DOES CHRONIC VENOUS INSUFFICIENCY PLAY A ROLE IN MS PATHOGENESIS?

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Chronic cerebrospinal venous insufficiency (CCSVI) is a syndrome characterized by flow blockages in the internal jugular and/or azygous veins (IJVs-AZ) with opening of collaterals and insufficient drainage proved by reduced cerebral blood flow and increased mean transit time in cerebral MRI perfusional study. As far as the origin of venous narrowing is concerned, phlebographic studies of the IJVs and AZ systems demonstrated that venous stenoses were likely to be truncular venous malformations. CCSVI condition has been found to be strongly associated with multiple sclerosis (MS), a disabling neurodegenerative and demyelinating disease considered autoimmune in nature. In several epidemiological observations performed at different latitudes on patients with different genetic backgrounds the prevalence of CCSVI in MS ranges from 56% to 100%. In this particular moment the status of the research cannot clarify at all if CCSVI should play a role in MS pathogenesis. There are 3 main research fields producing findings partially supporting this idea.

1. Brain pathophysiology assessed by non conventional MRI measures.

Brain pathophysiology is significantly modified by the presence of extracranial venous obstruction. Cerebrospinal fluid dynamics is the mirror of CCSVI, since reabsorption is of course hampered at the level of the dural sinus in consequence of the slight but significant increase of venous pressure. Redistribution of cerebrospinal fluid and brain volume in the skull is associated with the hemodynamic severity of CCSVI.

The vascular community is familiar with the increased iron deposition in the distal part of the territory not properly drained in consequence of chronic venous insufficiency. There are several papers describing the higher iron levels in the basal ganglia of patients affected by CCSVI and MS, the more distal territory drained by the parenchymal veins. A role for CCSVI in MS is consistent not only with the well known perivenular distribution of MS lesions, but also with recent studies that have found a central vein in the long axis of inflammatory MS lesions using ultra-high field MRI and abnormally high levels of redox active metals, particularly iron, identified with an MRI technique called susceptibility-weighted imaging (SWI). This is a new and sophisticated MRI technique developed by Mark Haacke in Detroit, capturing the interest of the neuroradiologists in this new field.

2. Pathology of the venous wall in course of CCSVI-MS

Specimen coming from jugular vein wall were analyzed and compared with control specimen. CCSVI-MS seems to be a peculiar disease, reinforcing the idea to be cause rather than product of MS due to the followings:

No T-cells infiltration in the vein wall

Prevalence of type 3 collagen respect to type 1, normally constituting the jugular wall in controls

Poor distribution of smooth muscle cells in the media with abnormal distribution in the adventitia, with arrangement in clusters rather than in longitudinal layers

Abnormal presence of intraluminal septum, flap, double channel, malformed valves clearly indicating problems in the development of the vein.

3. Genetics of CCSVI MS.

MS is a complex disorder thought to result from an interaction between environmental and genetic predisposing factors, which have not yet been characterised, although it is known to be associated with the HLA region on 6p21.32. It has been investigated in such region if a genotype-phenotype correlation might exist in MS people with evidence of the adjunctive CCSVI venous blockages phenotype. This was highly suspected due to the abnormal architectonics and molecular constitution of the jugular vein wall, above described. In order to explore the presence of copy number variations (CNVs) within the HLA locus, a custom CGH array was designed to cover 7 Mb of the HLA locus region (6,899,999bp; chr6:29,900,001-36,800,000).

The region we analysed contains 211 known genes. By using pathway analysis focused on angiogenesis and venous development, MS, and immunity, we tentatively highlight several genes as possible susceptibility factor candidates involved in this peculiar phenotype.

The CNVs contained in the HLA locus region in patients with the novel phenotype of CCSVI/VM and MS were mapped in detail, demonstrating a significant correlation between the numbers of known CNVs found in the HLA region and the number of CCSVI-venous stenosing malformations identified in patients. (Spearman: r=0.6590, p=0.0104; linear regression analysis r=0.6577, p=0.0106). Pathway analysis revealed common routes of interaction of several of the genes involved in angiogenesis and immunity contained within this region. Despite the small sample size in this pilot study, 15 patients, it does suggest that the number of multiple polymorphic CNVs in the HLA locus deserves further study, owing to their possible involvement in susceptibility to this novel MS/CCSVI plus phenotype, and perhaps even other types of the disease.