Integrating CCSVI and CNS autoimmunity in a disease model for MS

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Multiple sclerosis (MS) is currently classified as a cell-mediated, autoimmune disease on the basis of genetic, immunological, experimental and epidemiological data.[1] This widely accepted autoimmune model, in which the immune system is sensitized to myelin by external influences such as an infection, has recently been challenged by the observations that many persons with MS have a newly defined condition called chronic cerebrospinal venous insufficiency (CCSVI).2 CCSVI is characterized by impaired drainage of venous blood from the brain due to venous malformations. Such impairment can be detected by Doppler sonography with CCSVI being recognized as a condition in which two of five measured parameters of venous blood f10w from the brain are anomalous.[2,3]

Initial studies found that CCSVI exhibited a near 100% specificity and sensitivity for MS.[2, 3] These findings led to a new, vascular model for MS.4 In this mode!, venous blockages lead to reflux of blood into the brain which in turn leads to upregulation of adhesion molecules on the blood-brain barrier *(BBB),* iron deposition, subsequent inflammation, and breeches of the *BBB.* The passage of blood products into the CNS initiates inflammation and neurodegeneration which drive the neurological deficits that characterizes MS. Notably, the CCSVI model can account for various, previously inexplicable features of multiple sclerosis such as neurodegeneration, venocentricity of lesions and the common presence of iron deposits.[2,4] A1so, anecdotal findings of CCSVI in almost aIl MS patients evaluated for the condition (90%+) by' cIinicians in Poland, Jordan, and the USA, have added support to the mode!. A recent "Point of View" has challenged the mode!.5

Given that both the autoimmune model and the CCSVI model have robust data and theory to back them up, it may weIl be that both CCSVI and externally-driven, CNS autoimmunity are important contributors to MS. Recently released data from ongoing CCSVI studies at the University of Buffalo and at Georgetown University seem to favor an MS disease model which integrates both CCSVI and CNS autoimmunity.

The University of Buffalo study, led by Dr Robert Zivadinov and Dr Bianca Weinstock-Guttman, is an attempt to replicate the findings of Zamboni's research.[2,3] The Buffalo researchers are using the same Doppler technology and measuring the same five blood f10w parameters as the Zamboni team did in order to determine the presence or absence of CCSVI in 1600 subjects (950 CDMS, 100 initiaI demyelinating event, 300 other CNS diseases and 350 healthy controls). The results of Phase 1, which involved 500 patients (280 CDMS, 161 HC, 59 others), were recently released to the press.[6] Before discussing these results, it is important to discuss the results of another study which addresses a critical aspect of CCSVI.

Vascular researchers under the leadership of Dr Byung-Boong Lee of Georgetown University studied the nature and origin of the types of venous malformations which constitute CCSVI.[7, 8] A key finding of this work is that the venous malformations of CCSVI are of congenital origin and are not the product ofpost-birth, environmental insults or the MS disease process itself. This is a key constraint for any model involving CCSVI.

[Int AngioI2010;29:93-4]

Received on March 3, 2010; accepted for publication on March 9,2010.

The announced results of Phase 1 of the Buffalo study included:

1) 56% of persons with MS in the study had CCSVI;

2) 22% of healthy controls had CCSVI;

3) 38% of those with an initial demyelinating event had CCSVI;

4) 80% of those with more advanced MS had CCSVI.

The findings that 22% of the healthy controls and 56% of persons with MS had CCSVI indicate that CCSVI by itself does not cause MS. On the other hand, these results show that CCSVI is definitely associated with MS and, given that CCSVI is a congenital condition, this means CCSVI must be a part of the MS disease process. The final, intriguing result is that the higher the disability, the higher the chance that CCSVI is involved. Given the congenital origin of the vascular malformations, such a result indicates that CCSVI is an adjuvant to the MS disease process. This means, if one has MS and CCSVI, they have a much higher chance of progressing to a higher disability level than a person with MS but no CCSVI. This finding is not surprising considering the potential adverse effects of CCSVI-driven processes on the BBB and CNS. Overall, the Buffalo results indicate that neither the autoimmune nor the CCSVI model is adequate.

One model that can explain these recent results, and which honors the established data for MS, is that MS is a CNS autoimmune disease which, in many cases, is exacerbated by the chance presence of CCSVI. In this mode!, a prerequisite for MS would be the sensitization of immune cells to myelin although such sensitization would not guarantee a diagnosis of MS. The Buffalo results indicate that ~22% of the persons who develop a sensitization to myelin would also, by chance, have CCSVI. Given that CCSVI enhances autoimmunity by making it easier for immune cells to gain access to the CNS, it is assumed that most people with CCSVI and CNS autoimmunity will eventually progress to MS. Thus, it would not be surprising to find that a majority of those with MS would also have CCSVI. Furthermore, those with CCSVI would be more likely to progress to higher disability levels given the catalytic effect of CCSVI on CNS autoimmunity and the addition of neurodegeneration processes.

We can now say with confidence that CCSVI is a real phenomenon which is part of the MS disease process. This discovery provides better understanding of why MS is such a heterogeneous disease [9] that commonly includes substantial neurodegeneration.[1] Because of the effect of CCSVI on disease progression, it will be important for clinicians to determine whether or not CCSVI is present for each MS patient as soon as possible. Scans to determine the presence and nature of venous problems will be just as important as standard MRI scans when it cornes to diagnosing and designing treatment regimens for patients. CCSVI has ushered in a new era for understanding and treating MS.

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