

# **An Open Letter to the Authors of Chronic Cerebrospinal Venous Insufficiency and Multiple Sclerosis (Khan et al, 2010, Annals of Neurology)**

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Background: A week ago a “Point of View” article on Chronic Cerebrospinal Venous Insufficiency and Multiple Sclerosis was made available online at the website of Annals of Neurology. It was written by 11 authors, with both neurologists and radiologists being represented. Notably 7 of 11 authors (including the first four, senior authors) disclosed significant financial interests with pharmaceutical companies which produce drugs for MS (see Appendix).

In their opinion piece, the authors discussed Dr Zamboni’s published work on CCSVI and concluded it should be considered “preliminary”. To my knowledge no one has ever considered it to be otherwise. Most of the article consisted of points and arguments that suggest it is not reasonable to consider CCSVI to be the main cause of the MS disease process. Such a discussion has some value although I must point out few are claiming CCSVI is the main driver of MS. Dr Zamboni has been very clear on this and simply says CCSVI may be a significant contributor to MS onset and progression. Thus, in their Point of View, the authors essentially put up a straw man and then spend most of the article taking it apart. Overall, most of their arguments against CCSVI as the main cause of MS are readily dismissed once MS is seen as an autoimmune disease often exacerbated by the presence of CCSVI.

The only truly offensive part of the article was the authors’ attempt to rationalize their self-serving desire that no one with MS should be tested for CCSVI. They emphasized the very rare occurrence of a serious adverse event associated with endovascular treatment and totally neglected to discuss the risks of not being tested and treated for CCSVI. Such a one-sided rationalization which is nullified by a blatant conflict of interest of most of the authors cannot be taken seriously.

Below is an open letter to the authors.

Dear Dr Khan and fellow authors,

I recently read your opinion piece on CCSVI which was made available online in Annals of Neurology (Khan et al, 2010) last week. I see it as part of “MS Wars: Part II – The Medical Empire Strikes Back”. Overall, I enjoyed reading your article because I always find it useful to read the arguments of those who hold a different opinion than me on an important subject. I was also pleased that you restrained yourselves and did not follow Mark Freedman’s infamous lead and call Dr Zamboni’s work “a hoax”. The only part of the article I found distasteful was

your advice for persons with MS to not get tested for CCSVI for at least 5-10 years (while further research is being done). I discuss this point in detail later.

For a more up to date and more objective opinion piece on MS and CCSVI, I direct you to my recent article “CCSVI and Multiple Sclerosis: Integrating New Data to Help Guide Actions” which can be downloaded at <http://www.direct-ms.org/magazines/Embry%20New%20CCSVI%20Data%20for%20Guiding%20Actions%2002%2010.pdf> . This article interprets the relationship between the CCSVI and MS in light of the recently available results from CCSVI-related studies at the universities of Buffalo and Georgetown. Given you must have known this critical information would be available in early 2010, I am surprised you rushed into print before such crucial data were available. This made your “Point of View” hopelessly outdated on the day it became available. I can only surmise you did not want any solid data from the Buffalo and Georgetown studies to cause problems for your critique.

In my article I also address the question of whether persons with MS should get tested and treated for CCSVI as soon as possible or should wait 5-10 years until major clinical trials are completed and analyzed. A reasonable answer to this question depends on the major new data from the universities of Buffalo and Georgetown. Your analysis of this same question without the benefit of these crucial data is sadly premature and poorly supported. As I will discuss later, my advice on this key question is the opposite of yours and, unlike yours, mine is supported by the new data and is not hopelessly compromised by unacceptable and major conflicts of interest.

To me, given the robust results of the University of Buffalo Phase 1 study and the findings of hundreds of endovascular procedures which have already been done to relieve CCSVI (almost all have found major blockages in the veins draining the brain), there can be little doubt that CCSVI is associated with MS. And, as I argue in my article, because the vascular malformations which constitute CCSVI are mainly congenital (Georgetown data), there can be little doubt that CCSVI is an important factor in the MS disease process in many cases (definitely not all cases). Of course, without this new data, you could not offer any worthwhile opinions on whether or not CCSVI is part of MS.

Furthermore, any claim that the established, robust association of CCSVI and MS is purely coincidental cannot be taken seriously although I am sure such an implausible thought will be offered by some. In my article, I interpret MS as an autoimmune disease which, in many cases, is exacerbated by the co-occurrence of CCSVI (in 25% of the healthy population and perhaps up to 60% of persons with MS according to the University of Buffalo work). I find the “either it’s autoimmune or it’s CCSVI” polarity which dominates your article to be overly simplistic. An integration of the two phenomena is the most reasonable model because both have very strong evidence supporting their involvement in MS. Of

course, the new data were required for such an integrated model to become obvious.

Another key question which you could not evaluate without the new data is whether or not CCSVI contributes to MS progression. The University of Buffalo results nicely show that the higher the disability, the higher the chance that CCSVI is involved. The congenital origin of the vascular malformations dictates that such results mean that CCSVI is an adjuvant to the MS disease process. 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. Given the potential adverse effects of CCSVI on the CNS vascular system, such an empirically-supported association is certainly rational and plausible.

The argument that this relationship is due to MS causing CCSVI, an argument you mentioned in your article, is ruled out by the data although once again I am sure such an illogical interpretation will continue to be put forth. Many of you have experience with EAE, the animal model for MS as an autoimmune disease. I suggest you try to see the relationship of CCSVI and MS as being similar to the addition of tetanus toxin (opens BBB) to the myelin/adjuvant mix which drives autoimmunity in EAE.

Given the above, if one has MS, they would be wise to get tested for CCSVI and, if necessary, treated for it. This is based on the logical reasoning (precautionary principle) that the chance of harm associated with doing nothing (i.e. progressing more rapidly and farther if CCSVI is present) is substantially greater than the chance of harm associated with having endovascular surgery to relieve CCSVI (extremely rare, serious side effects). As Mark "It's a Hoax" Freedman correctly and perhaps prophetically said, "Time is Brain" (Freedman, 2009). With this, and the apparent role of CCSVI as an accelerant of the MS disease process, in mind, persons with MS do not have the luxury to follow your self-serving, time table and wait 5-10 years for what you see as required research to be completed.

Of course, most people with MS realize the obvious and are desperately seeking such testing and treatment. Who wouldn't if they had MS and were progressing (the current drugs really don't do much for most in the long run). Notably, most neurologists are unable to understand or empathize with such a logical decision to want to get CCSVI treated if present. The advice in your opinion piece of not to get treated for CCSVI for at least 5 -10 years from now is both irresponsible and dangerous. And this brings us to the topic of the serious lack of objectivity of such advice.

One big problem with you saying not to get treated for CCSVI is that almost all of you are closely aligned with the pharmaceutical industry and thus have a major conflict of interest when you offer such advice. Should we heed the advice of scientists closely allied with the petroleum industry when it comes how to address the potential problems of global warming? Of course not! We do not

heed it because they have a blatant conflict of interest so we just don't know if they are pulling a fast one or not. One thing we know for sure, it is highly unlikely their advice will be objective.

Like it or not, the long list of drug company associations for most of the authors (see appendix below) disqualifies your "Point of View" as being a credible source when it comes to advice on what to do about a non-drug treatment like CCSVI. I would stress, you can't have it both ways. You can't take money from drug companies and then turn around and offer advice on a treatment which potentially would harm the drug companies. Naturally your advice is going to be "Don't use the non-drug treatment. Use only the drugs". How can it be otherwise and that is why advice from those with obvious conflicts of interest is self-serving and worthless. It is too bad that most neurologists aren't like George Ebers of Oxford University and rise above the temptation to take the easy money from the drug companies and thus escape a barefaced conflict of interest.

In summary, your Point of View is completely out of date and your advice regarding CCSVI testing and treatment is totally compromised and of no value. It is also potentially very harmful for persons with MS. Five to ten years is a very long time to have to wait for testing and treatment of CCSVI and such a long time represents a huge amount of lost brain (Time is Brain). I can only suggest you try hard to take a patient-centred, evidence-based approach and do everything you can to make testing and treatment of CCSVI available as soon as possible.

Sincerely,

Dr Ashton Embry  
President, Direct-MS

#### Appendix- Financial Disclosures of the Authors

Dr Khan has received research support from the National MS Society (NMSS), the National Institutes of Health (NIH), Teva Neuroscience, Genzyme Corporation, Biogen Idec, Novartis Pharmaceuticals, and Acorda Therapeutics; consultancy and speaking honoraria from Teva Neuroscience, Biogen Idec, Novartis Pharmaceuticals, and Bayer Healthcare.

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