



Chronic Cerebrospinal Venous Insufficiency (CCSVI) in Multiple Sclerosis – From “The Big Idea” to “The Perfect Crime”?

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Multiple sclerosis (MS) is a chronic, primarily inflammatory demyelinating disease of the central nervous system (Compston and Coles, 2008). Pathogenesis is triggered by environmental factors in combination with genetic susceptibility. Typically migration of autoreactive lymphocytes across the blood-brain barrier initiates the activation of a complex autoimmune cascade, where monocytes and microglial cells then step in and further augment tissue damage by oxidative mechanisms. The histological hallmark of the disease is a perivenous sclerotic plaque, characterised by inflammation, oligodendrocyte depletion, astrocytosis, de- and remyelination as well as subsequent axonal degeneration (Lucchinetti et al., 2000).

This perivenous formation of the plaque has set the stage to introduce the hypothesis that a venous blockade may stand at the beginning of the chronic autoimmune process and may thus represent the true pathogenetic cause of the disease. A putative venous congestion has been discussed as a contributing factor to the pathogenesis of MS already 30 years before (Allen, 1981).

This discussion was resurrected in the year 2006 by Paolo Zamboni from Ferrara, Italy, who proposed parallels between an iron-dependent inflammation in chronic venous insufficiency (CVI) of the lower limbs and the perivenously located white-matter lesion in MS. He stated that his considerations may represent “The big idea” (Zamboni, 2006). Three years later, Zamboni et al. reported an impressive coincidence of MS and venous stenoses demonstrated with ultrasound investigations in various locations of deep cervical veins (Zamboni et al., 2009). This concept was then named “chronic cerebrospinal venous insufficiency (CCSVI). In this concept it is hypothesized that a blockage of venous flow leads to an increased venous blood pressure in the central nervous system, which in turn causes congestional bleeding with perivenous iron accumulation and subsequent inflammatory reactions (Zamboni 2009a).

In considering CCSVI as a highly specific finding in MS, it should be remembered that cerebral venous insufficiencies were already discussed as a causal factor in other neurological diseases such as transient global amnesia or idiopathic intracranial hypertension (Schreiber et al., 2005; Nedelmann et al., 2009). Furthermore, other conditions such as neck-dissection surgery result in changed venous outflow (Gius and Grier, 1950). There is no scientifically proven evidence for a higher incidence of MS in such patients with confirmed venous obstruction, so that serious doubts are raised about the conceptual plausibility of CCSVI as a significant factor. In addition, the spectacular findings of Zamboni

et al., reporting not only a high specificity but also a high sensitivity of venous pathology in MS, could not be reproduced by other groups.

In a small cohort of unselected MS-patients and matched controls in Bochum, Germany, only two fulfilled the required neurosonological features of CCSVI (Krogias et al., 2010). The group of Doepp et al. (Berlin, Germany), having a large experience of venous neurosonography, performed an extended study protocol in 56 MS-patients. None fulfilled the criteria for CCSVI (Doepp et al. 2010). At the 2010 annual meeting of the AAN, Zivadinov et al. (Buffalo, USA) reported the presence of venous constriction in more than 50% of MS patients, whilst CCSVI was also detected in about 30 % of the healthy controls (Zivadinov et al., 2010).

An Italian group from Padua (Baracchini et al., 2011) recently performed a very interesting study investigating 50 patients with a clinically isolated syndrome (CIS) and with additional evidence of dissemination in space of the inflammatory lesions (possible MS). In only eight (16%) of them were the CCSVI criteria fulfilled. In seven, additional selective phlebography was performed, revealing hypoplasia of internal jugular vein in one case as the only venous abnormality within the whole series. If CCSVI causes MS, one would expect the presence of CCSVI already at the onset of the disease. The findings of this Italian study do not support a causal relationship between CCSVI and MS.

These results are of special interest since Prof. Zamboni promotes endovascular intervention as a groundbreaking treatment of MS. An open-label trial was published by Zamboni et al. in the "Journal of Vascular Surgery" in 2009. In 65 patients with MS percutaneous transluminal angioplasty (PTA) was performed (Zamboni et al., 2009b). Most of the patients were on disease-modifying therapies. There was a lack of a control group. The authors claimed that this procedure has led to an improvement of the clinical outcome in relapsing-remitting MS (RRMS) patients. Being aware about the high variability of MS disease course, the improvement described may reflect the natural outcome, as clinical relapses mostly show remission. The effect on the annual relapse rate was not different from that reported from placebo treatment in placebo-controlled clinical trials. In patients with progressive forms of the disease no improvement was observed after PTA. Zamboni self-proclaimed this intervention as "liberation procedure". Unfortunately, such a name raises inappropriate expectations among MS patients.

Recently, a third German group (Frankfurt/Giessen) performed a sonographic study investigating 20 MS patients and 20 controls (Mayer et al., 2011). The only subject fulfilling the CCSVI-criteria was a subject from the healthy control group. As these findings cast serious doubt on the concept of CCSVI in MS, the authors entitle appropriately their paper "The perfect crime? CCSVI not leaving a trace in MS"

Conclusion and recommendations

Based on these extensive, scientifically solid data obtained from investigators outside of Ferrara, we see no rationale to support CCSVI as a key pathogenetic factor in MS. Furthermore an ongoing large multi-center Italian epidemiological study recruiting more than 1000 MS patients and about 1000 healthy controls and patients with other neurodegenerative diseases, promoted by the Italian Foundation of Multiple Sclerosis and endorsed by the Italian Society of Neurology will greatly augment our scientific knowledge about the relationship between CCSVI and MS.

There is the theoretical possibility that the venous drainage of autoimmune lymphocytes from the brain may cause some endothelial changes during the longstanding disease course of MS, maybe in combination with immunosuppressive therapies. Yet even if this were the case, this is insufficient to justify invasive, costly and potentially dangerous manipulations of the deep cervical venous system in MS patients.

Therefore, both the EFNS and the ENS Multiple Sclerosis Scientist Panel and ECTRIMS Executive Committee emphasize the high risk and absence of a scientific basis for 'liberation

procedures' in MS patients. All societies are in full accord with the **Multiple Sclerosis International Federation** statement on CCSVI (http://www.msif.org/en/research/msif_on_ccsvi.html)

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