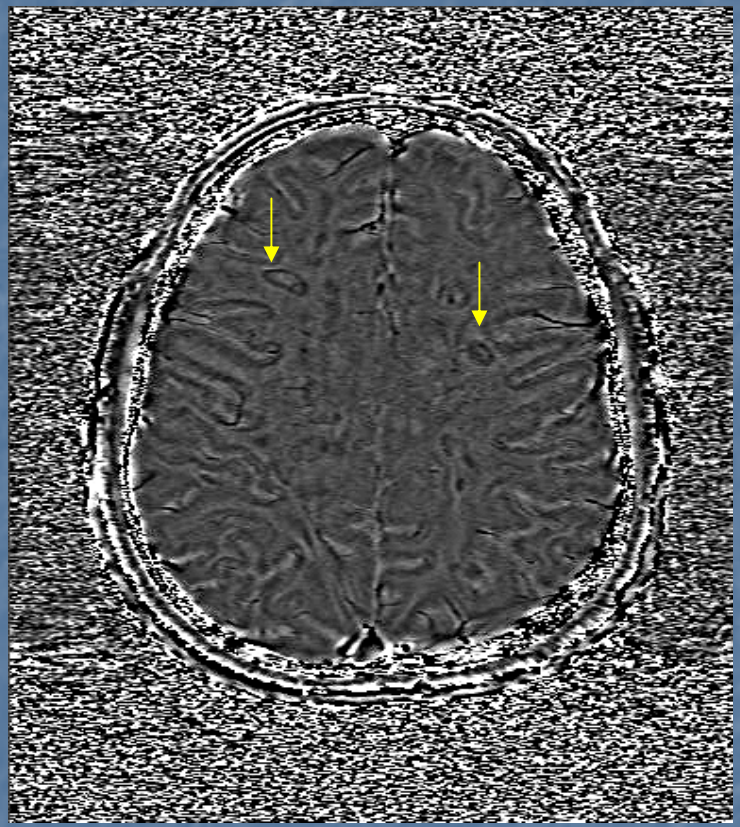


SWI: 500μ resolution

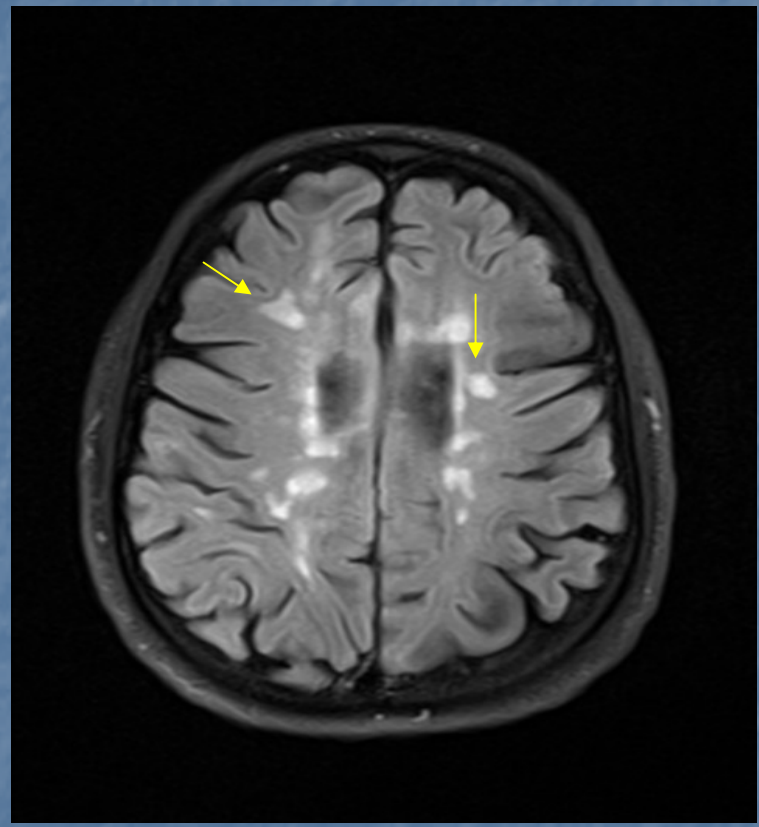
XRF: 50μ resolution

Brain Iron Detected by SWI High Pass Filtered Phase Calibrated with Synchrotron X-ray Fluorescence
Hopp et al, JMRI, tentatively accepted for publication.
Dept of Anatomy and Cell Biology, University of Saskatchewan.

SWI vs Flair

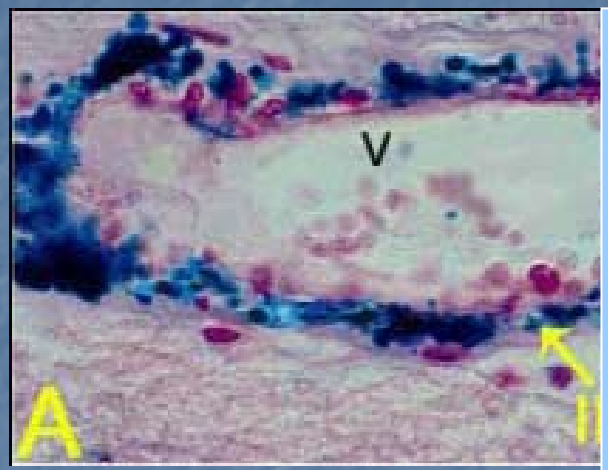


SWI 0.5x0.5x2 reveals iron rings surrounding many lesions and more uniform iron deposition in other lesions



Flair image 0.8x0.8x5

Perhaps the iron seen with SWI in MS is hemosiderin?



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

P. Zamboni, The Big Idea: Iron-dependent inflammation in venous disease and proposed parallels in multiple sclerosis.

J. Royal Society of Medicine, V99, Nov 2006 pages 589-593.

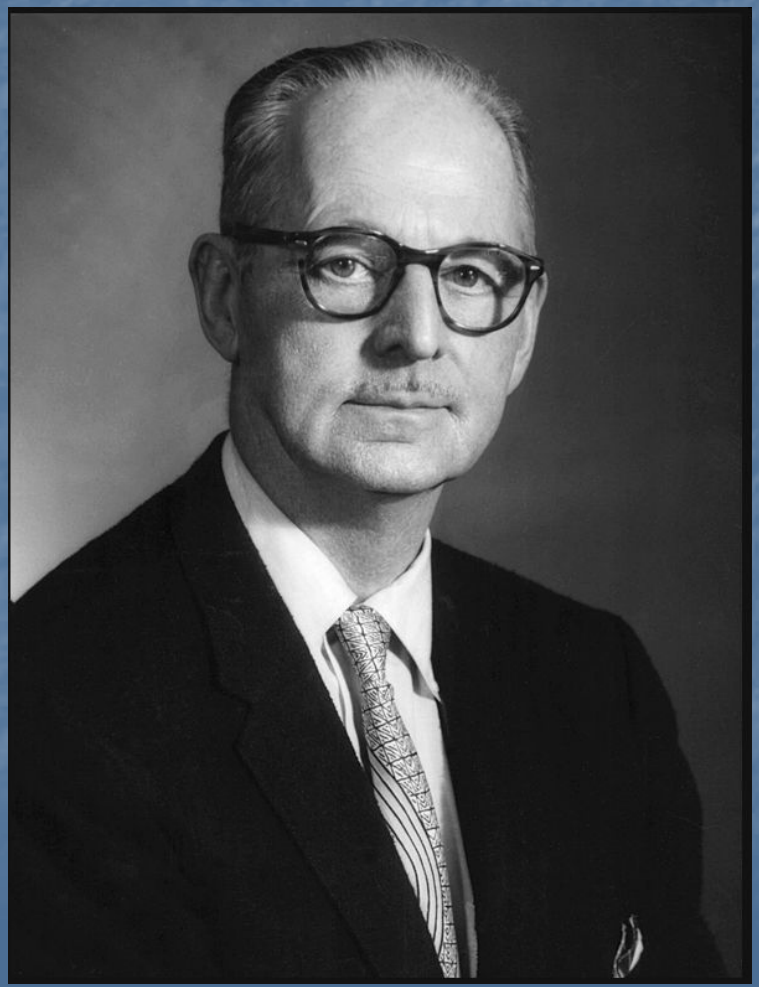
A short history of MS and veins

- Borst (1903). Die multiple sklerose des zentralnervensystems. Ergebnisse Allg Path Pathol Anat, 9: 67-187.
- Putnam (1935). Studies in multiple sclerosis: encephalitis and sclerotic plaques produced by venular obstruction. Archives of Neurology and Psychiatry. 33: 929-940.
- Putnam (1939). Evidences of vascular occlusion in multiple sclerosis and encephalomyelitis.
- Corday et al (1953). Cerebral vascular insufficiency. Arch of Neur and Psychiat 69, 551-570.
- Fog (1948). Rygmarvens patologiske anatomi. Munkgaards, Copenhagen.
- Fog (1963). On the vessel-plaue relations in the brain in multiple sclerosis.
- Allen (1981). Demyelinating diseases. The pathology of multiple sclerosis: fact, fiction and hypothesis. Neuropath and Applied Neurobiology 7, 169.

A short history of MS and veins

- Schelling (1986). Damaging venous reflux into the skull or spine: relevance to multiple sclerosis. Med Hypotheses. 1986 Oct;21(2):141-8.
- Adams (1987). Periventricular lesions in MS. Neuropathol Appl Neurobiol. 13: 141.
- Trojano M, Manzari C, Livrea P. Blood-brain barrier changes in multiple sclerosis. Ital J Neurol Sci 1992;13:55-64.
- Bergan JJ, Pascarella L, Schmid-Schonbein GW. Pathogenesis of primary chronic venous disease: Insights from animal models of venous hypertension. J Vasc Surg 2008;47:183-92.
- Zamboni (2009). Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 80:392–399.

Putnam proposes that the basic etiology of MS is venous obstruction



Tracey Putnam, Boston City Hospital, developed an experimental dog model of venous obstruction to study MS.

At the end of his paper, he stated:

"The similarity between such lesions and many of those seen in cases of multiple sclerosis in man is so striking that the conclusion appears almost inevitable that venular obstruction is the essential immediate antecedent to the formation of typical sclerotic plaques."

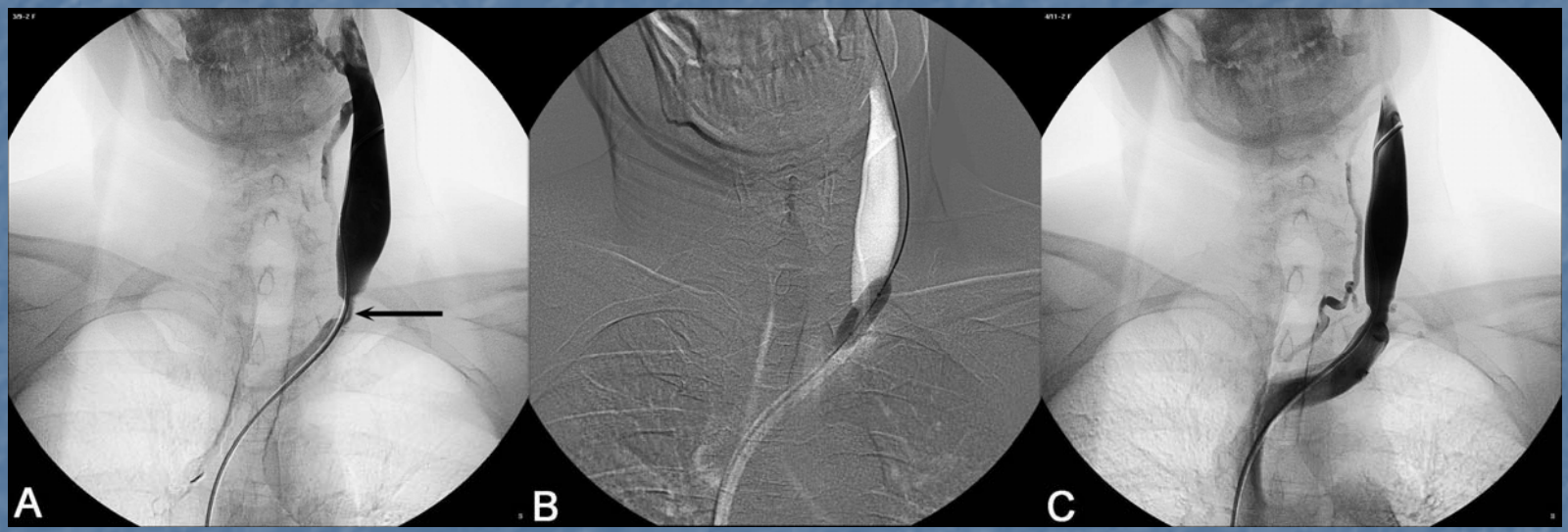
Putnam (1935). Studies in multiple sclerosis: encephalitis and sclerotic plaques produced by venular obstruction. Arch. of Neurol. and Psychiatry. 33: 929-940.

Vitamin D Deficiency and the Vascular System

- Vitamin D has been associated with a variety of cardiovascular diseases including atherosclerosis and increased hypertension.
- Nemerovski et al. Phamacotherapy 26; 691-708; 2009.

- "Vitamin D-deficiency has been associated with many systemic disorders, including infectious, inflammatory, and autoimmune conditions, cardiovascular disease, hypertension and atherosclerosis, neuromuscular function, cancer, neurodegenerative diseases, and neuropsychological and functional outcomes in the elderly population."
- Cekic and Stein. NeuroTherapeutics, 7; 81-90; 2010.

Paolo Zamboni and his team's direct angiographic proof



Severe stenosis of the jugular vein.

MULTIPLE SCLEROSIS

Imaging MS Patients with Ultrasound

Ultrasound (Dr. Zamboni's conditions) :

- Reflux constantly present in the IJV
- Reflux in the deep cerebral veins
- High resolution evidence of stenoses
- Flow not detectable in IJV or VV
- Decreases in IJV cross section when changing from sitting to supine

- Malfunctioning valves can be seen and
- Septal flaps (septum) can be seen.

MULTIPLE SCLEROSIS

Added value from MRI

- 3D structural information in the head and neck
- More than one stenosis can be seen in one sitting
- Numerous collaterals may be associated with MS
- Temporal information throughout the cardiac cycle across the entire cross section of the vessel is available for flow quantification
- Flow calculation easily performed for all vessels throughout the neck
- Monitor these changes pre and post treatment

MR Imaging

We propose a simple first pass protocol to include the following three scans for CCSVI:

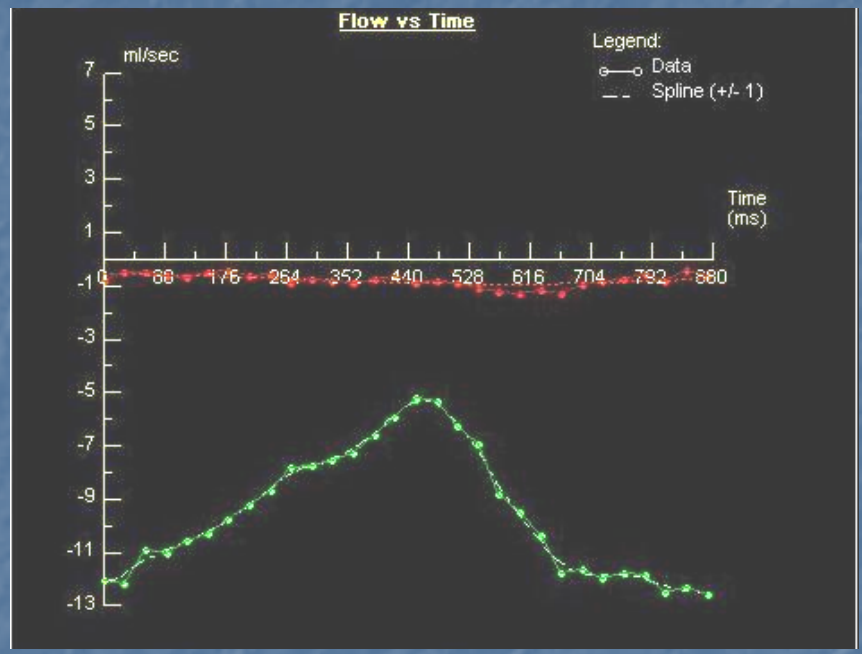
- ✓ ***Pre contrast 2D time of flight MRV***
- ✓ ***Post contrast time resolved MRA: to find the stenoses***
- ✓ ***Flow quantification: to find the abnormal fluid dynamics***

And for small veins and iron:

- ✓ ***3D SWI of the head and neck***

Please visit www.ms-mri.com for further details.

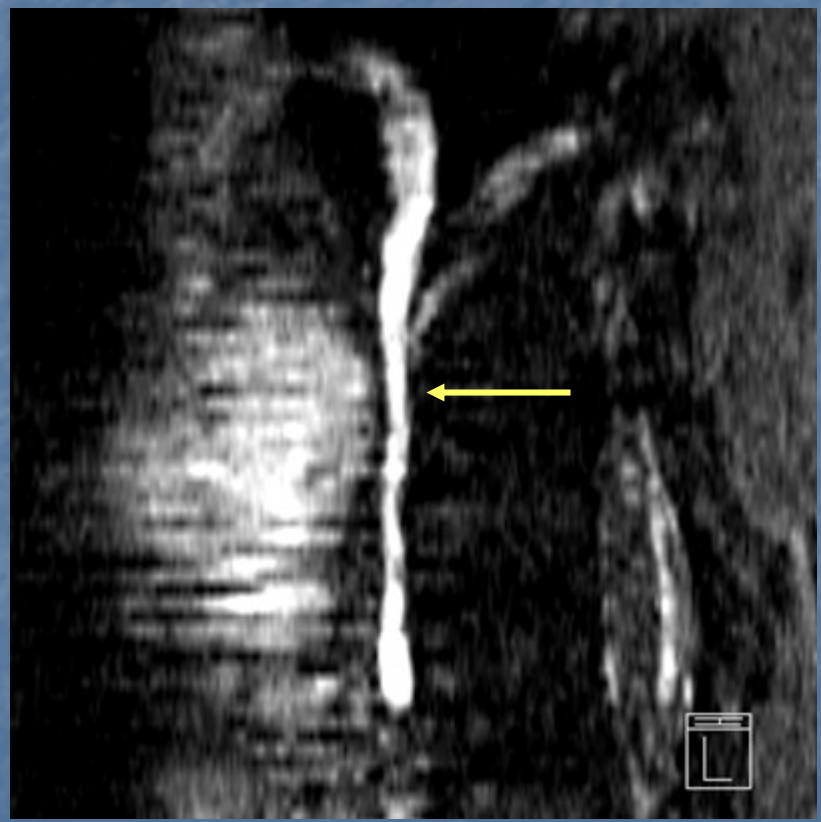
Time Resolved MRAV



Change in signal intensity suggests a vascular abnormality.

Flow is reduced in the right IJV.

2D TOF Imaging of the Azygous



Characterization of Lesions

- bone growth of the osteophyte from C1/C2 compressing the jugular
- ectatic carotid artery bifurcation angle causing compressed jugular
- long pencil like severe stenosis
- stenosis or occlusion of jugular veins
- stenosis or occlusion of vertebral veins
- stenosis or occlusion of azygous vein
- abnormal valves of jugular or brachiocephalic vein
- damaged vessel wall

The Hemodynamics of the Brain

- There is a great need to understand the fluid dynamics of the brain and how changes in flow affect the immunological system.
- One might consider calling this area of research:
  "vascular immunology"
- There are no textbooks that cover this topic nor one that covers a complete fluid dynamic study of the entire neurovascular system.
- Yet these studies have not yet been funded by federal sources because they have been considered too educational and not hypothesis driven. MS provides that hypothesis, but we should not have waited so long or we well might have discovered this source much earlier.

Implications of CCSVI on our understanding of the possible etiology of MS

- Stenoses leads to abnormal hemodynamics.
- Abnormal flow leads to endothelial damage.
- Vessel wall breakdown leads to local iron accumulation.
- Abnormal vessel wall with increased vesicles allows leakage of T cells and iron into surrounding tissue.
- Iron acts as an inflammatory agent exacerbating other effects of loss of vessel wall shear stress.
- Further breakdown of the microvascular system follows creating a pathology opposite to flow.
- Ischemic areas lose cerebral blood volume also from shunting of blood and atrophy of vessels.

Conclusions

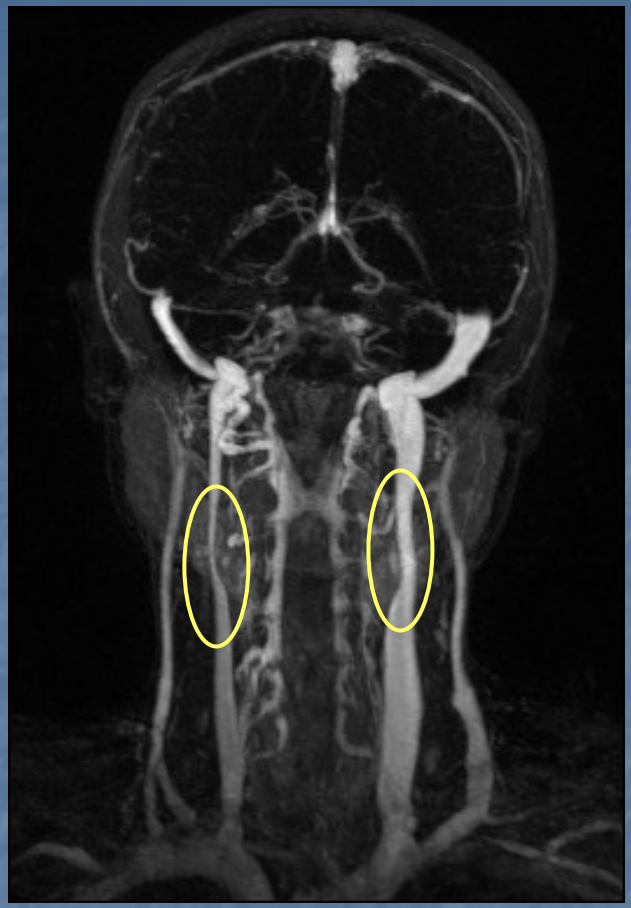
- MRI is a powerful means to collect 3D angiographic (both anatomical and functional) information.
- Ultrasound and MRI have the potential to screen MS patients for vascular abnormalities and should be both used.
- The venous system is very complex and flexible. Nevertheless, “multiple stenoses” even in the presence of collaterals which attempt to accommodate the required venous outflow may lead to major neurological problems.
- Knowing the vasculature of the head, neck and spine should lead to new methods of treatment and a better understanding of MS.

NICE AN International Database: We need rapid standardization

- Collecting an international database of imaging data should help characterize the various types of vascular abnormalities associated with MS and may also be a means by which to best determine who has the most serious form of vascular abnormalities for which something can be done.

- Creating such a database can be accomplished by a collective approach of contributing imaging data before and after treatment to NICE by private centers, hospitals and research centers to allow the collection of 10,000s of cases to characterize the types of vascular problems in MS.

- This would provide the fastest and most cost efficient means by which to investigate the role of CCSVI in MS.



How can we not image these MS patients who might have severe vascular abnormalities?

www.ms-mri.com

Acknowledgements

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