Chronic Cerebrospinal Venous Insufficiency

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Multiple Sclerosis

• Conventional wisdom
  – A relatively common disease of the central nervous system, with a prevalence of about 1 in 1000, affecting women more often than men, and onsetting usually between 20 and 50 (occasionally 5 – 65)
  – Autoimmune illness, with important environmental and genetic predisposing factors. The trigger for the immune problem not clear, but various viruses are the commonest suspects.
  – Results in activated T and B lymphocytes producing antibodies and inflammatory products called cytokines which result in inflammation then demyelination of the nerve pathways
MS is an Inflammatory Demyelinating Disease of the CNS

1. Immune cells pass through blood-brain barrier
2. Immune cells may re-activate and produce cytokines
3. Immune cells mount autoimmune attack against myelin

Multiple Sclerosis

– The actual nerve fibre or axon is also affected eventually, and now realize that there is a degenerative as well as an inflammatory/demyelinating aspect to MS

– Clinical course is very variable
  • Several subtypes or clinical courses are possible
Clinical Course of MS

Relapsing remitting (RR)

Secondary progressive

Primary progressive

Benign form of RR

Secondary progressive

Progressive relapsing
Current Treatments

• We have made headway in the last 17 years, and there are now 6 disease modifying therapies available.

• Our current treatments reduce total # of attacks by ~ 1/3 and more severe attacks by ~ ½. Reduce # of new lesions seen with MRI. Reduce progression of disability.

• But clearly there is a great need for better options: current treatments do not eradicate progression, side effects can be a problem, and patients with sustained progression don’t seem to benefit from our current therapies.
Veins and MS

• Demyelinating plaques and inflammation are predominantly situated around veins in the CNS
• Tracy Putnam
• Noted plaques of demyelination adjacent to veins in MS and post-infectious encephalomyelitis.
• Produced an animal model of demyelination in dogs by injecting tetanus toxoid into blood.
• Has little to do with current understanding of MS but does highlight that unwanted substances can start in the veins and eventually cause demyelination.
Iron in MS

- Recent developments in MRI scanning allow us to measure the iron content in the living brain (SWI)
- Some evidence of increased iron content in the deep nuclei of the brain in MS patients
- This is not all specific to MS, as it is reported in Parkinson’s and several other movement disorders with symptoms much different from MS
MRI in MS
Evidence of an increase in basal ganglia and thalamic iron content in multiple sclerosis and its vascular implications; courtesy Dr Mark Haake
Iron in pulvinar nucleus of the thalamus
CCSVI

• Zamboni, extrapolating on some earlier suggestions by others, postulated that the iron is the result of backup of blood in the draining veins, which are defective or partially blocked, and this leads to leakage of blood products (including iron in hemoglobin) across the veins into the tissues; and also may play a role in the inflammation centred about veins.
Overall the odds of having an ultrasound abnormality in 2 or more parameters was 43 times higher in MS pts than in normal controls.

### Table 1  Clinical and demographic characteristics of clinically defined multiple sclerosis (MS) patients

<table>
<thead>
<tr>
<th></th>
<th>Whole MS no = 65</th>
<th>MS relapsing-remitting no = 35</th>
<th>MS secondary progressive no = 20</th>
<th>MS primary progressive no = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41 (34 to 48)</td>
<td>35 (29 to 41)</td>
<td>45 (42 to 52)</td>
<td>58 (46 to 60)</td>
</tr>
<tr>
<td>Sex: percentage male, male/female</td>
<td>46%, 30/35</td>
<td>46%, 16/19</td>
<td>45%, 9/11</td>
<td>50%, 5/5</td>
</tr>
<tr>
<td>EDSS</td>
<td>2.5 (1 to 5)</td>
<td>1.5 (0.5 to 2)</td>
<td>5 (3.5 to 6.5)</td>
<td>4.3 (3 to 6.5)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>6 (3 to 13)</td>
<td>4 (1 to 7)</td>
<td>13 (6 to 21)</td>
<td>10 (5 to 14)</td>
</tr>
</tbody>
</table>

### Table 3  Transcranial and extracranial colour-Doppler high-resolution examination (TCCS-ECD) criteria of highly suspected anomalous venous outflow

<table>
<thead>
<tr>
<th>TCCS-ECD criteria</th>
<th>MS-relapsing-remitting (N; %)</th>
<th>MS-secondary progressive (N; %)</th>
<th>MS-primary progressive (N; %)</th>
<th>Whole MS (N; %)</th>
<th>Control populations (N; %)</th>
<th>Odds ratio all MS vs all controls (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reflux constantly present in IJVs and/or VVs with the head at 0° and +90°</td>
<td>27/35 77%</td>
<td>15/20 75%</td>
<td>4/10 40%</td>
<td>46/65 71%</td>
<td>0/235 0%</td>
<td>1123 (67 to 19 000)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2. Reflux in the deep cerebral veins</td>
<td>19/35 54%</td>
<td>12/20 60%</td>
<td>9/10 90%</td>
<td>40/65 61%</td>
<td>0/235 0%</td>
<td>748 (45 to 12 542)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3. High resolution B-mode evidence of proximal IJV stenoses</td>
<td>9/35 26%</td>
<td>10/20 50%</td>
<td>5/10 50%</td>
<td>24/65 37%</td>
<td>1/235 0%</td>
<td>137 (18 to 1041)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4. Flow not Doppler detectable in the IJVs and/or VVs despite numerous deep inspirations with the head at 0° and +90°</td>
<td>22/35 63%</td>
<td>7/20 35%</td>
<td>5/10 50%</td>
<td>34/65 52%</td>
<td>7/235 3%</td>
<td>36 (15 to 88)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5. Negative △CSA in the IJV</td>
<td>18/35 51%</td>
<td>13/20 65%</td>
<td>5/10 50%</td>
<td>36/65 55%</td>
<td>25/235 11%</td>
<td>10 (5 to 20)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

OR was calculated for each ultra-sonographic criterion by means of the two-sided Fisher exact test, by comparing the whole MS population with the control group. CSA, cross-sectional area of the internal jugular vein; IJV, internal jugular vein; MS, multiple sclerosis; VV, vertebral vein.
CCSVI

- Zamboni also reported initial results of interventions (J Vasc Surg; Dec 09)
- Same 65 patients. 35 RR (mean duration 4 yrs), 20 SP (mean duration 13 yrs), 10 PP (mean duration 10 yrs). EDSS 0 – 6.5 (ie asymptomatic up to moderately severe disease (needing a walker))
- Mean follow up only 18 months
- Underwent balloon catheter dilation of stenosed segment (balloon angioplasty)
CCSVI

• Complications relatively mild and infrequent
• Pressure across stenosed region decreased after treatment.
• Maintained patency in only 53% of internal jugular veins treated, versus 96% in azygous veins.
• RR pts: relapse free in 50% vs 27% pre-op (But annual attack rate not significantly lower)
  Gad +ve MRI lesions in 12% vs 50% pre-op
• MSFC (disability score) improved at 18 mths post-op in RR but not in SP or PP pts
CCSVI

• Caveats re CCSVI
  – Relatively small number of patients, at this point, so needs to be corroborated
  – If validated, we don’t know whether this is cause or effect of MS. The hypotheses about venous backpressure triggering inflammation are just hypotheses at this point

• Caveats re “Liberation Treatment”
  – Small number of pts, and short follow up
  – Regression to the mean (pts enter study after period of unusual excessive disease activity; often returns to more normal levels on its own, even without treatment). This is one reason why you need a control group that receives no active treatment.
  – Lack of blinding of evaluators
  – Lack of blinding of pts (placebo effects)
Placebo Effects

Avonex in RR MS

Annual Relapse Rate

Natalizumab in RR MS

Annual Relapse Rate

Why don’t we just start treating?
Why Don’t We Just Start Treating?

• The past gives us many examples of breakthrough treatments that haven’t panned out
  – hyperbaric oxygen
  – bee stings
  – removing mercury amalgam fillings
  – procarin patch
  – low dose naltrexone (LDN)

• This is most easily avoided by doing proper studies before exposing people to new treatments and potential complications
Proposed Study

• Start out by trying to replicate Zamboni’s observations and see if any abnormalities found (venous problems and iron levels) correlate with the duration of MS, type of MS, severity of MS, location of MS lesions, age, sex

• We propose to study 100 MS patients and 100 age and sex-matched controls.
  – Subjects will have MRI scan, MR venogram, MRI SWI images (for iron) and ultrasound