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Original articles:
Paolo Zamboni, Roberto Galeotti, Erica Menegatti, Anna M Malagoni, Giovanna Tacconi, Sergio Dall'ara, Ilaria Bartolomei, and Fabrizio Salvi
Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis
J Neurol Neurosurg Psychiatry 2008; O: jnnp.2008.157164vl [Abstract]

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Chronic cerebrospinal venous insufficiency: a potential weakening factor of the bloodbrain barrier

Marian Simka (29 December 2008)

Chronic cerebrospinal venous insufficiency: a potential weakening factor of the blood-brain barrier

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Send letter to journal:
Re: Chronic cerebrospinal venous insufficiency: a potential weakening factor of the blood-brain barrier

Email Marian Simka

Dear Editor,

Multiple sclerosis is believed to be an autoimmune pathology, yet the mechanisms triggering the disease remain elusive. Therefore, I read with great interest the paper by Zamboni and his team who investigated the venous hemodynamics in patients with multiple sclerosis. His findings that this disease might be attributable to venous refluxes shed new light on the facts that have been known for decades (1), but have been mostly ignored by the scientific community. It should be answered, however, how this pathological outflows in the extra-and intracranial veins could trigger autoimmune reaction.

The loss of integrity of the blood-brain barrier, which is primarily built by tight-junction complexes between adjacent endothelial cells of the cerebrovascular endothelium, is a hallmark of multiple sc!erosis. In this context, parallels between multiple sclerosis and chronic venous insufficiency of lower extremities (which is also an endotheliocyte-focused pathology) could be helpful. Yet, it should be remembered that endotheliocytes building the blood-brain barrier highly differ from those in the periphery. Moreover, venous hypertension in cerebral and spinal veins is unlikely to disassemble the cerebrovascular endothelial barrier (2). Indeed, although Zamboni has found increased venous pressure distally of venous stenoses, these pressure gradients were rather small. Thus, it is more likely that not venous hypertension, but pathological pattern of the blood flow-associated forces, decreased level of shear stress in particular, disassembles the blood-brain barrier and increases the transendothelial permeability. It has been found that an enhanced expression of pivotal tight junction proteins: occludin and ZO-1 in the cerebrovascular endothelium was associated with reduced transendothelial permeability and it has been shown, moreover, that an increased shear stress, especially with pulsatile flow characteristics, upregulated these proteins (3). By contrast, loss of shear stress after flow cessation enhanced the blood-brain barrier permeability (4). Therefore, a reduced shear, for instance as a result of the refluxing venous blood flow, could potentially result in the weakening of the blood-brain barrier. This in turn could initiate an autoimmune attack against nervous tissue.

Several questions, though, should have been answered before multiple sclerosis was recognized as a fundamentally hemodynamic disorder. First, if intracranial reflux is indeed the trigger of multiple sc!erosis plaques, and not an innocent bystander. This will require additional studies in a much larger cohort of multiple sclerosis patients. Second, if these refluxes only bypass an occlusion and affect exclusively large cerebral and spinal veins, or they extend also into smaller veins (probable, damage of the bloodbrain barrier can occur on condition that a decreased shear stress influence the cerebrovascular endothelium in the postcapillary venules). Third, mechanistic links between venous refluxes and cellular and molecular pathways that are responsible for autoimmune reaction should be determined, since such a discovery could result in the development of novel effective pharmacologic

agents. Regarding these mechanisms, it should be suspected that the low shear-induced expression of ICAM-1 (adhesion molecule, which is responsible for the firm adhesion of leukocytes to endothelia) by cerebrovascular endothelium, could be a criticai point in the initiation of multiple sclerosìs plaque, since the crosslinking of ICAM-1 with integrins expressed on the leukocytic surfaces leads to a weakening of the blood-brain barrier and facilitates the transendothelial leukocyte migration (5).

Furthermore, consequently to Zamboni's findings it may be speculated that at least for some anatomical variants of pathological venous outflow, surgical correction of steno-occlusions can be a therapeutic option in addition to or instead of pharmacotherapy.

In conclusion, investigations of the extra- and intracranial hemodynamic disturbances in multiple sclerosis patients appear to be a challenging avenue and may open a new chapter of therapeutic approach to this debilitating disease.

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There is no conflict of *interest regarding this letter.*