Chronic cerebrospinal venous insufficiency and multiple sclerosis: science or science fiction?

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In 2009, this journal published a manuscript by Zamboni et al that proposed a major paradigm shift in the pathophysiology and consequently the treatment of multiple sclerosis (MS).1 Using extracranial colour Doppler and transcranial colour coded Doppler sonography, Zamboni et al reported 100% of their MS patients and none of the healthy controls having impaired venous drainage from the CNS that fulfilled specific criteria for abnormal extracranial venous return, also proposed by Singh and Zamboni.2 This extracranial colour Doppler and transcranial colour coded Doppler sonography based phenomenon was described as chronic cerebrospinal venous insufficiency (CCSVI). The pathological consequences of CCSVI have been hypothesised to emanate from chronic venous reflux and hypertension leading to increased iron deposition in the brain and subsequent MS pathology, including inflammation and neurodegeneration.1 Since the initial publication in this journal, the debate on CCSVI and its relevance to MS has raged across scientific and patient communities, greatly facilitated by the media, including the internet blogs. Similar but much less robust data from collaborators of Dr Zamboni have been published in support of the existence and relevance of CCSVI to MS. Numerous commercial operations are underway offering diagnostic testing for CCSVI followed by interventional strategies, including venous stenting and angioplasty in MS patients.

Two studies3–4 cast serious doubt on the existence of CCSVI as a pathological entity and its relevance to MS (see pages 429 and 436). Wattjes et al reported a threedimensional MR venography study in 20 MS and 20 age and gender matched controls to examine intracranial and extracranial venous anatomy.5 The study employed phase contrast and dynamic threedimensional contrast enhanced MR venography as well as flow quantification of the cerebral venous vasculature, assessed by interventional neuroradiologists blinded to the diagnosis. Anomalies of the venous system and associated alternative venous drainage were found in nearly similar numbers of MS patients and healthy controls. Venous flow quantification showed no abnormality in any MS patient or control. The authors concluded that venous anomalies are neither exclusive to MS patients nor appear to be pathological in nature given the normal intracranial venous flow quantification results. In the second study, Mayer et al examined extracranial and intracranial venous flow direction and extracranial venous cross sectional area of the internal jugular vein and vertebral veins in 20 MS patients and 20 matched controls.6 Colour coded duplex sonography was used to assess the five previously proposed CCSVI criteria.1 No subject demonstrated retrograde flow of extracranial or intracranial veins. Interestingly, internal jugular vein stenosis (defined as venous cross sectional area ≤0.5 cm2) was found in 13 MS patients and 16 controls. A decrease in this cross sectional area was seen in all study subjects, indicating the physiological response. Only one healthy control and no MS patient fulfilled the criteria for CCSVI proposed by Zamboni and colleagues.1 Both studies3–4 are limited by the relatively small number of patients which is somewhat mitigated by the excellent Doppler methodology and blinding procedures adopted, particularly in the latter study.

At least three other studies5–7 have reported similar findings refuting the observations made by Zamboni et al,1 casting serious doubt on CCSVI as a scientifically plausible pathological entity in MS. Neither study supports the existence of CCSVI as a pathological entity in MS. In fact, somewhat ironically, no study published thus far has been able to reproduce the findings by Zamboni et al that reported 100% positive findings in MS patients compared with none in controls.1 This should also serve as a caution for those carrying out interventional procedures to ‘liberate’ their patients from MS. The Society of Interventional Radiology issued a position statement noting that, currently, there is insufficient evidence to support the use of interventional procedures as treatment modalities in MS.6 There is no question that the work by Zamboni et al has amplified the concept of ‘thinking outside the box’. However, larger, independently conducted and properly designed studies are needed to investigate the existence of CCSVI as a pathological entity in MS. This is likely to occur in the next couple of years as ongoing comprehensive studies examining CCSVI are completed. Until then, whether the existence and relevance of CCSVI to MS is science or science fiction remains unclear.

Competing interests None.

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