Veno-Occlusion in Multiple Sclerosis

Zamboni et al\textsuperscript{1}, recently reported a cohort of patients with MS with ultrasonographic stenoses of the veins draining the head and neck, reflux in these vessels and abnormalities in the postural down flow from the IJVs and vertebral veins (VVs). They stated that after percutaneous transluminal angioplasty (PTA) of the stenosed veins in patients with early stage disease, clinical and Quality of Life (QOL) parameters were significantly improved when compared with preoperative assessments. Zamboni then drew parallels with iron-dependent inflammation in venous disease and the microvascular abnormalities seen in 7-Tesla MRI in MS patients. His hypothesis is that venous obstruction and reflux causes loss of integrity of the blood-brain barrier, iron deposition, inflammation and demyelination. A similar hypothesis was proposed in 1935 by Putnam\textsuperscript{2}. Using Zamboni's criteria, a large number of MS patients show evidence ultrasonographically of "Chronic Cerebrospinal Venous Insufficiency" (CCSVI). The Australian MS community has subsequently sought PTA as a means of symptomatic relief and since neurologists do not give any credence to this theory, significant controversy and conspiracy theories of conflict of interest with "Big Pharma" have occurred.

Normally the size of the internal jugular veins in the neck vary from side to side, with the left being much smaller than the right, and also with position. When a person is erect the internal jugular vein empties almost completely while the vertebral veins remain filled.

Many patients with MS have either stenosis or occlusion of the internal jugular vein with a supine angiographic pattern similar to that seen in the erect position normally. Stenosis of the inferior jugular valve is also common. Angiographic demonstration of reflux in our experience is much less common but extreme venous reversals may occur.

Since patients without MS who have symptomatic stenosis or occlusion of the jugular or subclavian veins are offered PTA, we performed PTA on an unselected cohort of patients with MS who presented with an ultrasound examination demonstrating 2 or more of Zamboni’s 5 criteria of CCSVI.

A total of 36 patients with MS underwent venography, with an age range of 22 to 67 years, mean age of 43 years and median age of 41 years. There were 19 females and 17 males. No selection was made on the basis of MS type or severity. After informed consent a MSQOL-54 questionnaire similar to the one Zamboni used was completed by the patient before returning for angiography. The angiography included both internal jugular veins and the azygos vein in the supine position with and without breath hold. In most cases a partner or carer was permitted to observe the procedure from the control room. After the procedure the patient was given 100mg Aspirin orally and a second MSQOL-54 questionnaire was completed at one month post procedure. Existing MS medications were continued.

Zamboni described 5 patterns of abnormality identified as A through D depending on which combination of veins was affected.
• **Type A** pattern is characterised by significant stenosis of
  o the proximal azygous vein; or
  o one of the two internal jugular veins, with a compensatory contralateral internal
  jugular vein that appears enlarged
• **Type B** pattern is characterised by significant stenoses of both internal jugular veins
  and the proximal azygous vein.
• **Type C** pattern is characterised by bilateral stenosis in both internal jugular veins,
  with a normal azygous vein.
• **Type D** pattern is characterised by multi-level involvement of the azygous and lumbar
  systems.

In our cohort 11 patients were Group A, 8 were Group B, 14 Group C, 1 group D and 2
showed no angiographic abnormality. Jugular valve stenosis was the most common finding
(61% Left and 41% Right), 42% demonstrated a jugular vein stenosis just below the superior
bulb, 33% showed a segmental occlusion of the right internal jugular vein and 28% showed
an azygos vein stenosis. A long stenosis or hypoplasia of the internal jugular vein was seen in
14% (8% Left and 6% Right).

Although there was good correlation between an abnormal ultrasound and the presence of
angiographic abnormality, the exact site of stenosis or occlusion correlated poorly.

Angioplasty was performed with high-pressure balloons of a size relative to the vein above
and below the stenosis. For upper stenoses, the diameter of the sigmoid sinus was used as an
index of size.

**Quality of Life outcome**

<table>
<thead>
<tr>
<th></th>
<th>Pre-Angioplasty</th>
<th>1 month followup</th>
<th>Difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental QOL</td>
<td>55.41 (3.84)</td>
<td>74.96 (3.00)</td>
<td>19.88 (3.93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physical QOL</td>
<td>41.12 (2.87)</td>
<td>61.39 (3.51)</td>
<td>20.36 (3.07)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Overall QOL</td>
<td>51.08 (3.04)</td>
<td>62.24 (3.69)</td>
<td>11.33 (3.53)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

QOL values are given as the mean (standard error)

The MSQOL-54 instrument generates 12 subscales along with two summary scores, and two
additional single-item measures. The subscales are: physical function, role limitations-
physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions,
social function, cognitive function, health distress, overall quality of life, and sexual function.
The summary scores are the physical health composite summary and the mental health
composite summary. The single item measures are satisfaction with sexual function and
change in health.

The answers to the questionnaires are used to calculate a **physical health score** and a **mental
health score**. Each are derived from a weighted combination of scale scores. The scores are
also scaled and combined to form an **overall quality of life score**. The best possible score is
The most common change commented on by patient and carer alike was improvement in concentration and energy.

Ultrasound was repeated if the patient's symptoms recurred to pre-PTA levels and subsequent angiography showed recurrence of stenosis in 44% of patients overall. In 38% of patients with recurrence of symptoms, the restenosis occurred at 3 months. Further angioplasty was performed, with in most cases, a similar response to the first angioplasty. No patient has been returned completely to normal. One venous dissection occurred with the second PTA and three patients progressed from a severe stenosis to impassable occlusion after the first PTA.

One patient developed a severe MS relapse one week after her first PTA but had no similar experience after a second angioplasty which relieved her symptoms.

Since MS is a chronic relapsing disease with long and unpredictable periods of remission, it is easy to see why neurologists have a very sceptical view of Zamboni's hypothesis. Since most of the outcomes of angioplasty are very subjective, it is possible that a very large component of improvement is due to a placebo effect. However, compared to the costs of some drug therapy balloon angioplasty is a low-cost procedure of low morbidity and our patients claim that PTA has been a life-changing positive experience for them.

Clearly randomised double-blinded trials of PTA for symptomatic relief in MS patients is warranted.

References.
