Toward understanding the association of Chronic Cerebrospinal Venous Insufficiency and Multiple Sclerosis

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Pathology of Multiple Sclerosis

Potential Triggers for MS

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

MS = multiple sclerosis
Chronic Cerebrospinal Venous Insufficiency (CCSVI) and Multiple Sclerosis

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

CCSVI

Normal

IJVs
IJVr
IJV
VVs
SVC
AZY
Vplex
IVC
L-REN

HAZY

AZY

IJVs
Multimodal Diagnostic Approach for Detection of Abnormalities in the Extra-Cranial Venous System

**Non-invasive**
- Doppler sonography (DS)
- Magnetic resonance venography (MRV)
  - TOF
  - TRICKS
  - Phase contrast
- Computerized tomography venography (CTV)

**Invasive**
- Catheter venography (CV) - gold standard
- Intraluminal ultrasound (IVUS)
Intra-luminal (inside) and Extra-luminal (outside) Structural and Functional Venous Abnormalities Determined

**Intra-luminal structural abnormalities:**
- Web
- Flap
- Septum
- Membrane
- Malformed valve

**Extra-luminal structural abnormalities:**
- Stenosis
- Annulus

**Functional abnormalities:**
- Reflux/bidirectional flow
- Paradox
- No flow

**Collateral circulation:**
- Presence of collaterals
- Number of collaterals

**Intra-luminal structural abnormalities:**
- 70% of multiple sclerosis (MS) pts and 50% of healthy controls (HC) on DS
- No difference between progressive and non-progressive MS
- MRV and CTV have no resolution
- IVUS and CV confirmatory

**Extra-luminal structural abnormalities:**
- 25% of MS pts and 15% of HC on DS
- 35% of MS and 25% of HC on MRV
- 50% of progressive and 25% of non-progressive MS on MRV
- No data between MS and HC on CV
- IVUS confirmatory

**Functional abnormalities:**
- 55% of MS pts and 35% of HC on DS
- 60% of progressive and 55% of non-progressive MS
- MRV flow techniques
- CV and IVUS role

**Collateral circulation:**
- 90% of MS and 90% of HC have ≥1 collateral vein
- Mean of 2.5 in MS pts vs 2.1 in HC on MRV
- No difference in progressive vs. non-progressive MS
- CV, IVUS and DS role
43-year-old female MS patient

Shows a normal exam on 2D Time-of-Flight venography (TOF) (a) and 3D-Time Resolved Imaging of Contrast Kinetics (TRICKS) (b) of both internal jugular veins (IJV) pre-treatment. Doppler sonography (DS) (c) shows presence of a septum in the right IJV (upper image) and annulus in the left IJV (lower image). Catheter venography (CV) (d) confirms presence of a septum in the right IJV and annulus in the left IJV. The post-treatment, 6-month follow-up shows a normal examination on TOF (e) and TRICKS (f) and DS (g).
Origin of the Venous Anomalies

**Congenital**
- Truncular (embrionic) malformations
- Physiological

**Acquired**
- Aging related
- Inflammation
- Related to flow abnormalities at periphery
- Related to flow abnormalities in the central nervous system

Congenital vs. acquired (longitudinal studies needed)
Establishing “Association”

Is the risk of MS significantly higher or lower than normal based on the presence or level of CCSVI?

- Observational study designs, (e.g., multi-model diagnostic studies—which are used to understand associations—do not include interventions.
- Interventional study designs (e.g., our CCSVI Treatment Study) can help us understand causality.
Establishing “Association”

Is the risk of MS significantly different than normal based on the presence or level of CCSVI?

- Many with CCSVI have no MS
- Many with MS have CCSVI
- Some without CCSVI have MS

CCSVI is neither necessary nor sufficient for MS
Our findings

Establishing “Association”

- Many with CCSVI have no MS
- Many with MS have CCSVI
- Some without CCSVI have MS

**CCSVI is neither necessary nor sufficient for MS**

Yet an association still exists as long as the two proportions (MS with and without CCSVI) are very different; specifically, a higher percentage of MS patients have CCSVI than do not and those have more frequently progressive disease course.
One of the proposed theories

Hypothesis for Role of CCSVI in 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
- T cell activation
- Multiple Sclerosis

BWG
Establishing “Causality”...

<table>
<thead>
<tr>
<th>Bradford Hill criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength of association</td>
<td>Is the prevalence of the presumed cause relatively high compared to the prevalence of the effect?</td>
</tr>
<tr>
<td>Consistency</td>
<td>Have similar results been shown in other studies?</td>
</tr>
<tr>
<td>Specificity</td>
<td>Does the presumed cause lead to a specific effect?</td>
</tr>
<tr>
<td>Coherence</td>
<td>Is the association compatible with existing theory and knowledge?</td>
</tr>
<tr>
<td>Temporality</td>
<td>Does the presumed cause precede the effect?</td>
</tr>
<tr>
<td>Exposure-response</td>
<td>Is increased/decreased exposure to the presumed cause associated with a corresponding change in effect?</td>
</tr>
<tr>
<td>Biological plausibility</td>
<td>Is there a reasonable postulated biologic mechanism linking the possible cause and effect?</td>
</tr>
<tr>
<td>Experiment</td>
<td>Can the effect be altered by experiment?</td>
</tr>
<tr>
<td>Analogy</td>
<td>Are there other, parallel, well-established cause-effect relationships?</td>
</tr>
</tbody>
</table>

— **Bradford Hill criteria**

These criteria were originally presented by Austin Bradford Hill (1897-1991), a British medical statistician as a way of determining the causal link between a specific factor (e.g., cigarette smoking) and a disease (such as emphysema or lung cancer). Outline the minimal conditions needed to establish a causal relationship between two items.
Establishing “Causality”...

<table>
<thead>
<tr>
<th>Strength of association</th>
<th>56.1% in MS patients, 42.3% in those with other neurologic diseases (OND), 38.1% with clinically isolated syndrome (CIS) and 22.7% in healthy controls; potential statistical issues will be addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency</td>
<td>Clinical, MRI and other studies have not produced similar results</td>
</tr>
<tr>
<td>Specificity</td>
<td>Prevalence in healthy people and also other neurological diseases</td>
</tr>
<tr>
<td>Coherence</td>
<td>The central tension in this debate</td>
</tr>
<tr>
<td>Temporality</td>
<td>Not established, even among pediatric cases</td>
</tr>
<tr>
<td>Exposure-response</td>
<td>The severity of CCSVI (venous hemodynamic insufficiency severity score, VHISS) was associated with the increased brainstem disability, as measured by Expanded Disability Status Scale ($p = 0.001$) and trends were found for the pyramidal, cerebellar and sensory sub-scores</td>
</tr>
<tr>
<td>Biological plausibility</td>
<td>Dr. Zamboni may be credited with a plausible hypothesis, yet there are equally plausible alternative explanations (e.g., aging, inflammation).</td>
</tr>
<tr>
<td>Experiment</td>
<td>We have observed no “miracles”... no modification in the disease... only temporary quality of life benefits.</td>
</tr>
<tr>
<td>Analogy</td>
<td>Little is known about CCSVI and disease.</td>
</tr>
</tbody>
</table>
Jugular vein reflux in elderly

- 349 subjects (55.60 ± 17.49,16 to 89 y; 167 M/182 F)
- With increasing age
  - increased lumen area
  - decreased time-averaged mean velocity of bilateral IJV
  - decreased proportion of total flow volume, drainage in the left IJV
  - Increased frequency of left jugular venous reflux (JVR)

- 97 persons (aged 55–90 years, mean [standard deviation]: 75.77 [8.19] years; 55 men) from a medical center memory clinic
  - MRI (1.5T) and the semiquantitative Scheltens scale were used to investigate the severity of white matter changes
  - Subjects were classified into 3 groups (no, mild, and severe jugular venous reflux) by duplex ultrasonography

- People with severe JVR exhibited more severe age-related white matter changes, especially in caudal brain regions
- Age-dependent JVR effects on the severity of age-related white matter changes were demonstrated
Pathology of Multiple Sclerosis

Potential Triggers for MS

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

CCSVI

MS = multiple sclerosis
Association of CCSVI and MS

- CCSVI and clinical findings in MS
- CCSVI and genetic findings in MS
- CCSVI and MRI findings in MS

- Other more risk factor association studies are underway
The PREMiSe Study

- To test for the existence of CCSVI by using myriad diagnostic imaging tools.
- To test the safety and effects of treatment with balloon angioplasty on MS disease course and progression via a double blinded randomized design.

Prospective Randomized Endovascular therapy in Multiple Sclerosis

- IRB Approved
- A multidepartmental interdisciplinary collaboration between Neurology, Neuroimaging and Vascular Neurosurgery
- Funded by Kaleida Health (Parent Hospital Partner), Volcano Corp, Ev3 Corp, Codman Corp, Direct MS Foundation, smaller donors.
- No physician reimbursement, no professional fees associated
Prospective Randomized Endovascular therapy in Multiple Sclerosis (PREMiSe) study

Study Locations

- **CTV and CTP**
  Kaleida Health Millard Fillmore Gates Circle facility
- **MRI/MRV acquisition**
  Buffalo Niagara MRI Center of Kaleida Health in Buffalo General Hospital
- **Selective venography & balloon angioplasty**
  Kaleida Health Millard Fillmore Gates Circle facility (UB Neurosurgery)
- **Phase I (10 RRMS)**
- **Phase II (20 RRMS)**
- **Image analysis**
  Buffalo Neuroimaging Analysis Center (BNAC)
- **Sonography**
  Buffalo Neuroimaging Analysis Center (BNAC)
- **Clinical examination**
  Baird MS Center Jacobs Neurological Institute
Prospective Randomized Endovascular therapy in Multiple Sclerosis (PREMiSe) study

Study Population

**Inclusion criteria**

- Age 18-65 years
- EDSS 0-5.5
- Diagnosis of relapsing-remitting MS according to the McDonald criteria (Polman et al., 2005)
- Be on treatment with currently FDA approved disease-modifying treatments excluding Tysabri (Natalizumab)
- Evidence of ≥2 sonographic parameters of suspicious abnormal extra-cranial cerebral venous outflow
- Normal renal function: creatinine clearance level of >60

**Exclusion criteria**

- Relapse, disease progression and steroid treatment in the 30 days preceding study entry
- On Tysabri therapy
- Pre-existing medical conditions known to be associated with brain pathology
- Severe peripheral chronic venous insufficiency
- Abnormal renal function
- Severe contrast allergy (anaphylaxis)
- Not accepting to undergo the endovascular treatment
Prospective Randomized Endovascular therapy in Multiple Sclerosis (PREMiSe) study

Phase I (10 pts) — Completed. No safety issues.

Phase II (20 patients)

Visit, LAB, AE, MRI, Doppler, EVT

0-30 days

0–180 days
Prospective Randomized Endovascular therapy in Multiple Sclerosis (PREMiSe) study

Study Objectives

1. To assess the safety of endovascular therapy (balloon angioplasty) for venous stenoses in MS patients with CCSVI as documented by sonographic (extracranial echocolor-Doppler (ECD) and transcranial color Doppler (TCD)
2. To study the morphology of the venous anomalies by using intraluminal ultrasound (IVUS).
3. To evaluate preliminary efficacy of endovascular therapy (angioplasty) as measured by clinical (relapse rate, disability progression (EDSS), sonographic (ECD/TCD) and MRI/MRV parameters.
4. To evaluate change in patients self-reported QOL following the therapeutic angioplasty
5. To evaluate whether changes in QOL, fatigue, MSFC, cognitive assessments (BVMTR, SDMT) or attention following therapeutic angioplasty are associated with brain changes as measured by functional MRI (fMRI).
6. To evaluate changes in retinal nerve fiber layer (RNFL) thickness by using optical coherence tomography (OCT).
Prospective Randomized Endovascular therapy in Multiple Sclerosis (PREMsiSe) study
Prospetive Randomized Endovascular therapy in Multiple Sclerosis (PREMiSe) study

Treatment Outcomes

**Primary**

1. Percent (%) of patients with Severe Adverse Events (SAE) measured at 24 hours (Immediate) and 1 month (Short term) post-surgical safety outcome in MS patients diagnosed with CCSVI that underwent therapeutic angioplasty
Treatment Outcomes

Secondary

1. Restoration of venous outflow (to 75% or better from the normal outflow) as measured by the combined ECD/TCD and MRV at 1, 3 and 6 months following the angioplasty as compared to baseline as well as compared to a parallel control group of MS patients that will undergo only selective venography without balloon angioplasty (sham angioplasty).

2. Change in clinical (relapse rate and disease progression) measured with Kurtzke Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC) (at 1, 3 and 6 months), will be compared to baseline as well as to the change seen in the parallel control group of MS patients that will have only a selective venography (sham angioplasty).

3. Change in radiographic disease progression based on brain MRI parameters at 1, 3 and 6 months will be compared to baseline as well as to the change seen in the parallel control group of MS patients that will have only a selective venography (sham angioplasty).
Tertiary

1. Patient self-reported quality of life as measured by general QOL questionnaires (MSQOL-54) and specific MS fatigue questionnaires (the Fatigue Severity Scale (FSS)), as well as the general patient impression of status change including (Beck Depression Inventory Fast Screen (BDIFS), and MS Neuropsychological Screening Questionnaire (MSNQ), Cognitive assessments including Single Digit Modalities Test (SDMT), and Brief Visuospatial Memory Test Revised (BVMTR). The SDMT and BVMTR will be completed at baseline, 1 and 6 months. All other questionnaires will be completed at baseline 1, 3 and 6 months by all patients and will be compared to changes seen in the parallel control group of MS patients that will have only a selective venography (sham angioplasty).

2. Assess the feasibility of 4D CT venogram (CTV) and CT Perfusion (CTP) with assessment of mean transit times using a 320-slice CT scanner and comparison with Doppler in detecting patients with venous stenosis and as a tool for assessing CCSVI before and after endovascular therapy at baseline and at 1 month post therapy in all patients with angioplasty or sham-angioplasty.
3. Brain fMRI parameters using an Attention Task Visual Task at 1 and 6 months will be compared to baseline as well as to the change seen in the parallel control group of MS patients that will have only a selective venography (sham angioplasty).

4. Blood draw (45cc) in serum, EDTA, and CPT tubes at baseline and then at 1, 3 and 6 months for all patients for potential immunologic marker or genetic studies in the future.

5. Change in RNFL thickness at baseline, 1, 3 and 6 months by using OCT.

6. Measurement of manometric venous pressures above and below lesions using manometer and pressure sensitive wire (RIJ, LIJ, Azy)

7. Measurement of pre and post (plasty vs sham) venous blood gas for each vessel (RIJ, LIJ, Azy)
Sealed and numbered envelopes with pre-stated treatments (sham vs angioplasty) are opened upon initiation of selective venography.

Patients are consciously sedated using Fentanyl and Versed intravenously till they are no longer actively conversing, yet are easily arousable when spoken to.

Relatively loud music of patients choice is played so that procedural conversation is inaudible.

The operating room staff is acutely aware of blinding requirements and has been trained to avoid any loud procedure related conversation.

The X-ray shields are covered with opaque sterile covers to avoid glancing by patients.

The monitors are angled to avoid any incidental visualization by patient.

All patients receive a rigorous sternal rub (painful stimulus) upon insertion of angioplasty balloon regardless of inflation.

A blindness assessment survey is administered the following morning prior to discharge.
Prospective Randomized Endovascular therapy in Multiple Sclerosis (PREMiSe) study

Intent to Treat (ITT)

- Endovenous balloon dilatation (EVBD) will be performed on MS patients with significant stenoses in the main extra-cranial cerebro-spinal out-flow routes
- Selective direct venography (phlebography) to verify a cranial venous outflow obstruction caused by an obstructive venous malformation at or above the thoracic level
- Significant stenosis is defined as luminal reduction greater than 50% of normal proximal venous diameter or a significant flow disruption
- Upon confirmation a non-compliant balloon with nominal diameter at least 80% of the proximal vein (of interest) will be placed across the stenosis and inflation will proceed slowly
- The goal is to restore the venous outflow stricture to at least 75% of normal proximal venous diameter and resolve flow disruption and pressure gradient
- Additional angioplasties will be performed if needed

- Post-surgery observations and medications
  - All patients will be started on Aspirin 325mg 5 days before procedure and remain on it for 21 days post procedure
  - All patients will remain of subcutaneous Lovenox 1mg/kg once a day (Prophylactic dose) for 21 days post procedure
Data Safety Monitoring Board

- Four physicians, two neurologists, a biostatistician and a neurosurgeon not involved in the study will meet quarterly to evaluate the study safety data.

Study Discontinuation

- The PI will continuously monitor the AE and the study will be stopped if the percentage of SAE exceeds 20% at any time point.
- The AEs will be constantly reported to the IRB and the DSMB.
Prospective Randomized Endovascular therapy in Multiple Sclerosis (PREMiSe) study

Progress

Phase I: Completed

- 10 RRMS diagnosed with CCSVI based on Zamboni criteria
- Baseline physical and neurological evaluation (EDSS, MSFC); brain MRI (including fMRI, cervical MRV, CTV and CTP; questionnaires)
- Selective Venography followed by balloon angioplasty procedure within 30 days from baseline evaluations
- Reassessed at 1 month after angioplasty with physical exam, AE assessment, ECD/TCD, MRV, CTV and CTP, MRI (including fMRI)
- 3 and 6 months AEs will be recorded and patients evaluated with clinical (EDSS, MSFC), QOL questionnaires, Doppler (ECD/TCD), cervical MRV and MRI of the brain (fMRI will be performed only at the 6 month time point).
Progress

Phase II: Recruiting

• Upon completion of Phase I with an acceptable AE profile (assessed upon completion of 30 days post procedure evaluation of the last patient) IRB and DSMB review was requested.

• We received approval to proceed with a second cohort of 20 RRMS diagnosed with CCSVI which are being enrolled.

• Patients are being randomized to one of the 2 arms:
  – Active arm: Selective Venography followed by therapeutic balloon angioplasty
  – Control arm: Venography and sham angioplasty. Patients are being assessed and followed in a similar schedule as the patients from Phase I (Safety) study.
Avoiding Other Research Pitfalls of

**Chance, Bias, and Confounding**

We have taken extraordinary measures in a climate of keen interest and controversy

**Financial disclosure** – American College of Physicians’ standard of transparency

**Transparency** – Funded through independent contributions, supplemental patient contributions, and internal resources

**Peer Review** – Prior to publication, agreements are signed

**Audited data** – Independent audit, beyond typical requirements of research like this

**Responsibly acknowledge doubt** – Real answers are necessarily obscured by many confounding factors.
All Play Important Roles

**We must** restrict our activities to comply with ethical, legal, medical, and practical constraints

**We cannot recommend treatment** – We are pursuing placebo-controlled studies

**We cannot engage in an Internet debate** – Conventional, legal agreement with the study publisher limits our dialogue to their forum, however we are more than open to discuss from time to time our findings in educational programs like today

**We must adhere to our mission** – Our purpose is research. Our pursuit is truth in whatever direction it will take us.
The Value of the Work

The Value of Truth

Patients – We are advancing knowledge... the surest path to cures
Funders – We are moving our understanding and the debate forward
Researchers – We are working transparently and collaboratively
Clinicians – We are providing honest, reliable guidance

We are opening new doors and more fruitful paths...
Two Important Inquiries Ahead

Understand *why* CCSVI is associated with MS

Understand CCSVI as a general medical condition and its association with other disease types
Enriching, not abandoning the pursuit of a cure for MS

Understanding Association

Harboring no “favorite” conclusion regarding CCSVI and MS; simply seeking greater understanding

Planning new studies to explain the mysteries of now-established association
Combined Transcranial and Extracranial Venous Doppler Evaluation in Multiple Sclerosis and Related Diseases

Zivadinov et al. Neurology, 2011
1,000 subjects (500 subjects already recruited in phase 1 and 500 subjects to be recruited in phase 2)

CTEVD Study Population (821 enrolled by April 1, 2011)

- 30 Pediatric MS
- 50 CIS
- 20 RIS
- 450 Adult CDMS
  - 250 RRMS
  - 100 SPMS
  - 30 PPMS
  - 20 NMO
- 200 Adult Healthy and Familial Controls
- 100 Pediatric Healthy and Familial Controls
- 75 CNS Autoimmune-Vascular Disorders
  - SLE
  - PALP
- 75 CNS Neurodegenerative Disorders
  - AD
  - PD
  - Epilepsy
- 50 CIS
- 20 RIS
- 30 Pediatric MS
- 100 Pediatric Healthy and Familial Controls
- 75 CNS Autoimmune-Vascular Disorders
  - SLE
  - PALP
- 75 CNS Neurodegenerative Disorders
  - AD
  - PD
  - Epilepsy
Immediate Research Questions

- What is the best screening non-invasive diagnostic tool for CCSVI diagnosis in MS?
- Should MS patients with negative CCSVI screening pursue further invasive diagnostic testing?
- Role of endovascular treatment and disease outcomes
- Explore relationship between MRI hemodynamic measures and CCSVI
- Longitudinal clinical, MRI, genetic and immunologic studies in relation to CCSVI

CTEVD and PREMISE may answer most of these questions
Our deepest gratitude...

Thank you.

We would like to express our deepest appreciation to the patients, donors, staff, university partners, preceding and collaborating researchers, peers...

...And, yes, to the bloggers, the tweeters, the readers, the listeners, and the countless others who continue to make our work possible, challenging, and rewarding.
Questions

Blinding in CTEVD Phase 1 and Phase 2

- Instructing subjects not to reveal their disease status during examination
- Including patients with no disability or walking difficulties to ensure blinding between nondisabled patients and both healthy and non-healthy controls
- Including patients with substantial disability, but no diagnosis of MS, who presented with problems similar to those of patients with MS
- By using an ultrasound technologist unfamiliar with the signs and symptoms of either MS or other neurologic diseases
- Positioning of the subject by non-ultrasound personnel and covering of the subjects in Phase 2

Unblinding of the CTEVD subjects

- Multimodal confirmation studies; CTEVD phase 2; follow-up study
Questions

How was prevalence determined in the study groups?
- Negative vs. positive for CCSVI
- Borderline cases included in the negative CCSVI group
- One VH criteria positive

Why were there borderline cases (VH criteria 2 in 52 subjects)?
- Technical issues (artifacts, no visualization)
- Reproducibility of VH criteria 2 is questionable

Why were borderline cases included in the negative group?
- Conservative approach

Why did we include familial healthy controls?
- To study familial relationship
- No difference between familial (48) and non-familial (115) healthy controls
Questions

What are pediatric prevalence data suggesting?
- These are not patients at first clinical onset; 50% were negative; other pediatric healthy controls also presented with CCSVI

How did we interpret our data with respect to causality vs. association?
- Non-primary role of CCSVI in development of MS can be established

Is CCSVI a result of MS?
- It can be not excluded that CCSVI is contributor to MS progression
- It can be not excluded that CCSVI is a consequence of MS progression

We are open to other suggestions and future findings