Invited Commentary

CCSVI: Is Blinding the Key?

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When Zamboni et al. presented a new pathophysiological hypothesis, proof of concept and possible cure for multiple sclerosis (MS) in 2009,1–3 many were intrigued by the simplicity of the ‘chronic cerebrospinal venous insufficiency’ (CCSVI) hypothesis. This concept transferred the known pathophysiology of chronic venous insufficiency (CVI) from the leg to the brain, as Zamboni et al. proposed that the formation of MS lesions in the brain was a consequence of intracerebral erythrocyte extravasation due to elevated transmural venous pressure, followed by erythrocyte degradation and iron-driven phagocytosis.4

The first open-label interventional study by Zamboni et al.2 aimed to explore the efficacy and tolerability of transluminal venoplasty (PTA) for the treatment of ‘CCSVI’ in 65 patients. It reported a doubling of the rate of relapse-free patients in the RRMS-group from 27% to 50%, a reduction in the rate of contrast-enhancing lesions in MRI from 50% to 12% of patients and a significant improvement in the MSFC-score. These controversial findings were, however, subjected to critical scrutiny because of crucial shortcomings in trial design.4–6

Three major omissions cast doubt on the validity of these data2: First: no blinding was applied to either the ultrasonographer who assessed post-interventional vascular outcome measures or the evaluating physician who assessed EDSS-, MSFC- and QOL-scores, despite the recognized susceptibility of these assessments to rater bias. Second: no sham intervention was performed to exclude placebo effects, while third: no information was provided as to whether venoplasty patients were prescribed (or were already taking) any other disease modifying medications at the time of their procedure.

In this issue of the EJVES,1 Zamboni et al. present the results of another interventional study, where they applied PTA to 15 ‘CCSVI-positive’ MS patients. The group was divided into an ‘immediate treatment group’ (ITG) and a ‘delayed treatment group’ (DTG: where PTA was performed after a delay of 6 months). The trial yielded apparently corroborative data, in particular a relapse rate reduction of 80% at 1 year follow-up in the ITG group. In this paper, Zamboni et al. state that their preceding study had been ‘criticized because of the lack of a control group and blinded, objective MRI measurements’.5 Given the methodological shortcomings of his earlier study, the reader would surely then expect the authors to have met basic scientific requirements in their latest study. In the introduction to their paper, Zamboni et al. reflected on these concerns, stating that: ‘the present study was designed to address these criticisms and to determine whether treatment of CCSVI with PTA affected disease progression in patients with MS’.1

However, a careful review of the methodology of the new study still raises the question as to what extent these demands were satisfied, given that no specific information concerning blinding precautions were provided. First, Zamboni et al. failed to inform the reader how clinical and MRI assessors of the post-interventional outcome were blinded toward the ITG/DTG group assignment of the patients. The failure to ensure safe exclusion of assessor bias is a fundamental methodological failure, which gives rise to substantial doubts regarding the validity of the new data. Second, in the absence of a sham-procedure, the patients included in this trial were aware of their intervention and therefore susceptible to well recognized placebo effects.

Accordingly, the added value of this study for assessing the therapeutic effect of PTA in MS must be regarded as minimal in absolute terms. Data which are obtained whilst ignoring the importance of assessor bias and placebo effects should not serve as supportive evidence for the efficacy of endovascular treatment in MS. As we have learned from preceding publications,5,6,7 ‘truth’ in the CCSVI hypothesis is crucially dependent on the awareness of both the evaluating physician and the evaluated patient. Therefore, independent, randomized double-blinded trials (including sham intervention) are warranted in order to obtain valid and reliable data to prove or refute this therapeutic algorithm for MS.

As a consequence of these methodological and ethical concerns, practice statements (like those recently published by the EFNS and ENS Multiple Sclerosis Scientist Panel and ECTRIMS Executive Committee8) are essential, given the prominence accorded to lay discussions regarding the CCSVI hypothesis in the print media, internet blogs and social networks. A lack of scientific evidence has been substituted by emotional testimonials from treated patients, leading to the development of a lucrative industry of dubious ‘CCSVI-centres’9,10 who are eager to respond to patient demands by offering them ‘liberation’ (according to Zamboni) at costs ranging from $640010 to $980011,12 but without any serious or independent corroborative scientific evidence.10

The consequence of this unprecedented, erratic development in modern medicine presents the medical community with a two-fold challenge: namely that of maintaining scientific rigor regarding the performance and interpretation of CCSVI trials and then the ethics of translating the results of these trials into treatment recommendations. Given the absence of proven therapeutic benefits and
the potential for serious side effects following endovascular treatment of 'CCSVI',\textsuperscript{13,14} interventional treatment of 'CCSVI' outside standardized clinical trials is unethical and must be strongly discouraged. If such clinical trials are to be performed, they must adhere to the basic standards of a double-blind randomized, sham controlled study.

References