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Chronic Cerebro-Spinal Venous Insufficiency in Multiple Sclerosis: Is It the End?

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Dear Editor:

It was published the long awaited Italian clinical trial investigating the safety and efficacy of a venous percutaneous transluminal angioplasty (PTA) to treat patients with multiple sclerosis (MS). According to the authors, venous PTA has proven to be a safe but largely ineffective technique; the treatment cannot be recommended in patients with MS [1].

Anyone who read the seven-page study, however, would have found a second, somewhat contradictory conclusion—that magnetic resonance imaging (MRI) results showed some people with MS, a degenerative condition of unknown origin, benefitted from improved cerebral blood flow, and further study was warranted: The delayed effect of venous PTA six months after the procedure on the MRI biomarker suggests a possibility that PTA may produce benefit for a sub-group of patients with MS. According to the authors this should be further analyzed and investigated [1].

Eight years ago, Paolo Zamboni, an Italian vascular surgeon, created a firestorm in the MS community with his hypothesis that MS, long believed to be an autoimmune disease, could have a vascular connection: his research indicated people with MS had restricted venous flow from the brain and spinal cord, a condition he named as chronic cerebro-spinal venous insufficiency, or CCSVI. His small 65-person observational study found PTA of venous strictures in patients with CCSVI is safe, and especially in patients with relapsing-remitting (RR) MS, the clinical course positively influenced clinical and quality of life's parameters of the associated MS compared with the preoperative assessment [2].

MS neurologists, the official MS gatekeepers, dismissed, even mocked Zamboni's theory and the scientific integrity of his research. Nonetheless, thousands of Italians with MS sought treatment, spurred by anecdotal reports of improvements spread on social media (Incidence of MS is high in Italy. In Italy, people with MS pressed to have venoplasty for MS covered by healthcare in Italy). They also called for a randomized, double-blinded placebo-controlled trial of the sort used to test new drugs.

Reported responses to CCSVI treatment were as varied as the MS population itself: some people experienced lasting benefits in terms of renewed energy, better balance and improved bladder control [3]. For others, early improvements vanished with time; a percentage saw no benefit and experienced complications; three deaths were associated with the treatment [4]. In time, the idea that CCSVI was the cause of MS, and that treating it could be a cure,was abandoned; people with MS, many of them disillusioned with or unable to take MS drugs, sought symptom relief and improved quality of life.

Zamboni's theory propelled wide-ranging research and the creation of a multidisciplinary society (International Society for Neurovascular Disease) to investigate neurovascular diseases. MS neurologists conducted research reluctantly; their studies, found that CCSVI is not associated with MS [5].

Zamboni was the principal investigator and senior author of the newly published Italian study, named "Brave Dreams" (Brain Drainage Exploited Against Multiple Sclerosis) [1].

The study wanted to provide an answer regarding the

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efficacy of PTA on patients' functional disability in balance, motor, sensory, visual and bladder function, cognitive status, and emotional status, which are meaningful clinical outcomes, beyond investigating the effects on inflammation. In fact, an important part of patients' expectations, sustained and amplified by anecdotal data, has to do precisely with these functional aspects.

The study was rigorously designed but marred by limitations. One was its small size. Originally designed for 430 participants, only 115 patients were enrolled (76 had PTA; 39 received a sham procedure, the surgical equivalent of placebo); as such it was underpowered to answer the questions it sought to investigate. The low enrollment is explained in the study as the result of MS patients' lack of willingness to undergo the sham procedure.

The data did confirm a high prevalence—74%—of CCSVI in people with MS. It also found various and complex types of venous malformations, including closed jugular vein valves. Only 53% of people who received PTA had blood flow restored; it was ineffective for the remainder.

The study concluded that PTA did not result in functional improvements (for example, improvements in gait, balance, bladder control, fatigue, etc.), nor did it reduce the mean number of new combined brain lesions on MRI at 12 months.

The one aspect of the study that calls for further inquiry is the finding that 77% of treated patients, 22% more than the sham group, were free of gadolinium-enhancing lesions at 12 months. The importance of this was explained in the study: "Gadolinium enhancement is a marker of damage to the blood-brain barrier, whose time course depends on lymphatic drainage and hence on venous drainage from the skull".

The study was accompanied too by an editorial written by three MS neurologists that is scathing in its denouncement of CCSVI, CCSVI advocacy and the role of social media in spreading ineffective medicine. The study is rigorous and definitive, the authors declare and its result is unequivocal [6].

CCSVI enthusiasts have done much to spark a line of investigation for treatment of MS. Optimism and enthusiasm, however, now require responsibility to perform and to report proper clinical trials either to validate a new treatment for MS or to close the door on what also may be an ineffective intervention [7].

The relative inefficiency of a surgical technique does not mean that CCSVI theory should be rejected in MS.

New approaches involving completely different pathogenic mechanisms in neurological diseases are rarely discovered. CCSVI represented a new hypothesis to attempt to explain the pathogenesis of MS [8].

On August 16, 2017 it was published a study titled "Factors influencing the hemodynamic response to balloon angioplasty in the treatment of outflow anomalies of internal jugular veins" [9].

According to the authors of this paper PTA of the internal jugular veins (IJVs) has been proposed in recent years to treat chronic cerebrovascular venous insufficiency, with discordant results. Moreover, very little is known about the efficacy of PTA in restoring a normal cerebral venous outflow. The aim of their study was to investigate the anatomic factors and patient characteristics that might influence the efficacy of PTA of the IJV.

PTA resulted in an increased outflow through the IJVs in most patients. However, younger individuals with transverse endoluminal defects and higher pre-PTA flows are more likely to respond well to PTA compared with those who exhibit hypoplasia, stenosis, or longitudinal endoluminal defects.

In conclusion their study identified the factors that influence and could predict the efficacy of PTA in the treatment of the IJV anomalies.

On January 23, 2018 it was published a new study titled "Mid-term sustained relief from headaches after balloon angioplasty of the IJVs in patients with multiple sclerosis" [10].

According to the authors, the intervention of PTA was associated with a large and sustained (>3 years) reduction in Migraine Disability Assessment score in both RR and secondary progressive (SP) MS patients. While a similar initial post-PTA reduction in Fatigue Severity Scale score was also observed, this was not maintained in the SP and primary progressive patients, although it remained significant at follow-up (>3 years) in the RR MS patients. This suggests that venoplasty might be a useful intervention for treating patients with persistent headaches and selected concomitant obstructive disease of the IJVs.

Therefore, in my opinion the intervention for CCSVI may still have a role in carefully selected cases.

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