CCSVI and Multiple Sclerosis: Integrating New Data to Help Guide Actions

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Introduction

Over the last few months, the world of multiple sclerosis has been in chaos over the intense debate of how a completely new concept, that of chronic cerebrospinal venous insufficiency (CCSVI), is part of the MS disease process. Furthermore, the debate has also included heated discussions of whether or not treatment of the CCSVI condition should be part of multiple sclerosis treatment in the near term. This debate has polarized the multiple sclerosis community into two basic camps. One camp, composed mainly those living with MS (patients, care givers, patient-centred charities), sees CCSVI as the likely primary cause of multiple sclerosis and have advocated for CCSVI testing and treatment being available for anyone requesting it.

The other, much more conservative camp, composed mainly of those living off MS (researchers, neurologists, big charities), is much more skeptical of the role of CCSVI in MS. Notably, some prominent MS researchers with strong ties to the pharmaceutical industry have publicly labeled the CCSVI concept as valueless, ethically questionable and a hoax. This camp, which basically represents those in power, is strongly against any testing or treatment for CCSVI until clinical research has demonstrated that resolution of CCSVI provides a clear benefit. This will, at best, happen in a time frame of 5-10 years.

Some people with MS are already getting tested and treated for CCSVI in developing countries because they feel they have much more to gain than they have to lose. It is important to base decisions for action on all available data and in the last few weeks some important new data have become available on CCSVI and MS from two different and very reliable sources (University of Buffalo and Georgetown University).

I have written this article to summarize these new data, to integrate them into my interpretations of the relationship between CCSVI and MS, and finally, on the basis of these new interpretations, to recommend a course of action for those with MS. We will of course be getting more data and it is possible my interpretations will change somewhat. However, the current new data are reasonably robust and I am confident the main thrust of the interpretations and the consequent recommendations for action will not require much, if any, revision.

CCSVI Review

CCSVI refers to a condition in which the drainage of venous blood from the brain is impaired due to venous malformations. Such impairment can be detected by Ultrasound Doppler technology which measures speed and direction of blood flow in the main veins which drain the brain (jugulars, azygos, vertebratal). The venous malformations which

are the cause of CCSVI are imaged by either MRV or venography. This novel concept was first introduced by Italian researchers in 2007. In December 2008, a paper entitled "Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis" and written by Dr Paolo Zamboni and colleagues was made available online by the prestigious Journal of Neurology, Neurosurgery and Psychiatry and it was formally published in April, 2009.

In their studies, Dr Zamboni and his team measured five parameters of venous flow from the brain using an Ultrasound Doppler technology and the reader is referred to their paper (Zamboni et al, 2009; http://jnnp.bmj.com/content/80/4/392.full.pdf) for further details. Zamboni and colleagues defined CCSVI as a condition in which two of the five measured parameters of venous blood flow from the brain were anomalous. The researchers found that almost all persons with MS (65 subjects) exhibited CCSVI and that very few controls (235) had such a condition. They also used venography to image the venous system and to document venous malformations which were responsible for the CCSVI they had recognized. However, it is important to note that CCSVI is defined on the basis of the occurrence of 2 or more Doppler-measured blood flow anomalies and does not depend on venography.

With this study, the Zamboni team seemed to have identified a never before seen, rare condition in MS and that it had a near 100% specificity and sensitivity. Such results were nothing short of astonishing. Given the very high specificity and sensitivity and the fact that impaired venous drainage could account for various, previous inexplicable features of multiple sclerosis (e.g. venocentricity of lesions and associated iron deposits), it was hypothesized that CCSVI was an important part of the MS disease process and perhaps even the primary cause of the disease. Dr Zamboni provided reasonable interpretations regarding how CCSVI might well contribute to the MS disease process through degrading the blood-brain barrier and promoting neurodegeneration. He also conducted an initial phase 1 trial of relief of CCSVI for MS. This trial demonstrated that relief of CCSVI is safe and may well be beneficial for MS.

Perhaps the most astonishing aspect of the revolutionary Zamboni findings was the fact that they were completely ignored by almost the entire MS research community, MS neurologists and all the large MS charities. However, persons with MS picked up on the Zamboni research within days of the availability of the watershed article in December 2008 and CCSVI soon became the biggest topic of online discussion in the MS patient community throughout 2009. MS patients began independently getting treatment for CCSVI by interventional radiologists in a few centres in the spring of 2009. In the fall of 2009, a powerful documentary on the Zamboni discoveries and his phase 1 trial results was made by Avis Favaro and Elizabeth St Philip of the CTV network of Canada and the "CCSVI Cat" was let out of the bag. Within 24 hours of the airing of the documentary, MS researchers, neurologists and charities throughout the world were scrambling to address the topic of CCSVI due to an unprecedented and very annoying (from their perspective) show of interest in the topic by their clients.

University of Buffalo Study

In 2008, two open-minded and forward-thinking MS researchers at the University of Buffalo, Dr Robert Zivadinov and Dr Bianca Weinstock-Guttman, recognized the great potential importance of Dr Zamboni's research and decided to undertake a major study to see if Dr Zamboni's impressive results could be replicated. Clearly, if they could be confirmed, then it will be very difficult to deny that CCSVI is a significant factor in the MS disease process. Furthermore, an unequivocal demonstration that CCSVI is associated with MS would be enough to justify a proper clinical trial to test the hypothesis that resolution of CCSVI is an effective treatment for MS, especially in the early stages.

Drs Zivadinov and Weinstock-Guttman began their study in 2009 and it was called "Combined Transcranial and Extracranial Venous Doppler (CTEVD) evaluation in MS" and in this article I will simply refer to it as the Buffalo Study. The Buffalo study will include about 1600 subjects and is being done in three phases. Phase 1 has recently been completed and it involved 500 patients with included 280 persons with MS, 161 healthy controls and 59 subjects who either had experienced a clinically isolated syndrome (CIS) (in most cases (80%+) a precursor to MS) or who were suffering from either a neurological or autoimmune disease. The Buffalo researchers used the same Ultrasound Doppler technology and measured the same five blood flow parameters as the Zamboni team did in order to determine the presence or absence of CCSVI in all 500 subjects.

The biggest questions regarding CCSVI that might be answered by the Buffalo study are 1) Is CCSVI clearly associated with MS? and 2) Is CCSVI part of the MS disease process? Researchers at the University of Buffalo recently released some results from the completed Phase 1 of their study. Although the released results are "preliminary", the large populations of MS patients and controls in the Phase 1 study have yielded some statistically significant and robust answers to the two questions listed above. I will provide my interpretations of the Buffalo results after I briefly describe the other important recently published study which addresses a key aspect of CCSVI.

The Origin of Venous Malformations which Cause CCSVI

One of the big questions regarding CCSVI is when does the condition originate. Is it present at birth (congenital), or does it form after birth but before MS is diagnosed due to various environmental insults, or is it a product of the MS disease process (i.e. an effect rather than a cause)? The answer to this question obviously bears on the question of whether or not CCSVI is a causal factor of MS.

A study which addressed the types of venous malformations which constitute CCSVI and their origin has been undertaken by vascular researchers under the leadership of Dr Byung-Boong Lee of Georgetown University in Washington DC. Dr Lee and his colleagues have written two comprehensive papers on this topic and currently they are

"in press" in the scientific journal, International Angiology. A few weeks ago, Dr Lee generously shared preprints of both papers with me.

One paper is entitled "Diagnosis and treatment of venous malformations: Consensus Document of the International Union of Phlebology (IUP)-2009" and it presents a solid case that the venous malformations of CCSVI are congenital in origin. Notably, this interpretation is a consensus opinion of vascular researchers from 27 countries and thus it is very hard not to take it as gospel at this time. The other paper is entitled "Embryological Background of Truncular Venous Malformation in the Extracranial Venous Pathways as the Cause of Chronic Cerebro-Spinal Venous Insufficiency" and it provides very detailed data on the venous malformations of CCSVI as well as their embryological development.

The bottom line from the exceptionally important research of Dr Lee and his colleagues is that **the origin of CCSVI is congenital** (in utero) and is not the product of post-birth environmental insults or the MS disease process. This means, if CCSVI can be shown to be closely associated with the MS disease process, then it is almost certainly a causal factor of MS. The alternative interpretation would demand an incredible chance coincidence of CCSVI and MS and it cannot be considered plausible. So now we will return to the Buffalo results which provide the answer to the question of whether or not CCSVI and MS are associated.

Results of Phase 1 of the Buffalo Study.

On Tuesday, February 11, 2010 some of the main results of Phase 1 of the Buffalo Study were made public in a press release. Importantly, a few other results were released in a CBC document. These results consist of:

1) 55% of persons with MS in the study had CCSVI
2) 22% of healthy controls had CCSVI
3) 10% of subjects tested (50) were classified as borderline and were included in the non-CCSVI category for the above statistics. When these individuals were excluded from the statistical analysis, 62% of persons with MS had CCSVI and 26% of healthy controls had CCSVI.
4) 38% of those with Clinically Isolated Syndrome (CIS) (start MS in most cases) had CCSVI
5) 80% of those with more advanced MS (EDDS levels not specified) had CCSVI

To me these results are nothing short of spectacular and, in combination with Dr Lee's results discussed above, provide us with some very solid answers to our two main questions. They also allow a number of other reasonable interpretations to be made and I think we now have a very good understanding of how CCSVI fits together with MS. I suspect my explanation will not be embraced by either those who see CCSVI as the primary cause of MS or by those who see CCSVI as "interesting" but likely of not much importance. My model, which integrates CCSVI and MS on the basis of the new data, provides a third, less extreme option. This option accommodates all we know about MS

and does not include any special pleading, a problem which continues to plague the other two options.

CCSVI and Multiple Sclerosis – New Interpretations

The combination of the Buffalo data with the recently established, congenital origin of the vascular malformations which cause CCSVI have led me to the following interpretations regarding CCSVI and MS:

1) The occurrence of CCSVI in approximately one quarter of the healthy controls strongly indicates that **CCSVI by itself is not a big deal** (one person at every bridge table has CCSVI). However, we cannot exclude the interpretation that CCSVI may be a risk factor for other neurological diseases which occur mainly in later adulthood (more on this later). There is now little doubt that, in most cases, **CCSVI by itself does not cause MS**. If this was so, MS would be a very common disease.

2) The occurrence of CCSVI in 55/62% of all persons with MS and only in 22/26% of healthy controls demonstrates CCSVI is 2.4 times more common in persons with MS. Given the large number of subjects studied, this establishes beyond a reasonable doubt that **CCSVI is associated with MS**. This established association, in combination with the congenital origin of CCSVI, dictates that **CCSVI is a causal factor of MS** in many cases.
   The determination that 62% of all persons with MS had CCSVI (borderline cases eliminated) and that it was present in 38% of those with CIS (start of MS in most cases), have led me to the interpretation that CCSVI is a causal factor of MS in 50% to 75% of all cases and, conversely, is NOT a causal factor (i.e. not present) in 25 to 50% of MS cases. These ranges of percentages are based the established statistic that 80-90% of CIS cases progress to MS and that more refined technology may well identify more cases of CCSVI (i.e. currently more false negatives than false positives). However, better detection of CCSVI will not notably change the current ratios (e.g. CCSVI is about 2.4X more common in PwMS than healthy controls) which are the keys to my interpretations.

3) Given about 25% of healthy controls had CCSVI and about 40% of those with MS did not have CCSVI, **CCSVI cannot be seen as the sole primary cause of MS.** However, I would again stress CCSVI is definitely an important causal factor in many cases**.** This tells us that **other significant causal factors have to be part of MS.** Given all the genetic, epidemiologic and immunologic data demonstrating MS is an autoimmune disease in most cases, two obvious candidates for such factors are EBV infection and vitamin D deficiency as has been discussed by numerous authors. It is reasonable to assume that other causal factors exist. I refer the reader to my 2004 paper which looked at potential environmental factors in MS (http://www.direct-ms.org/pdf/Ashton/Embry-Darwinian.pdf). I identified 7 plausible, causal factors and I would now add CCSVI to that list.

4) It would appear that **CCSVI not only is a causal factor but that it also contributes to the progression of MS**. Such an interpretation is very hard to dispute given the findings that 38% of CIS (start MS) subjects have CCSVI, 55/62% of all persons with MS have CCSVI, and a whopping 80% of persons with more advanced MS have CCSVI. These data demonstrate a clear and impressive increase in the percentage of persons with both MS and CCSVI with increasing disability level. Such a finding can only be realistically interpreted to mean that **CCSVI is a significant accelerant of the MS disease process.** Thus, persons whose MS includes CCSVI have a much greater chance of progressing to higher disability levels.
   I would emphasize that the alternative explanation - that CCSVI increases with increasing disease state because of the MS disease process itself - can be effectively ruled out by the well supported interpretation that CCSVI is congenital in origin.
   This interpretation also provides a good explanation why the earlier, smaller studies, which included almost exclusively persons with higher disability levels, found a high occurrence of CCSVI in their patients (90+%). Finally, such an interpretation makes solid theoretical sense in the widely accepted model of MS as an autoimmune disease. CCSVI can negatively affect the integrity of the blood-brain barrier (BBB) and thus would make it much easier for autoaggressive immune cells to access the CNS and promote the disease process.

5) The occurrence of multiple, causal factors in MS with perhaps none of them being a prerequisite for all cases, nicely explains the well established heterogeneity of MS and the observations of Lucchinetti et al (2000) that four, distinctly different types of MS lesions can be recognized. For example, one type of MS might be purely autoimmune and not involve CCSVI. On the other extreme, CCSVI might be by far the main causal factor in some cases and these would have only a little, if any, autoimmune involvement. **Many cases of MS likely involve both autoimmunity and CCSVI with the CCSVI component accelerating the autoimmune process and the accumulation of disabilities**. One would assume most cases of benign MS would not involve CCSVI whereas most severe cases of MS would. This inference is easily tested and, if proven correct, would strongly support this key interpretation.

6) The occurrence of CCSVI in 26% of healthy controls (borderline cases omitted), in combination with the formation of iron deposits as a consequence of CCSVI and the occurrence of iron deposits in other neurological diseases such as Alzheimer's and Parkinson's, has led me to speculate that **perhaps CCSVI is also a risk factor for other neurological diseases**. I hope research will be soon started to test such a hypothesis. This could possibly lead to ways to prevent, or at least significantly modify, these terrible diseases.

These new interpretations which are based on the recently released data on CCSVI by the universities of Buffalo and Georgetown, dictate that a new etiopathogenic model for MS must be developed. Neither the standard autoimmune model nor the recently proposed

CCSVI as the sole primary cause model are compatible with these new data and interpretations. A new model for MS, which combines both autoimmunity and CCSVI, will be the topic of a forthcoming article.

Recommended Actions for Persons with MS

The above, very well supported interpretations of the relationship between MS and CCSVI (causal factor in many cases, disease accelerant) lead to obvious and straight forward recommendations for all persons with MS.

1) **Because of the adverse effect CCSVI has on disease progression, it is essential that every person with MS be properly tested for CCSVI as soon possible.** It is stressed that, given the newness of the Ultrasound Doppler technology for diagnosing CCSVI and the need for special training, it is imperative to establish the expertise of a given clinic before being tested for CCSVI.

2) If CCSVI is detected, **it is then necessary to properly image the venous malformations which are causing it**. A debate is presently ongoing whether venography or MRV or some combination of the two technologies is best for imagining the venous problems and it will be important to stay abreast of this debate.

3) Once the nature of the venous malformations is established**, it is most important to get the impaired venous blood flow corrected.** Given the high likelihood that CCSVI accelerates the disease process, **persons with MS and CCSVI do not have the luxury to wait 5-10 years before the MS researchers prove the obvious** through a major clinical trial. Once again, expertise and experience are critical when it comes to the endovascular procedures necessary to relieve CCSVI and any patient looking for such a treatment should be very diligent in their investigation of the credentials and experience of the doctor who will perform such a procedure.

4) In an ideal, rational world, your neurologist would help you get tested for CCSVI and, if found positive, treated for CCSVI resolution. However, neurologists tend to be very conservative and currently only very few have embraced the need to test for and treat CCSVI. It seems that currently **CCSVI treatment, like all non-drug therapies for MS, will have to be done outside of conventional neurological practices**.
   I would note that almost all neurologists do not even test their patients to see if they have an optimal blood level of vitamin D, let alone recommend a proper vitamin D supplement regimen (5000-8000 IU in most cases) to ensure the attainment and maintenance of an optimal level. If neurologists don't even facilitate such an easy, cheap and completely safe action regarding vitamin D, a well established factor in MS, then it is highly unlikely that they will address the CCSVI issue in the near future.

5) **The most important therapy persons with MS can use before and after CCSVI treatment is to use nutritional strategies** which offset CCSVI, BBB breakdown and autoimmune reactions. These nutritional strategies are found on the Direct-MS website (http://www.direct-ms.org/recommendations.html). A good exercise program would also be of considerable benefit. The use of an MS drug is also an option. However, to use only a drug would not be wise because the presently available data indicate the current drugs do little for slowing disease progression. This is not surprising because the drugs only somewhat address autoimmunity and do not affect CCSVI at all.

Summary

The recent scientific results on CCSVI and MS from both the University of Buffalo and Georgetown University have essentially left very little doubt that CCSVI is a causal factor in MS in the majority of, but not all, cases. Furthermore, persons with MS with more disability are much more likely to also be affected by CCSVI and thus there is little question that CCSVI accelerates the MS disease progression.

Given the above, every person with MS should be tested for CCSVI. If CCSVI is detected, it should be treated as soon as possible. Persons with MS do not have the luxury to wait five to ten years for research to prove what is reasonably well established at present. Nutritional strategies which counter CCSVI, BBB breakdown and autoimmune reactions are essential both before and after CCSVI treatment.