

An Open Letter to the Honourable Gene Zwozdesky, Alberta Minister of Health Regarding the August 6, 2010, Alberta Health Services Report on MS and CCSVI

Dear Minister Zwozdesky,

Introduction

I recently read the “Alberta Health Services Information Sheet On Multiple Sclerosis (MS) and Chronic Cerebrospinal Venous Insufficiency (CCSVI)” which was prepared by members of your department and made available to the public on August 6, 2010. I found this report to contain numerous factual errors, misleading statements and half truths. It also included blatant, fear mongering and an incredibly biased view of the relationship between the pathology of chronic cerebral spinal insufficiency (CCSVI) and multiple sclerosis (MS). Given that the authors of this “Information Sheet” are public civil servants who report to you, and who are ultimately responsible to the citizens of Alberta, I felt compelled to write to you to both point out the major deficiencies of this report and to ask for a retraction of it.

You also need to investigate whether or not any of the authors/contributors have a conflict of interest regarding a non-drug therapy for MS. As discussed later, the existence of such conflicts of interest is the only reasonable explanation for the erroneous and biased nature of the report. Given that the public relies on AHS information sheets as sources of factual and unbiased data and analyses, I am sure you agree that those who write AHS information sheets must be free of such conflicts of interest. I also assume that the existence of conflicts of interest will not be tolerated by your department.

I am writing to you in various capacities including: 1) An Alberta taxpayer, 2) A research scientist who is very familiar with the MS data base and the only Albertan scientist who has published on CCSVI and MS in a recognized medical journal (Embry, 2010), 3) The president and research director of Canada’s second largest MS charity, Direct-MS (www.direct-ms.org), and 4) A father of a person with MS. The combination of these roles gives me a unique perspective as well as the expertise and the incentive to comment on the AHS report. I would have expected an AHS report to contain factual information and unbiased analyses on CCSVI and MS but I found just the opposite.

I will now provide comments on numerous statements in the report that conflict with either the established science or with the data we currently have at hand regarding CCSVI and MS. I will also highlight statements which have no basis in fact and are merely unfounded and unjustifiable speculations. I hope you agree that Albertans should expect AHS information sheets, on important health issues which affect our citizens, to be fact-based and objective.

Publicly funded AHS staff members, who are responsible for the production of such reports, must be counted on to be “honest brokers” of scientific information so as not to jeopardize the health of the citizens of Alberta or your department’s credibility. Given that the authors of the MS and CCSVI information sheet ultimately report to you, and that you are ultimately responsible for the information being given to Albertans, I hope you will take my evaluation of the AHS information sheet seriously and then act to rectify a most unfortunate and potentially harmful situation.

Section 1 “Are CCSVI and MS related?”

The first unwarranted statement in this section is “CCSVI and MS *may* be related” (emphasis on the word *may* from the report). Currently, and at the time the report was written, there is no reasonable doubt that MS and CCSVI are associated - that is, there are abundant data that demonstrate that a significantly higher % of persons with MS have CCSVI as compared with the general population.

The University of Buffalo work demonstrated an almost 3X higher prevalence of CCSVI in persons with MS in a large study of 500 people (University of Buffalo, 2010). Notably, the person doing the determination of whether or not CCSVI was present was properly trained and had months of experience. Most importantly, the results were checked and corroborated with selective venography, the accepted gold standard for the determination of CCSVI, and thus can be considered to be very reliable.

The AHS report also refers to the recently published Doepp et al (2010) study which found no CCSVI in persons with MS. Notably this study was done in a few months, included only a small number of subjects, and the technician doing the CCSVI detection was not properly trained in venous ultrasound work (much different from arterial ultrasound work). Furthermore, this study did not include any selective venography to demonstrate the reliability of the ultrasound interpretations. Given the above, this study is widely discounted as highly suspect science within the CCSVI research community.

It was very surprising that the AHS report did not refer to other published studies of CCSVI/MS association which include Al-Omari and Rousan (2010) which found 84% of persons with MS had CCSVI (sample size 25) and no healthy controls had CCSVI (sample size 25) and Simka et al (2010) which found CCSVI in 90% of persons with MS (70 sample size). Notably, both these results were supported by selective venography which leaves no doubt as to the accuracy of these data. Given there are not a large number of references on CCSVI and MS, the omission of these key references, which are readily found on Pubmed, shows a definite lack of scholarship by your staff regarding the question of CCSVI and MS association.

Furthermore, given the importance of the question of the association of CCSVI and MS, your staff should have contacted the various centres around the world

which are presently testing and treating persons for CCSVI. Importantly, these centres are doing selective venography as part of the testing. If they had done such a common sense and fundamentally necessary investigation, they would have found that all centres are reporting 80 – 95% of the MS patients they are seeing have CCSVI and that number now exceeds 2000 subjects. Furthermore, Dr Sandy MacDonald, a vascular surgeon in Barrie Ontario, testified before a Parliamentary Subcommittee on Neurological Diseases in June (available for viewing on the Internet) that 95% of almost 300 MS patients that his clinic tested had CCSVI. The omission of these most important data is most troubling.

In summary, the current information leaves no reasonable doubt that CCSVI is strongly associated with MS. Thus the claim made by the authors of the AHS report that this is not yet established is not true and is very misleading.

It is accepted that the established association of CCSVI with MS does not mean that CCSVI is necessarily a causal factor for MS. The second paragraph of this section looks at the important question which naturally stems from an established CCSVI/MS association - Does CCSVI contribute to the MS disease process, that is, does it have a causal role in MS?

The question of cause for an established association of a condition such as CCSVI with a disease needs to be addressed by examining various criteria that were first clearly enunciated by Hill (1965) in a classic paper entitled “The Environment and Disease: Association or Causation”. In this paper, Hill demonstrated that for a causal relationship to be reasonably well established, the important criteria that need to be satisfied are a consistent association, the occurrence of the condition before the disease onset, and biological plausibility for the condition to contribute to the disease process.

The two examples provided by the authors in the second paragraph of the AHS report to support their contention that association does not prove cause include differences in genetics (male versus female) and the concept that some tested therapies don't work. Both these examples have absolutely nothing to do with determining if an association is causal or not. It is imperative that your staff take the time to read the Hill (1965) paper which sets the standards for evaluating cause versus association. It was disconcerting to read this paragraph because of the lack of reasoning regarding association versus cause.

The third paragraph in this section also shows a major lack of understanding of CCSVI and a complete unfamiliarity with the CCSVI literature. The statement “the association between MS and CCSVI may actually be explained by *MS causing CCSVI* (original emphasis on “MS causing CCSVI”) is not tenable because it has been established that the venous malformations, which are responsible for CCSVI, are congenital in origin (i.e. formed during pregnancy) (Lee et al, 2009; Lee et al, 2010).

If the authors had done adequate research into the types of venous malformations constituting CCSVI, they would not have made such a

scientifically unsupportable statement. A few examples of the venous malformations associated with CCSVI include completely inverted or missing jugular valves, bony spines impinging on a vein, a completely absent jugular vein, and grossly malformed veins. A number of others such as septa and webs within the veins are described in the literature and are readily viewed on online videos produced by vascular surgeons.

It is untenable to postulate that “inflammatory proteins” could be responsible for such venous malformations and abnormalities. It is clear the authors of the AHS report lack basic knowledge about the vascular malformations which cause CCSVI. Their speculation that the malformations are the result of “inflammatory proteins” has no basis or merit and is very misleading as to the relationship of CCSVI and MS.

Section 2 “How could MS actually cause CCSVI?”

The information in this entire section is completely irrelevant and inappropriate given that the established data show beyond a reasonable doubt that the venous malformations which constitute CCSVI are congenital in origin and could not have been caused by “inflammatory proteins” by any stretch of the imagination. It is very clear the authors of the AHS report have no idea as to the nature of the venous malformations in CCSVI and it is important for them to do proper research on this subject. The data which answer the question of the origin of the venous malformations are readily available. The irrelevant and erroneous speculations which constitute this entire section of the AHS report, reflect badly on the credibility of your department.

Section 3 “What is the relationship between CCSVI, MS, and iron accumulation in the brain?”

I am not sure why the authors included this section in the report but I can only assume they did so because they are trying to discredit the concept that CCSVI is a causal factor of MS. As they note, iron is associated with MS lesions and this has been known for a long time. One possible explanation is that it is contributed by oligodendrocytes which die through some MS disease process. It is equally possible that the iron deposits are related to CCSVI as described in detail by Singh and Zamboni (2009). A key point these authors make is that iron deposits are associated with venous problems in other parts of the body (e.g. legs, torso) and thus it would be consistent to have iron deposits associated with extra-cranial venous problems.

In this regard, I refer you and the authors to the Zavadinov et al (2010) paper which concludes on the basis on some robust and impressive MRI-based data, that “CCSVI may be an important mechanism related to iron deposition in the brain parenchyma of MS patients”.

In summary, the available data and theoretical considerations support the concept that CCSVI might be responsible for some, or even all, the iron

associated with MS lesions. Thus the occurrence of iron adds support to the proposition that CCSVI is a causal factor in MS. The authors' statement that "studies of iron in the brain do not help sort out the relationship between MS and CCSVI" is both erroneous and misleading. We can definitely say that the current data tell us that the study of iron may well sort out the relationship between MS and CCSVI but that we need more studies in this field. The authors' failure to reference and discuss the findings of Singh and Zamboni (2009) and Zivadinov et al (2010) regarding iron and CCSVI again reveals a distinct lack of scholarship and understanding of the CCSVI literature.

Section 4 "Why do most neurologists doubt that MS could be caused by blocked or sluggish veins?"

This is the strangest part of the AHS report and the authors provide little scientific support for rather bold statements which are stated as "beliefs". Beliefs belong more to religion than they do to science and what is required are cogent, properly referenced statements and arguments rather than unsupported "beliefs".

For example we have the statement "They [neurologists] also know that MS or an MS-like condition has never been shown to be a result of blocked or sluggish veins". Exactly how neurologists know this is of course unknown (extrasensory psychic powers?), and such pompous bluster has no place in an objective analysis of an important health issue.

Currently, the possibility exists that CCSVI (blocked veins) may well be a causal factor in MS and we know this by applying the criteria of Hill (1965) for determining cause from association. It is well established that:

- 1) CCSVI is strongly and widely associated with MS and this has been demonstrated by using selective venography in centres around the world (USA, Canada, Italy, Poland, Bulgaria, India, Jordan to name a few).
- 2) CCSVI is congenital in origin and thus precedes the start of the MS disease process.
- 3) There are a number of plausible biological mechanisms which relate CCSVI to the MS disease process, including decreased perfusion, upregulation of adhesion molecules and deposition of iron.
- 4) Animal experiments carried out by Putman (1935) showed that blockages in the extra-cranial veins of dogs produced CNS lesions which closely resembled those of MS.

The sum of all these criteria, which essentially satisfy Hill's criteria for causation, leave little doubt that CCSVI is very likely a causal factor in MS. Any other interpretation would require incredible special pleading and astronomical odds for chance co-occurrences.

Thus, although the authors believe that neurologists believe that CCSVI cannot cause CCSVI, they do not provide any solid reasoning to support such beliefs. I would further note that arguments presented in this section such as "There are many people with true venous insufficiency but they never get MS" are simplistic

and irrelevant. No one is saying CCSVI is the only causal factor of MS and it is openly acknowledged that most people with CCSVI (20-25% of the population) do not get MS.

There is no doubt that MS involves a number of causal factors including genetic susceptibility, vitamin D deficiency and Epstein-Barr infection (Ebers, 2008). The key point is that, when CCSVI is present in a person with MS (perhaps as often as 75-80 % of the time), it contributes to the disease process as determined by the data discussed above. This is also nicely shown by the University of Buffalo data that revealed that those persons with MS and CCSVI have more severe disease than those with MS and no CCSVI (University of Buffalo, 2010). This is exactly what would be expected if CCSVI is one of the causal factors of MS in many cases.

In the next two paragraphs in this section, the authors argue that blockages are not present in the veins of persons with MS. Notably, they ignore all the published imaging and venous flow data from Ultrasound and MRV studies that demonstrate beyond any doubt that such blockages are present. They also ignore all the venous catheter interventions which actually found the blockages in thousands of people.

As part of their circuitous arguments they state “Dr Zamboni reported that venous pressure did not differ above and below the regions of narrowing”. Such a statement is completely false and in the 2009 article that first discussed CCSVI in MS, Zamboni et al state “the pressure gradient measured in CDMS across the stenoses was significantly different” (Zamboni et al, 2009, p.395). Such blatant errors in the AHS report demonstrate a further lack of scholarship and call into question the accuracy of all statements.

The last two statements in this section are especially egregious and unscientific. Firstly the authors state “Neurologists are not convinced that there are truly blockages in the veins of people with MS, unless the vein is frankly clotted. This latter condition is only seen in some MS patients after they have angioplasty.” This statement has no scientific basis and represents fear mongering.

The neurologists have apparently not looked at the overwhelming database that has demonstrated the existence of the blockages. Furthermore they are ignoring the fact that every day 75 venous angioplasties are done in centres in many parts of the world (over 2000 procedures done so far) and this daily number continues to increase as more centres open up. If the venous blockages did not exist there would not be a large and ever expanding medical service which treats such blockages in centres as reputable as the prestigious Arizona Heart Institute in Phoenix, Arizona.

The claim of the authors of the AHS report that the only venous blockages that do exist are clots caused by angioplasty is not true and is another blatant example of fear-mongering.

The last statement in this section was bolded – **“Thus, without blockage, it is hard to imagine how venous angioplasty can possibly do anything but risk injury to a vein.”** This baseless, inflammatory, fear-mongering statement, which has no place in an AHS information sheet, leaves little doubt as to the anti-CCSVI bias of the authors of the AHS document.

Section 5 “Arterial angioplasty is done all the time. What is the concern about angioplasty for CCSVI?”

The first three paragraphs describe arteries and problems associated with them. There are various inaccuracies such as the statement that “a stent will only get properly secured into an artery by its high pressure blood flow.” It is well known that stents stay in place due to the fact they are flexible and are chosen so that they are slightly larger than the artery. Furthermore, the arterial epithelial cells grow into the stent mesh thus incorporating the stent into the artery wall. Stents have been used in low pressure veins for a number of years using the same principles.

The authors of the AHS report rightly note that veins opened by angioplasty can suffer restenosis and no one is arguing this point. We currently do not have enough data on the rate of restenosis or on which angioplasty techniques are best for preventing restenosis. Notably such experience for arterial angioplasty was developed during the first 5 years of doing the procedure and the same thing is happening right now as venous angioplasty becomes more and more common a procedure in centres throughout the world. This is how all medical procedures are improved upon and the thesis put forward by the authors of the AHS report that venous angioplasty should not be done because we don't know the restenosis rate is illogical and meaningless.

The authors statement that **“there are no situations where venous angioplasty is an accepted and satisfactory treatment.”** (original bolding) is not factual. A quick search of Pubmed reveals the use of venous angioplasty for various conditions including its use in kidney patients. There is no doubt it is not perfect (few if any medical procedures are) but is certainly often satisfactory in that it achieves the desired result. At present no one is claiming venous angioplasty is routinely done and the reason for this is, that in the past, there has not been a widespread need for such a procedure.

The final bolded statement in this section – **“However, given that we can be confident that many people will sustain completely occluded veins from the procedure, we must be very sure that there is enough evidence to suggest that CCSVI actually contributes to ongoing brain injury in MS before we undertake such trials.”** – is a most curious and somewhat confusing one. First of all there is no basis whatsoever to “be confident” that many people will sustain completely occluded veins following venous angioplasty. In fact this problem has not been reported by any of the clinics doing venous angioplasty and again this is another example of blatant fear-mongering. The strangest thing about this statement is that the neurologist have been repeatedly saying that only proper

trial results will tell us if CCSVI is related to the MS disease process and now this statement says we need evidence that CCSVI is part of the MS disease process before trials are done. They have constructed a classic Catch-22 out of no data and no logic.

In summary, venous angioplasty is an accepted procedure but has been used sparingly in the past for a variety of somewhat rare conditions. Its current use for opening up blockages in extra-cranial veins in persons with MS is no different than its previous usages and no vascular doctors have raised any concerns about this usage. In fact, more and more interventional radiologists in centres around the world (including numerous sites in the USA) are doing venous angioplasty on blocked extra-cranial veins. This trend has been steadily growing over the past year indicating that the procedure is not causing any problems that would have resulted in reassessment and pull back.

Section 6 “What does it mean when people return from having venous angioplasty elsewhere and report that they feel better?”

In this section the authors of the AHS report try to discount the very numerous anecdotal accounts of substantial improvements that persons with MS have enjoyed after having their extra-cranial veins opened by angioplasty. Such accounts have been described in detail in various media including newspaper articles, TV documentaries and short clips, and video and written personal accounts on the internet. The one thing that stands out about these very numerous accounts is that the gained benefits are very substantial and tend to address balance, fatigue and brain fog issues. Furthermore, never in the history of MS has any conventional (e.g. drugs) or unconventional treatment ever resulted in such a huge volume of positive reports of major gains. There is no doubt that the positive results from venous angioplasty are unprecedented in their strength and numbers.

The authors of the AHS are suggesting that all the major benefits reported by hundreds of patients from numerous different countries are all due to placebo effect. This is completely unsupportable given the types and strengths of improvements that have been reported and the fact they have remained or, in many cases, got even better with time. The placebo effect does not allow a person who could barely get out of bed most days before angioplasty to start running 10 km marathons a month after venous angioplasty.

The statement that **“As of today, no Canadian neurologist has found significant or sustained improvement upon examination of patients who had had venous angioplasty performed, despite the fact that most returning patients report feeling better and sometimes note improvement in sensation or walking.”** (original bolding) has absolutely no basis in fact. First of all this implies that the authors contacted every neurologist in Canada to determine if any of their patients had actually improved after venous angioplasty. We can be sure the authors of the report did not do this. Furthermore, I know of a number of cases where people have enjoyed major gains and that their

neurologists were impressed and pleased with such gains. Once again the inclusion of patently false statements in the AHS report is most disturbing and causes one to have little faith in the veracity of any information in the report.

In the last paragraph of the report the authors offer the advice to “Be careful about where you get information” and I can only second this. The AHS report, with its lack of scholarly research, numerous false statements, fear mongering and illogical discussions, is a good example of questionable information which is best avoided. Although not mentioned in the AHS report, the best information on CCSVI and its treatment can be obtained from vascular doctors and interventional radiologists. Seeking advice on impaired venous drainage from doctors who do not specialize in vascular issues is probably not a good idea.

Summary

The authors of the AHS report have done an unacceptable job of presenting the facts about CCSVI and its treatment and have included inaccurate information and fear mongering statements. This report is below any acceptable standard for a government information sheet which should include only factual data and an objective analysis of it. The AHS report is blatantly biased in its anti-CCSVI stance that one has to wonder about the motivations behind its origin and the expertise of its authors.

The main failings of the one-sided report include:

- 1) The overwhelming database which indicates CCSVI and MS are associated is not acknowledged and key references on this topic were omitted.
- 2) The data and reasoning which demonstrate CCSVI is most likely a causal factor in MS were not properly addressed and an untenable and baseless speculation of “inflammatory proteins” causing CCSVI was emphasized.
- 3) The relationship between iron and CCSVI was poorly analysed and the two key references on this subject were omitted.
- 4) The overwhelming evidence for the existence of impaired venous drainage in many persons with MS was completely ignored and was replaced by unsubstantiated pronouncements and unsupportable “beliefs” that such blockages simply do not exist.
- 5) Fear mongering, which has no place in an AHS document, is commonly used and included the false claims that the only venous blockages that exist are clots caused by angioplasty and the only results of venous angioplasty are injuries to the vein.
- 6) The established and widely accepted use of venous angioplasty for various conditions is ignored and unsupported insinuations are made that venous angioplasty is a very unsafe, experimental procedure.
- 7) All the impressive improvements reported by hundreds of persons with MS who have had venous angioplasty done are simply written off as placebo effect despite the impossibility of this in many documented cases. The authors fail to recognize the unprecedented strength and numbers of the reported improvements.

- 8) Outright erroneous statements such as there is no pressure gradient across the venous stenosis, and no neurologist has seen any improvement in a person who has had venous angioplasty, are scattered throughout the report.

Given that we can assume the AHS was written by professionals, the only reasonable interpretation of why the report lacks scholarly and unbiased information is that the one or more of the authors had a conflict of interest. Consequently, it is most important that your department do an investigation of the authors to determine if any of them has a conflict of interest when it comes to CCSVI and its treatment.

One obvious conflict would be past or current ties to pharmaceutical companies that manufacture drugs for MS. Because the treatment of CCSVI has the potential to replace current drug treatments, it is to be expected anyone with financial ties to pharmaceutical companies might have the incentive to denigrate and marginalize CCSVI as a phenomenon in MS and venous angioplasty as a useful treatment for MS because of potential future financial losses. Needless to say this is a very important and sensitive issue that needs immediate attention.

I assume that the report will immediately be retracted if such conflicts of interest are found. Furthermore, failure to investigate such likely conflicts of interest would itself constitute a serious breach of ethics given the potential influence of AHS information sheets and the need for them to be factual and unbiased.

Finally I would like to express my thoughts on the AHS report from the four perspectives that I have.

- 1) As an Alberta taxpayer I am most disturbed that my tax money was spent on such an unscientific and biased report. Government revenues should be spent on fact-based, objective reports on important subjects which allow the consumer to make informed decisions regarding their health care.
- 2) As a research scientist, I am dismayed that AHS would publish such an unscientific document. I expect good, solid scientific analyses of important issues, not unsubstantiated opinions and vapid pronouncements.
- 3) As the president and research director of Canada's second largest MS charity, I am disappointed by the lack of honest, unbiased and worthwhile information in the AHS report. Persons with MS need reliable information and thoughtful and unbiased analyses of such data to help them make important decisions regarding their treatment choices and ultimately their health. All the erroneous conjecture and misinformation in the report is potentially harmful for persons with MS.
- 4) As a father of a person with MS, I am very angry that I cannot count on the government of Alberta to provide reliable information to help our family deal in the best possible way with a serious disease.

The people of Alberta, and especially all those who are dealing with MS, deserve far better from the government of Alberta when it comes to providing factual and objective data and analyses on the important topic of CCSVI and its treatment.

I look forward to hearing from you in the near future regarding the results of the investigation into probable conflicts of information of the authors and what your department plans to do to rectify the unacceptable and potentially harmful situation regarding the current lack of reliable and objective information on CCSVI and its treatment from AHS.

Sincerely,

Dr Ashton Embry

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