CHRONIC CEREBROSPINAL VENOUS INSUFFICIENCY THEORY AFTER THE BRAVE DREAMS STUDY

Marian Simka

Department of Anatomy, University of Opole, Opole, Poland

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Address for correspondence
Marian Simka
Department of Anatomy
University of Opole
11a Kopernika Pl.
45-040 Opole, Poland
e-mail: mariansimka@poczta.onet.pl

Multiple sclerosis (MS) is a chronic disease of the central nervous system. It is generally accepted by neurologists that it is an autoimmune disease, which is caused by an attack against nervous tissue antigens, primarily myelin, and that this reaction is executed by reactive T cells. However, what is actually causing this immune reaction still remains enigmatic. Moreover, there is strong evidence that MS, in addition to its immunoinflammatory aspect, at its core is a neurodegenerative disorder, casting doubt at the autoimmune paradigm [1-3]. Therapeutic strategies for MS predominantly target inflammatory cascade or modify the immune response. These pharmacological treatments are somewhat effective, but they cannot cure patients or protect them from the disability that is usually seen in those with long-lasting MS.

About 10 years ago an Italian vascular surgeon Paolo Zamboni strode into this rather murky milieu with his chronic cerebrospinal venous insufficiency (CCSVI) theory. He demonstrated that MS patients present with haemodynamically significant lesions in the extracranial veins draining the brain, primarily in the internal jugular veins (IJV) – an entity that had not been known before [4, 5]. He also challenged the autoimmune paradigm, claiming that these venous blockages play a primary role in initiating pathological reactions of MS, including inflammation and chronic cerebral ischaemia. At that time Zamboni and his colleagues also presented results of a pilot study, which showed clinical improvement in MS patients after endovascular balloon angioplasty of pathological IJVs and azygous veins [6].

Consequently, the CCSVI hypothesis began to be hotly debated within the scientific community. Not surprisingly, this new idea was generally welcomed by vascular interventionalists [7] but vigorously challenged by neurologists [8]. During following years a number of open-label studies on endovascular management of CCSVI lesions were published. These treatments usually utilised balloon angioplasty, but in some patients an off-label stenting of the IJVs was also performed. These studies demonstrated the safety of such treatments, especially if balloon angioplasty was used [9-14]. On the other hand, these surveys revealed that endovascular angioplasty in this venous territory is not easy. Technical success after standard balloon angioplasty could be as low as 50%. This rate could be improved using high-pressure balloons and long inflation times, but at the cost of acute thrombosis or subsequent scarring recoil in some patients. Some centres implanted stents if balloon angioplasty alone was not able to restore proper flow. This strategy, which is widely accepted in patients presenting with iliac vein stenosis and is both safe and effective in this area, in the case of abnormal IJVs was often followed by severe intimal hyperplasia, resulting in stent occlusion. In some patients even stent migration to heart chambers or pulmonary arteries occurred. In addition to these technical problems, although the majority of these studies demonstrated clinical improvement after endovascular treatment, all these studies had an open-label design and therefore the placebo effect could not be ruled out. Other researchers reported the presence of CCSVI in patients with non-MS neurological diseases, also in healthy individuals, so this condition did not seem to be exclusively associated with MS, as was initially claimed by Zamboni *et al.* [15-17]. Finally, analysis of the characteristics of CCSVI lesions has revealed that these venous abnormalities are probably not causing MS, but rather they represent permissive pathology, which can be responsible for clinical progression of MS but not its initiation [18].

The results of a randomised prospective controlled trial on venous angioplasty for CCSVI in MS patients

were long awaiting by the medical community. Such a trial would definitively answer the question of whether clinical improvements revealed by open-label studies were associated with placebo effect or were indeed related to the procedure itself. Although initially a number of such trials were planned, most of them were not performed, either due to lack of funding or because of problems with recruitment of enough patients to demonstrate statistically significant differences between treatment and sham groups. By 2014 only one trial (USA) had been completed and its results published. However, in this study only a small number of patients were managed, so no valid conclusions could be drawn, except for the safety of the procedure [19]. Other studies that were planned and registered, for example American and Australian trials, were cancelled because doctors were unable to recruit enough patients. In 2017 the results of a Canadian study were revealed. Here researchers did not find different clinical outcomes in patients who underwent angioplasty and those who received only a sham procedure [20]. However, the description of the endovascular technique used by this team suggests that the patients probably received suboptimal treatment, and the lack of improvement could be associated with unsuccessful angioplasties and not the fact that such a procedure was not clinically beneficial. This year the results of a multicentre Italian trial (the Brave Dreams study) were published [21]. This study was planned to involve at least 300 patients, but only 112 completed the study. Similarly to the Canadian trial, the Brave Dreams study has shown that venous jugular angioplasty in MS patients is safe but largely clinically ineffective. Similarly to the former study, a substantial proportion of angioplasties were haemodynamically ineffective. The Italian study has, however, demonstrated that patients who received the treatment had no new MRI-detectable lesions (this composite is routinely used for the assessment of the pharmacological agent used in the treatment of MS). This effect was not statistically significant but could have reached the level of $p < 0.05$ if more patents had been recruited [22, 23]. This effect, however, was seen only in a subgroup of patients.

This year the results of another study were published, which are contradictory to the previous ones. In this study the authors demonstrated improvement after endovascular angioplasty of IJVs in MS patients in terms of relief from headaches and chronic fatigue accompanying MS [24]. Similarly to the Brave Dreams study, this improvement occurred only in a subgroup of patients. Importantly, it was significantly correlated with the technical success of the procedure defined as improved flow after angioplasty.

How do we summarise all these contradictory findings? Not surprisingly, the majority of neurologists concluded that management of malformed veins in MS patients has been proven ineffective and no further research is needed [25, 26]. Nevertheless, it seems that there are a group of MS patients, primarily those who present with relapsing-remitting course of the disease, especially if MS presents with headaches and severe chronic fatigue, who could potentially benefit from correction of malformed veins. In addition, if in such patients' venous anatomy is favourable, which means that they present with venous stenoses that can easily be corrected using balloon angioplasty alone (it has been demonstrated by many interventionalists that such lesions as stenoses of distal and middle part of the IJV, external compression of these veins, tight stenoses, and long intraluminal flaps respond poorly to balloon angioplasty) [27], these patients could be safely relieved from some troubling symptoms of MS. However, to demonstrate this potentially beneficial effect, another prospective study should be performed [28]. Taking into account how difficult it was to perform the previous studies on this topic (funding, recruitment, approval by authorities, etc.), it is unlikely that such a new study will be conducted.

The author declares no conflict of interest.

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