

‘Venous insufficiency’ is not the cause of multiple sclerosis (MS) (but it could be a risk factor for MS and for different brain disorders)

Alfredo Romani, MD^a, Gisel Viselner, MD^c, Roberto Bergamaschi, MD^a, Stefano Bastianello, MD, PhD^{a,c}, Fabrizio Calliada, MD^{b,c}

^a IRCCS C. Mondino National Institute of Neurology Foundation, Pavia, Italy

^b IRCCS S. Matteo Hospital, Pavia, Italy

^c University of Pavia, Pavia, Italy

In the last four years several studies have been conducted and many articles have been published on the possible role of venous insufficiency in multiple sclerosis (MS).

In a preliminary study, published in 2007 by Zamboni et al., 89 MS patients and 60 healthy subjects were investigated using the transcranial color-coded duplex sonography technique and it was found that hemodynamic alterations of brain venous drainage were significantly more frequent in MS patients than in controls (1).

Zamboni et al. (2) continued their research and in a later study, they investigated 65 MS patients and 235 controls using transcranial and extracranial color Doppler and selective extracranial venography targeting the internal jugular and azygos veins. They found that all MS patients had evidence of multiple extracranial venous stenosis compared with the stenosis-free controls. This functional and/or anatomical venous abnormality defined by the presence of at least two of five Doppler criteria was named chronic cerebrospinal venous insufficiency (CCSVI). CCSVI is characterised by multiple stenoses of the extracranial venous drainage pathways, i.e. the internal jugular veins and the azygos veins, with flow alterations and collateral formation. A consequent failure of the blood-brain barrier and CNS accumulation of iron have been postulated, which could trigger and maintain the autoimmune cascade in MS (1-3).

Quickly, the news of a ‘new theory’ on MS etiology, implying possible therapeutic ‘liberation’ interventions, spread from the scientific context to patient organisations and to the general public. Websites, Facebook pages, blogs and other social network media promoted the venous theory. Thousands of MS patients worldwide were submitted to venous angioplasty outside controlled scientific contexts and before the actual prevalence and the biological meaning of CCSVI had been clearly established.

Over the past couple of years, several groups have published further research into CCSVI, the results of their studies showing considerable discrepancies and significant differences in the prevalence of CCSVI between MS patients and controls (4-9).

The high prevalence of CCSVI in MS patients observed by Zamboni and colleagues has been confirmed by other independent groups (4-6), but at the same time, several other authors were unable to document the presence of extracranial venous stenosis using the same or other methodologies (7-9). As a result, currently there is not even a general consensus on the actual existence of the phenomenon. Unfortunately, even part of the scientific community seemed, on occasions, to abandon the lay position and divided, in a rather fideistic manner, into ‘pro-CCSVI’ and ‘anti-CCSVI’ factions.

Recently, we had the opportunity to perform an international multicenter study on CCSVI, collecting the largest sample of MS patients yet published (10). Despite great between-center differences in CCSVI figures (suggesting that assessing techniques should be improved), we found consistent associations between CCSVI and MS phenotype. The type of associations found (older age at onset and greater disease severity in CCSVI-positive subjects) suggested to us that CCSVI may act on MS as a ‘risk factor’ in a multifactorial causal relationship.

Recently, different studies have demonstrated the presence of significant associations between extracerebral abnormal venous flow and other neurological disorders, including transient global amnesia (11-13), transient blindness (14), cough headache, exertional headache (15), and idiopathic intracranial hypertension (16). However, most physicians do not assign practical importance to the cerebral venous circulation, probably due to poor knowledge of the venous system, its great anatomical variability and the consequences of its malfunction. It is easy ‘to forget’ the venous system, as disturbances of arterial blood supply and cerebrospinal fluid circulation are considered more clinically relevant.

It goes without saying that it falls to the medical community to answer, in a rigorous scientific way, the questions currently posed by MS patients, but the influence of extracerebral abnormal venous flow on disease risk and evolution must be explored not only in multiple sclerosis but also in other neurological disorders.

References

1. Zamboni P, Menegatti E, Bartolomei I et al. Intracranial venous haemodynamics in multiple sclerosis. *Curr Neurovasc Res* 2007;4:252-258
2. Zamboni P, Galeotti R, Menegatti E et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2009;80:392-399
3. Zamboni P. The big idea: iron-dependent inflammation in venous disease and proposed parallels in multiple sclerosis. *J R Soc Med* 2006;99:589-593
4. Al-Omari MH, Rousan LA. Internal jugular vein morphology and hemodynamics in patients with multiple sclerosis. *Int Angiol* 2010;29:115-120
5. Zivadinov R, Marr K, Cutter G et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. *Neurology* 2011;77:138-144
6. Simka M, Kostecki J, Zaniewski M, Majewski E, Hartel M. Extracranial Doppler sonographic criteria of chronic cerebrospinal venous insufficiency in the patients with multiple sclerosis. *Int Angiol* 2010;29:109-114
7. Doepp F, Paul F, Valdueza JM, Schmierer K, Schreiber SJ. No cerebrocervical venous congestion in patients with multiple sclerosis. *Ann Neurol* 2010;68:173-183
8. Yamout B, Herlopian A, Issa Z et al. Extracranial venous stenosis is an unlikely cause of multiple sclerosis. *Mult Scler* 2010;16:1341-1348
9. Baracchini C, Perini P, Calabrese M, Causin F, Rinaldi F, Gallo P. No evidence of chronic cerebrospinal venous insufficiency at multiple sclerosis onset. *Ann Neurol* 2011;69:90-99
10. Bastianello S, Romani A, Viselner G et al. Chronic cerebrospinal venous insufficiency in multiple sclerosis: clinical correlates from a multicentre study. *BMC Neurology* 2011;11:132 <http://www.biomedcentral.com/1471-2377/11/132>
11. Sander D, Winbeck K, Etgen T, Knapp R, Klingelhöfer J, Conrad B. Disturbance of venous flow patterns in patients with transient global amnesia. *Lancet* 2000;356:1982-1984
12. Schreiber SJ, Doepp F, Klingebiel R, Valdueza JM. Internal jugular vein valve incompetence and intracranial venous anatomy in transient global amnesia. *J Neurol Neurosurg Psychiatry* 2005;76:509-513
13. Chung CP, Hsu HY, Chao AC, Chang FC, Sheng WY, Hu HH. Detection of intracranial venous reflux in patients of transient global amnesia. *Neurology* 2006;66:1873-1877
14. Chung CP, Hsu HY, Chao AC, Cheng CY, Lin SJ, Hu HH. Jugular venous reflux affects ocular venous system in transient monocular blindness. *Cerebrovasc Dis* 2010;29:122-129
15. Doepp F, Valdueza JM, Schreiber SJ. Incompetence of the internal jugular valve in patients with primary exertional headache: a risk factor? *Cephalalgia* 2008;28:182-185
16. Nedelmann M, Kaps M, Mueller-Forell W. Venous obstruction and jugular valve insufficiency in idiopathic intracranial hypertension. *J Neurol* 2009;256:964-969