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Extracranial Veins in Multiple Sclerosis: Is There a Role for Vascular Surgery?

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PRO: P. ZAMBONI

Brave Dreams (Brain Venous Drainage Exploited Against Multiple Sclerosis) is likely to be the first multicentre double blinded randomised sham controlled trial in the history of vascular surgery. It assesses the efficacy and safety of venous percutaneous transluminal angioplasty (PTA) of extracranial and extravertebral veins that contributed to chronic cerebrospinal venous insufficiency (CCSVI) in patients with multiple sclerosis (MS). Relapsing–remitting (RR) and a small group of secondary progressive (SP) MS patients, who were positive for CCSVI at echo color Doppler (ECD) screening, were randomly assigned (2:1) to receive PTA or catheter venography (sham). The primary endpoints were a combined measurement of five functional indices: walking, balance, manual dexterity, bladder control, visual acuity, and new/enlarged magnetic resonance imaging (MRI) lesions (T1 Gad+, T2 hyperintense, combined T1–T2). In both arms of the study, patients were under immunomodulatory treatment. Venous PTA had no additional effect on either measure in the RRMS group at the 12 month follow up.[1] It is worthy of note that 73% of the PTA group had no new gadolinium enhancing lesions compared with 50% in the sham group (unadjusted $p = .02$).

It was planned to recruit slightly more than 400 RR and 200 SP patients, but only 115 RR and 15 SP patients were randomised. The study is clearly underpowered but, interestingly, about 75% of the selected patients were recognised to be positive at ECD screening for CCSVI. The high prevalence at ultrasound of associated CCSVI in MS patients was confirmed by the means of gold standard catheter venography in 93% of cases.[1]

THE BRAIN DRAINAGE HYPOTHESIS AND LIMITATIONS OF VENOUS PTA

The hypothesis of Brave Dreams was to assess whether venous blood flow restoration could improve symptoms and reduce the accumulation of new brain lesions on MRI. Unfortunately, only 54% of the angioplasty group experienced restored blood flow, indicating either limited efficacy of PTA in treating the different presentations of CCSVI or the inadequacy of this technique for exploring the initial hypothesis.

In a recent paper, Giaquinta et al.,[2] analysing almost 800 CCSVI patients who underwent balloon angioplasty of the jugular veins, demonstrated that younger individuals with transverse endoluminal defects and higher pre-PTA flows are more likely to respond well to treatment than those who exhibit hypoplasia, external compression, or longitudinal endoluminal defects.[2] Commenting on these findings, Moneta[3] observed that if Brave Dreams failed to show any benefit of venous angioplasty for the treatment of MS, additional post hoc analysis focusing on the PTA responders group identified by Giaquinta et al. would help guide future investigation in this field. The above findings raise the hypothesis of a subgroup of responders with CCSVI presentation favourable to balloon treatment.

IS THE HYPOTHESIS TO BE REJECTED?

Considering that the hypothesis of Brave Dreams was that subjects with restored flow could have a better outcome, a post analysis was performed. The unified PTA arm (RRMS and SPMS) group ($n = 81$) was subdivided into two subgroups, and compared the subgroup of patients with restored monodirectional flow at the level of the jugular–subclavian junction (J1), to those with absence of Doppler detectable flow at 12 months. Given the 90% study power estimate, the flow data of the PTA arm was matched with a tough endpoint such as the accumulation of new lesions on MRI. The unadjusted OR of the two subgroups is significantly different in favour of patients with restored brain outflow, considering new T2 MRI lesions developed between months 6 and 12 (OR = 5.27, 95% CI 1.50–18.69, $p < .007$) (Fig. 1). At 0–12 months new T2 MRI lesions were always in favour of the restored flow subgroup (OR = 2.90, 95% CI 0.98–8.66, $p < .05$) (Fig. 1). The same comparison was performed for the 44 patients in the sham arm. No association between flow and MRI lesion development was found. As patients were taking the current therapies for treating MS in both arms of the trial, it would therefore appear that the subgroup of patients that reached the objective of restoring jugular flow may achieve significant additional benefits with respect to pharmaceutical treatment alone. As far as the clinical outcomes are concerned, the one year follow up is too short to assess significant functional changes. However, the clinical measures will also

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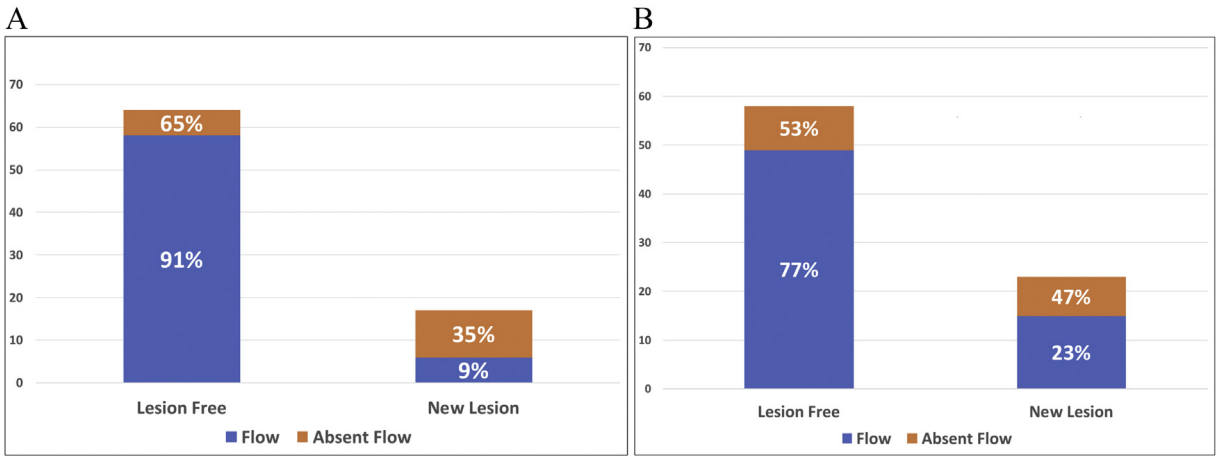

Figure 1. (A) Increased probability of developing new MRI lesions with absent flow in upright position at 6–12 months from the procedure (35% of patients vs. 9%). In contrast, when PTA restored the flow in the internal jugular vein in favour of gravity, 91% of patients did not develop new T2 MRI lesions ($p < .007$). (B) Although less significant, the flow dependency of new T2 lesion formation is also confirmed at 0–12 months ($p < .05$).

be subjected to a similar post hoc analysis to understand whether it is more likely for patients with restored flow to achieve functional benefits. These results will be presented in secondary articles. The next step will be to verify in advance which types of CCSVI presentation can benefit from balloon treatment so as to provide a treatment indication.

CONCLUSIONS AND PERSPECTIVES

From a pathophysiological point of view the post hoc analysis reported above suggests a role of impaired extracranial venous flow in lesion development in patients with MS, as well as the probability of significant advantages when the brain outflow is restored. This finding continues to support the CCSVI hypothesis and the contribution of the jugular flow to cerebral inflammation.

CCSVI still represents a new hypothesis to attempt to explain the pathogenesis of MS, but has not ultimately led to a viable minimally invasive surgical treatment option for all patients with this condition.[1,2] CCSVI presentation is complex, mostly with compressions associated with long endoluminal obstacles, where, as reported above, PTA is safe but often ineffective. We also know that the improvement of jugular vein flow achieved by open surgery in the vast majority of MS patients correlated with improved cerebral perfusion and decreased brain ventricle volume.[4] But, of course, an open surgery option cannot be offered widely. Alternatively, of particular interest for the vascular surgeon and/or the interventional radiologist would be further technological development of venous stents. The latter would take into account the compliance properties of the vein wall, which, at the level of the internal jugular vein, causes a sixfold reduction in the cross sectional area when passing from the supine position to the sitting position.[5]

CCSVI created a great deal of controversy in the neurological community, but undoubtedly contributed to a better understanding of the function of the extracranial venous system.[6]

It has been demonstrated how extracranial venous function might influence brain perfusion, cerebrospinal fluid (CSF) flow, and CSF absorption.[4,7,8] In other independent studies, the extracranial venous system was also found to be associated with other neurodegenerative conditions including Parkinson's, Alzheimer's, and Meniere's diseases, suggesting the need for further investigations.[9–12] Vascular science is beginning to bridge the knowledge gap between the extracranial veins and the brain.

This development of vascular studies in the field of neurodegeneration is to be considered of extraordinary interest. In my opinion the cerebral vascular system plays a prominent role in the understanding of these pathologies, and the main extracranial vessels and vascular surgeons cannot be kept out of the game.

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CON: R. ZIVADINOV

A multicentre, double blind, randomised, sham controlled trial Brave Dreams (Brain Venous Drainage Exploited Against Multiple Sclerosis),[1] settled a scientific debate about the role of percutaneous transluminal angioplasty (PTA) to correct for chronic cerebrospinal venous insufficiency (CCSVI) in patients with multiple sclerosis (MS). In this trial, Zamboni et al.[1] reported that PTA was safe but ineffective in restoration of venous outflow at the end of the study compared to baseline in almost half of the treated patients. In addition, the procedure was ineffective in altering clinical outcomes including relapse rate, disability accumulation or functional composite measure, and MRI detected lesion activity or proportion of patients being free from new/enlarging T2 lesions over 12 months. Most importantly, Brave Dreams settled an important debate among MS patients themselves, which is related to whether PTA for CCSVI correction can improve symptoms of the disease, such as walking, balance, autonomic dysfunction, fatigue, and vision. In fact Brave Dreams was designed to use a functional composite measure of five functions (i.e., walking control, balance, manual dexterity, post-void residual urine volume, and visual acuity), as its primary endpoint, based on a previous report suggesting that PTA can influence clinical and quality of life outcomes in relapsing MS patients in an open label study.[2] No difference on the total functional composite or its five subcomponents was detected at any time point of the study, between the treatment groups.

Brave Dreams was a negative clinical trial and the authors themselves concluded "Venous PTA has proven to be a safe but largely ineffective technique; the treatment cannot be recommended in patients with MS." Therefore, based on the findings from Brave Dreams,[1] and from another recent randomised, double blind, controlled trial for PTA correction of CCSVI in MS (PREMiSe)[3] that showed no effectiveness of venous outflow restoration in modifying clinical and MRI outcomes, it can be concluded that there is no future role for PTA in the treatment of CCSVI in MS.

Both Brave Dreams[1] and PREMiSe,[3] showed that PTA was an inadequate technique to restore extracranial venous outflow, as more than half of the MS patients at the end of the study re-presented with CCSVI. However, it is highly questionable whether the extracranial venous outflow has to be restored in MS patients, as CCSVI has also been detected frequently in healthy subjects and patients with other neurological disorders.[4,5] This is line with previously published cross sectional studies showing no association between CCSVI and cognitive[6] or MRI[7] outcomes of MS disease severity.

In this Debate (PRO), Dr. Zamboni argues that post hoc analyses should further explore whether a PTA correction of CCSVI in MS may identify a subgroup of PTA responders with a more favourable outcome in the Brave Dreams trial.[1] He further reports that patients with restored brain outflow showed lowered accumulation of new T2 or the new combined T1 Gad+ and T2 MRI lesions over 6—12 months, compared with those without flow restoration. However, these subanalyses are based on small study subgroups and a low number of events, and therefore are heavily skewed, not being predetermined, as reported in the original publication.[1] For example, in the PREMiSE study, the opposite was found, that is higher MRI activity over 6 months was observed in patients who had their venous blood outflow restored. While exploratory post hoc analyses should provide more insight into the value of procedures employed in clinical trials, it seems that these are misplaced in this context. There are more than 14 approved disease-modifying treatments (DMTs) for MS by the FDA, and the majority of those have shown a robust effect on decreasing relapse rate, accumulation of inflammatory T1 Gad+ and T2 MRI lesions, disability progression, and development of brain atrophy.[8] Some of those DMTs are able to almost completely arrest the accumulation of T1 Gad+ and T2 MRI lesions over time.[9,10] Therefore, in my opinion, the use of vascular surgery as a therapeutic strategy to decrease anti-inflammatory MRI activity in MS is inappropriate.

In addition, while originally the extracranial venous abnormalities, indicative of CCSVI, were linked to MS,[11] there is increasing evidence that extracranial arterial abnormalities are also present in MS.[12] Therefore, the vascular neck vessel pathology in MS patients has to be examined in the

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context of the presence of cardiovascular disease and ageing, and their altered morphology does not necessarily represent pathological findings which necessitate vascular surgery correction. It is well known that cardiovascular risk factors contribute to MS susceptibility and disease severity.[13] It could be hypothesised that the arterial vessels supplying the central nervous system are possibly subject to particular atherosclerotic harm. Therefore, the decreased arterial and venous lumen of the carotids, vertebral arteries, internal jugular veins, and secondary neck vessels found in MS patients[12] may suggest that inflammatory mechanisms contribute to early atherosclerosis in MS patients. This may also explain why the hypoperfusion of the normal appearing white matter, commonly detected in MS patients, may be partially linked to the morphological differences of the neck arterial and venous system.

The CCSVI was a new hypothesis for explaining MS pathogenesis, but did not lead to a new therapeutic option in MS patients. However, CCSVI contributed to a better understanding of the function and role of the extracranial venous system. In the future, we should use this knowledge to study more appropriately the interaction between the arterial and venous neck vessel system, as well as the dysfunction of the heart, all of which can contribute to focal or diffuse hypoperfusion of the central nervous system. It could be hypothesised that this initial hypoperfusion condition, in conjunction with specific environmental and genetic risk factors, can predispose phenotypic characterisation and onset of various neurological diseases.

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