LEADING ARTICLE

The Chronic Cerebrospinal Venous Insufficiency Debate

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Multiple Sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system. The pathogenesis of MS is as yet unknown, although the most widely accepted hypothesis is a T-cell mediated autoimmune response.1

Chronic cerebrospinal venous insufficiency (CCSVI) is a fairly recent hypothesis diverging from the generally accepted theories regarding MS aetiology. Developed by Professor Paolo Zamboni of the University of Ferrara, it has been defined as “a syndrome characterised by multiple stenoses of the internal jugular and/or azygous veins and formation of collateral venous channels”.2 The hypothesis, or “Big Idea” as described in his 2006 paper,3 suggests a link between these anatomical abnormalities and MS by drawing parallels with the pathophysiology of chronic venous disease. According to the CCSVI theory, chronic cerebral venous hypertension, secondary to ineffective drainage by abnormal venous channels, may trigger an inflammatory process leading to the development of MS.

Certainly, there are parallels between the two disease processes. The demyelinating plaques characterising MS form in a perivenular distribution,4 and histological studies have revealed evidence of venous damage in the form of fibrin cuff formation, haemosiderin deposition, and thrombosis.5 These findings are similar to the damage that perivenous tissues display in the lower limbs of patients with chronic venous insufficiency. However, excess iron deposition and inflammatory lesions are not specific to MS and are also found in other neurodegenerative disorders, including Alzheimer’s and Parkinson’s disease,5 as well as in the ageing brain.

Over the last 7 years, the CCSVI theory has been a cause of turmoil in the MS community, involving patients, neurologists, and vascular surgeons. This has led to the literature being inundated with highly heterogenous reports, some supporting the theory and others challenging it. The first issue is the actual definition of CCSVI. According to the “Zamboni criteria”, CCSVI is a diagnosis made on duplex imaging, where two out of five standards based on the detection of reflux or stenosis in the extracranial venous system6 are required to diagnose the condition. One of Zamboni’s earliest publications on the subject revealed a 100% correlation between the presence of CCSVI and MS. None of the matched healthy controls were found to fit the criteria on either duplex or venography.6 A further study revealed 100% sensitivity and specificity for the application of the criteria in the diagnosis of MS.7

However, these findings have not been replicated by other study groups,3,9 with the presence of CCSVI in MS patients ranging from 0%10,11 to 76%.12,13 Those reports identifying an increased prevalence of CCSVI in MS could not support a causative relationship.12,13 This heterogeneity was recognised by Zamboni himself, and was deemed to be due to differing duplex techniques, training, and experience in individual units.14 However, a more recently published large, multicentre case-control study found no association between CCSVI and MS.15 Furthermore the European Society of Neurosonology and Cerebral Haemodynamics issued a statement criticising and raising concerns with regards to the Zamboni criteria, describing them as incorrect and not validated.16 Recent studies suggest that extracranial venous haemodynamics naturally fluctuate,17,18 making Duplex ultrasound (US) assessment completely unreliable.

The issue of reproducibility of venous duplex assessment is crucial to the CCSVI debate. Rodger et al.10 addressed this in their recent case-control study. This Canadian group imaged neck and deep cerebral veins using US and magnetic resonance imaging (MRI), with the primary objective being the detection of the “Zamboni criteria” in 100 randomly selected patients with different subtypes of MS compared with age- and sex-matched healthy controls. Bearing in mind the debate surrounding duplex US, the Canadian group had also ensured that their ultrasonographers were trained under Professor Zamboni and his colleagues via direct supervision in Ferrara. Despite using the same imaging methodology, Rodger et al. were unable to replicate the previously published results by the Zamboni group, identifying only one MS patient out of their 200 participants in whom the duplex criteria for CCSVI were met. In addition, magnetic resonance (MR) venography assessment found no significant evidence of structural venous abnormalities in the extracranial vessels between MS patients and controls. Assessment of both intra and extracranial venous blood flow also failed to reveal any significant difference between the two groups. This paper, by using the same diagnostic criteria as the Zamboni group and reproducing their US findings via MR venography, provides compelling evidence against the existence of CCSVI in MS.

In addition to the discrepancies in the reported rates of CCSVI amongst MS patients, the Zamboni criteria have also been observed in other neurological diseases12 and in
healthy controls, with a range of 2–36% in case-control studies. Thapar et al. also found variability in the sensitivities and specificities of CCSVI for MS, highlighting the heterogeneity in published studies.

Given the conflicting evidence in the literature, especially the recent Canadian study, it is there evidence/justification to “treat” this condition by endovascular means (venoplasty and/or stenting). Once again, opinion is heavily polarised. Supporters of the CCSVI theory suggest that by treating the anatomical abnormalities via the “liberation procedure”, the signs and symptoms of MS can be improved. In the original pilot study, Zamboni performed percutaneous transluminal angioplasty of the internal jugular and/or azygos veins reporting promising results, with no adverse events, a significant improvement in functional scores, and a reduction in T2 lesions on MRI. Other studies have reported outcomes supporting endovenous intervention, describing low complication rates and improved functional outcomes.

There are, however, plenty of worrying reports in the literature regarding this mode of treatment. Published complications of the “liberation procedure” include arrhythmias, direct trauma to or dissection of the vein, thrombosis, puncture site complications (including haematoma formation), and fatal myocardial infarction. Fatal intracranial haemorrhage and stent migration requiring thoracotomy have also been described. Patients have presented to geographically distant units with complications of their initial procedure. A largely unknown number of patients, desperate for intervention, have resorted to a form of medical tourism, with interventions being carried out privately abroad. Reports include travel to the USA, Bulgaria, Poland, and Mexico. Procedures in these countries may be performed privately in an unregulated manner, making it all the more challenging to treat patients presenting with complications. Unfortunately, complication data reporting is sparse and lacking long-term follow-up.

Following the positive results of the original pilot study, endovenous treatment of CCSVI has gathered momentum among patient groups. In the era of social media, information on the condition and its treatment has spread like wildfire, enabling patients to actively engage in the debate. Social media portals (including blogs, Facebook, and YouTube) have been employed by patients to describe their post-treatment experiences, which are largely positive. Public opinion generally holds CCSVI in high regard, with those challenging the theory being described as conspiring to deny treatment to patients. It is clear to see why this might be. While current treatment for MS is aimed at reducing the severity and frequency of attacks, and to slow disease progression, a cure still does not exist. The development of an intervention that could free patients from a debilitating, chronic disease is obviously extremely desirable.

Despite the media hype, the evidence for intervention in CCSVI is confusing, at best, and needs to be interpreted with caution. The Cardiovascular and Interventional Radiological Society of Europe released a statement in 2011 warning against intervention in CCSVI owing to the lack of high-quality, randomized trial data. They recommended that percutaneous angioplasty or stenting should not be offered to MS patients unless within a clinical trial. In 2012, the US Food and Drug Administration released a statement warning of the potential dangers of intervention in CCSVI and advising against experimental procedures.

New theories such as CCSVI should, however, be welcomed and openly investigated using high-quality studies such as blinded randomised controlled studies. However, this should be under the strict regulation of ongoing clinical trials or as part of registry data collection, so as to ensure that patients are adequately followed up and long-term data analyses are possible. Randomised trials are currently underway to investigate intervention in CCSVI and the results are awaited. Until then, the debate continues. However, there is increasing evidence that the initial excitement with respect to CCSVI has not been supported by the more recent cohort studies and the early randomised controlled trials.

REFERENCES


