

Chronic Cerebrospinal Venous Insufficiency

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Dear Editor:

I read with interest the article published by Kugler et al. [1]. Regarding the duplex ultrasound examination the author didn't consider the paper by Zamboni et al. [2] published in December 2011 on international angiology.

In this document the authors noted that a high prevalence ranging from 62% to 100% of obstructive lesions has been found by some teams in patients with multiple sclerosis (MS) compared with a lower prevalence of 0%-25% in controls. However, absence of such lesions or a lower prevalence (16%-52%) has been reported by others. This variability could be the result of differences in technique, training, experience or criteria used. The current lack of a methodology shared among experts is a confounding element in epidemiologic studies, and does not permit further Bayesian or other kind of analysis. In order to ensure a high reproducibility of Duplex scanning with comparable accuracy between centers, a detailed protocol with standard methodology and criteria is proposed. This is also necessary for training. It has been shown that inter-rater variability increases post-training (from $k=0.47$ to $k=0.80$), while within-rater reproducibility in trained operators was $k=0.75$. Finally, the consensus document proposes a reporting standard of Duplex measurements, and future research to answer areas of uncertainty.

Dr. Paolo Zamboni do and did not have any personal financial conflict of interest. His centre received only equipment from Esaote (and not from SoNos) as wrote by Kugler et al. [1] exclusively for research and educational purposes. This was stated in the articles cited by Kugler et al. [1].

Regarding the study published by Rodger et al. [3], Dr. Paolo Zamboni and Dr. Mirko Tessari wrote a reply letter

published in Plos One comments: <http://www.plosone.org/attachments/pone.0072495.comment1.pdf>.

Regarding the study by Traboulsee et al. [4], according to Zamboni [5] the rate of stenosis in angiography is calculated by comparing the diameter of the stricture with that of the segment immediately preceding it. In this article it has been proposed a novel method which compares, along the entire anatomical length of the internal jugular vein, the widest with the narrowest point. However, the jugular in normal cases is characterized by a big variability in size, with >50% variation of the diameter by comparing the bulb with any other point of the vein. This is the reason because the proposed methodology was unable to separate healthy controls from MS cases. If someone should be interested in the assessment of primary venous obstruction please read Zamboni [5]'s study.

Regarding the meta-analysis by Tsvigoulis et al. [6], Zamboni [7] get the impression that the dispute about chronic cerebrospinal venous insufficiency (CCSVI) is a common place without the possibility of bringing out the ongoing contributions that emerge from the literature. This appears especially when some studies which denies the contribution of CCSVI to neurodegeneration, show an unexpected and unusual media coverage. This of course generates confusion among patients. But also among colleagues who do not have cerebral venous return as primary interest. In short, there are 3 meta-analyses available from: Laupacis et al. [8], Tsvigoulis et al. [6], and Zwischenberger et al. [9]'s studies.

All the 3 above-mentioned meta-analyses confirm a significant prevalence of CCSVI in MS. Only six out of 19 comparable studies deny the association between CCSVI and MS. But while the first two meta-analysis showed

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heterogeneity among the studies, the third demonstrated clearly a significant double risk in having MS when CCSVI is detected, without any heterogeneity. The mass media should require a good communication of Science when scientific press releases are solicited. In controversy regarding prevalence and risk factors, to consult meta-analysis is a good tool to balance the communication.

Finally, in 2013 Zamboni et al. [10] published on *Veins and Lymphatics* journal a review. According to the authors, studies of prevalence show a big variability in prevalence of CCSVI in MS patients assessed by established ultrasonographic criteria. This could be related to high operator dependency of ultrasound. However, 12 studies, by the means of more objective catheter venography, show a prevalence >90% of CCSVI in MS. Global hypo-hypoperfusion of the brain, and reduced cerebral spinal fluid dynamics in MS was shown to be related to CCSVI. Postmortem studies and histology corroborate the 2009 International Union of Phlebology Consensus decision

to insert CCSVI among venous malformations. Safety of balloon angioplasty of the extracranial veins was certainly demonstrated, while prospective data on the potential effectiveness of endovascular treatment of CCSVI support to increase the level of evidence by proceeding with a randomized control trial (RCT).

Taking into account the current epidemiological data, including studies on catheter venography, the autoptic findings, and the relationship between CCSVI and both hypo-perfusion and cerebro-spinal fluid flow, they conclude that CCSVI can be definitively inserted among the medical entities. Research is still inconclusive in elucidating the CCSVI role in the pathogenesis of neurological disorders. The controversy between the vascular and the neurological community is due to the great variability in prevalence of CCSVI in MS patients by the means of venous ultrasound assessment. More reproducible and objective CCSVI assessment is warranted. Current RCT may elucidate the role of CCSVI endovascular treatment.

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