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Multiple Sclerosis and Chronic Cerebrospinal Venous Insufficiency: The Neuroimaging Perspective

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generally provided to the reader as much as it is to the author. It is important to keep in mind that just because a book failed to gain attention from a large publisher does not mean it is bad; it only means that the publisher thought it would not make the company enough money. POD services such as the one the *American Journal of Neuroradiology* uses for its *Special Collection* series share nothing with vanity publishing. Vanity and scientific POD publishing may use the same digital printing techniques, but that is about it.

In the late 1800s and early 1900s, vanity and self-publishing were popular and had a better reputation than they do today. Renowned authors such as Carroll, Twain, Poe, Kipling, and Thoreau self-published some of their books. Vantage Press (founded in 1949) and Dorrance Publishing (founded in 1920) are 2 of the best-known vanity publishers. Although their current Web sites clearly reveal their pay-for-service nature, it seems that not all authors are happy with this.[8,9] Vantage Press was found guilty in a massive class-action suit by authors who complained the services offered in their contracts had not been honored.[10] Regardless, vanity publishers continue to proliferate and are becoming on-line–only or combined electronic/print enterprises.

A well-known one is Xlibris. Xlibris charges nothing for its basic program but demands a fee for services such as editing and galley proofs. Its CEO recently stated that the company will turn a profit even if does not sell a single book.[11] This has not escaped the attention of venture capitalists, and Xlibris is now partly owned by Random House and others, while Barnes and Noble and Time Warner have started similar operations. The Xlibris catalogue lists a whooping 25,000 books from 20,000 authors![12] Barnes and Noble's company, MightyWords, did poorly and closed in 2001. Another called iPublish is dedicated to electronic-only publishing.[13] It is said that some of these companies make a profit by selling as little as 5 copies of a book.[14]

As the number of readers in the United States has progressively decreased (last year 40% read 1 book or less), the number of would-be authors has increased nearly 25% in a 1-year period according to the previously cited *New York Times* article.[14] Vanity companies claim their publishing constitutes the democratization of literature. While in the past writing was the domain of a small elite, now anyone can write and publish a book. For as little as $3, one can upload a book onto a vanity Web site that uses POD and sell it via the giant on-line retailers. Because cost decreases as the size of the print run increases, traditional publishers must print and sell thousands of books to recuperate their investment and be able to offer the books at a reasonable price. This is not the case with vanity presses that use POD.

During the recent economic meltdown, popular books geared to entertainment showed significantly lower sales, while specialized niche books continued selling well, a fact stressed by the vanity media. Vanity companies also will tell you self-publishing may lead to being noticed by literary agents and it gives you an opportunity to sell your book to one of the major publishing houses (similar to posting a movie on YouTube and then getting an offer from a major Hollywood studio). Some individuals argue that vanity publishing serves smaller disciplines well, such as poetry, where getting published and recognized is very difficult. When governments impose censorship, vanity printing may help promote resistance and distribute ideas. The most famous example of this was the Soviet "Samizdat" movement during the Communist era. At that time, Bukovsky said, "I myself create it, edit it, censor it, publish it, distribute it, and get imprisoned for it."[15]

To me, vanity printing falls into the same category as vanity plates for your car or vanity telephone numbers. I cannot imagine telling someone to call me at 1-800-CAS-TILLO or driving around in a car tagged EIC-AJNR. There are many things that make you feel cool, but vanity publishing shouldn't be one of them.

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EDITORIAL

Multiple Sclerosis and Chronic Cerebrospinal Venous Insufficiency: The Neuroimaging Perspective

In patients with multiple sclerosis (MS), Zamboni et al[1] described anomalies of venous outflow at color Doppler high-resolution examination and multiple severe extracranial stenosis at venography, affecting the internal jugular, the vertebral, and the azygous veins. The authors focused their evaluation on 5 anomalous parameters of cerebral venous drainage and defined as abnormal the presence in a single subject of at least 2 of these parameters. This picture was termed "chronic cerebrospinal venous insufficiency" (CCSVI) and was found in all patients with MS studied and in none of the controls.

Starting from this first report,[1] several other articles[2-5] from the same group were published that might support the theory of a role of cerebral venous circulatory abnormalities in the pathogenesis of MS. This stimulated a wide array of dis-

cussion in the scientific and patient communities, as well as a significant amount of publicity via lay media. Because the CCSVI theory, if confirmed, may open new therapeutic venues for MS, a significant effort has been and continues to be devoted to proving or disproving it, especially in that the proposed surgical intervention to restore normal venous outflow is not risk-free and can have serious consequences, which have already occurred in 2 patients.[6]

Several studies which are receiving substantial grants from national and international MS societies are currently being performed, to scrutinize the CCSVI theory. The technical limitations of the approach applied by Zamboni et al[1] and its conceptual shortcomings have been discussed previously by groups of experts in the field.[7,8] Remarkably, a recent survey performed at the Department of Neurology of the University of Buffalo, in cooperation with Dr Zamboni's group, reported a narrowing of the extracranial veins in only 55% of the first 500 patients with MS enrolled, but also in 25.9% of the 161 healthy controls. Clearly, these findings[9] are much less striking than the 100% separation initially reported. Independently, an extra- and transcranial color-coded sonography study of 56 patients with MS and 20 controls performed by a German group of investigators[10] not only was unable to replicate Zamboni's original findings but found no significant difference in the cerebral and cervical venous drainage between patients and controls, with the exception of a higher blood volume flow in patients with MS in the upright position, but not in the supine position (a finding that might reflect vascular dysregulation likely due to MS affecting the autonomous nervous system).

This commentary focuses on the contribution provided, so far, by MR imaging and other neuroimaging studies in shedding light on the value of the CCSVI theory in MS.

Neuroimaging Studies Directly Assessing the CCSVI Theory

Phase-contrast MR images allow noninvasive evaluation of the flow direction, velocity, and volume of extra- and intracranial blood and CSF. This technique has been recently combined with contrast-enhanced MR angiography at 3T to test the CCSVI theory in 21 patients with relapsing-remitting (RR) MS compared with 20 healthy volunteers.[11] This study found no difference between patients and controls regarding internal jugular venous outflow, aqueductal CSF flow, or the presence of internal jugular blood reflux, whereas internal jugular vein stenoses were documented in 3 patients with MS.

Abnormalities of blood flow patterns due to CCSVI have been proposed as causing increased iron deposition in the brain,[12] a finding that is indeed frequently observed in patients with MS. Iron deposition in the human brain occurs also with normal aging and in the course of many neurodegenerative diseases,[13] which reportedly have not been associated with CCSVI. Although the mechanisms related to increased iron deposition in neurodegenerative conditions (including MS) are not fully elucidated, inflammation in MS has been thought to cause local accumulation of iron via a disruption of the blood-brain barrier,[14] accumulation of iron-rich macrophages,[14] and reduced axonal clearance of iron.[15] Iron accumulation has been proposed as having a pathogenic role in MS, via secondary injury related to oxidative stress, lipid peroxidation, and free radicals.[16]

Among other techniques, susceptibility-weighted imaging (SWI) has been applied to assess iron deposition and cerebral venous oxygen level changes in patients with MS. These studies have confirmed previous results based on different MR imaging modalities[13,17-21] and have shown an increased iron concentration in the deep gray matter (GM) nuclei in patients with MS compared with healthy controls.[22,23] In a pilot study of 16 patients with RRMS, such an increased iron concentration was related to the number of abnormal venous sonographic criteria fulfilled.[23] However, an SWI study at 3T demonstrated a significantly reduced visibility of the venous vasculature in the periventricular white matter (WM) of patients with RRMS.[24] In line with previous positron-emission tomography studies, which showed a reduction of oxygen use and extensive hypometabolism in the GM and normal-appearing (NA) WM of patients with MS,[25,26] this reduced visibility and volume of the cerebral venous system, reflecting a decreased venous blood deoxyhemoglobin concentration, can be interpreted as a result of a decreased oxygen extraction in the diseased MS tissue. On the contrary, occlusion of the venous vasculature should lead to an intracranial venous engorgement (increased visibility and volume) and enhancement of susceptibility effects, due to increased oxygen extraction.

Overall, these findings do not support the CCSVI theory in MS, and most of all, they do not support endovascular procedures suggested as a potentially effective treatment.

MS and Brain Vasculature

An association between plaques and veins in the central nervous system (CNS) of patients with MS has been reported by seminal pathologic[27,28] and MR imaging[29] investigations. Using susceptibility-weighted MR venography based on SWI, which is sensitive to deoxygenated blood, Tan et al[29] identified a central vein in 94/95 lesions from 17 patients with MS. The typical ovoid shape and orientation of the long axis of MS lesions correlated well with the course of the veins. The introduction in the clinical arena of high- and ultra-high-field-strength scanners is further elucidating the relationship between plaque location and morphology and CNS vasculature in MS. A few preliminary studies performed at 7T[20,30-32] showed the ability of MR imaging to define the morphologic characteristics of MS lesions in the WM and GM at a resolution that resembles that of the pathologic assessment. Remarkably, some of these studies[20,30,31,33,34] also allowed a better definition of the relationship between demyelinating lesions and the deep venous system and confirmed that most MS plaques are centered around the microvasculature. While such a perivascular distribution of MS plaques fits with the notion of the inflammatory and immunologic nature of the disease, it does not support the CCSVI theory. Indeed, venous occlusion should result in venous hypertension, which, in turn, should cause abnormalities such as edematous swelling[35,36] and hemorrhagic and ischemic infarctions,[36] findings that are not seen in demyelinating plaques of patients with MS.

Abnormalities of regional cerebral hemodynamics in MS have been investigated by using perfusion MR imaging. These studies have, for the most part, demonstrated widespread hypoperfusion in focal lesions, NAWM, and the cortical and deep GM of patients with MS with the main clinical pheno-

types.[37-39] This finding is consistent with earlier histopathologic studies reporting vascular occlusive changes in MS, characterized by thrombosis of small veins and capillaries, vein wall hyalinization, and intravascular fibrin deposits.[40] To assess whether NAWM hypoperfusion in MS may be related to a primary vascular etiology or rather may be secondary to hypometabolism, a recent study correlated diffusivity measures with perfusion findings in the corpus callosum of patients with RRMS. These authors reported a correlation between decreased perfusion and decreased mean diffusivity, a finding more consistent with what would be expected in primary ischemia than in secondary hypoperfusion.[41] The notion that ischemia may play a role in the pathogenesis of a subset of MS lesions is also supported by the in vivo descriptions of reductions in the apparent diffusion coefficients in new focal lesions of patients with MS[42,43] and by pathologic observations showing that in some patients with MS, lesions share similarities with tissue alterations seen in the early stages of ischemia.[44] Remarkably, a longitudinal study[45] showed that abnormalities of cerebral perfusion may precede overt change of blood-brain barrier permeability during the development of focal MS lesions; these abnormalities suggest the presence of inflammation-related vasodilation in the acute stage of lesion formation.

Additional mechanisms have been considered to explain NAWM hypoperfusion in MS, including the following: 1) a diffuse astrocyte dysfunction, possibly related to an abnormal release of K^+ in the perivascular space and, thereby, a reduced degree of vasodilation[46]; and 2) mitochondrial injury,[47] secondary to toxic inflammatory mediators, reactive oxygen, and nitric oxide species. Moreover, given the tight coupling between arterial flow, tissue metabolism, and venous flow, the reduced intracranial venous volume and structural changes in extracranial veins draining the CNS in patients with MS may simply represent an adaptive physiologic response to low intracranial vascular (arterial) input and low brain metabolism. Given the elasticity and collapsibility of veins, in some patients with MS, narrowing and stenosis may occur as a result of the disease process, but it would follow along these lines that opening these collapsed veins would not benefit patients.

In short, the present understanding of MS as an immune-mediated inflammatory-demyelinating disease suffices to explain these findings.

Conclusions

CCSVI is a sonographic construct that is poorly reproducible and questionable in terms of known pathophysiologic factors established in MS. The neuroimaging findings reviewed here do not support the CCSVI theory in MS, but rather point to a concomitant disturbance of the brain microcirculation in patients with MS, which deserves further investigation but can be well explained by secondary vascular inflammatory changes known to occur with this disease.[44,48,49] As a consequence, endovascular treatment of presumed vascular abnormalities in MS should be discouraged vigorously.

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EDITORIAL

How Everybody Wins When Playing by the Rules: The Benefits of Investigator-Initiated Industry-Sponsored Clinical Trials

The medical device industry is a fast-growing field contributing many new treatment options for a variety of conditions every year. In the field of interventional neuroradiology, many devices are approved for use each year by the United States Food and Drug Administration (FDA) with little meaningful data.[1] While industry-sponsored trials for medical devices can help physicians further understand the safety and efficacy of medical devices, there is reason for concern regarding bias in the results of these trials.[2-4] Many studies have demonstrated that industry-sponsored clinical studies are significantly more likely to demonstrate positive results for industry-developed devices than their non-industry-sponsored counterparts.[2-4] Furthermore, there is much concern regarding real and potential abuses of physician-industry relationships. With so many approved devices on the market with little or no meaningful data, postmarket industry-sponsored research is essential in presenting more data to physicians and regulatory boards. However, the intrinsic qualms associated with industry-sponsored research provide a certain dilemma regarding improved postmarket surveillance.

How We Got Here

Medical devices in the United States are subject to significantly less regulation than pharmaceuticals. The FDA has "classes" of medical devices ranging from class I (with minimal potential harm, such as elastic bandages, surgical gloves, and so forth) to class III (which support or sustain human life; are of substantial importance in preventing impairment of human health; or which present a potential unreasonable risk for illness or injury; devices such as deep brain stimulators fall into this category).[5] Class III devices require the most rigorous scientific and regulatory review to assess their safety and efficacy. Most devices in interventional neuroradiology fall into Class II. Clearance for marketing of Class II devices means that the device must be "substantially equivalent" to previously ap