



August 6, 2010

## **Multiple Sclerosis (MS) and “Chronic Cerebrospinal Venous Insufficiency” (CCSVI):**

### **Alberta Health Services Information Sheet**

#### ***Are CCSVI and MS related?***

**Many people hope that CCSVI will prove to be the *cause* of MS but, at present, this idea is not supported by fact..**

**CCSVI and MS *may* be related.** Current information from Buffalo suggests that people with MS have a 56.4% chance of having CCSVI, and that those without MS have a 22.4% chance. In addition, over 40% of people with other neurological diseases have vascular changes consistent with CCSVI. However, other groups (Doepp et al, 2010 Annals of Neurology) have not found an increased rate of CCSVI in British and German people with MS as compared to “control” persons without MS. In contrast, Dr. Zamboni reported that 100% of the CCSVI patients he studied had MS but none of his controls had CCSVI. While the final answer is not clear, anyone following CCSVI through the social media knows that many people with MS do not have the imaging changes that define the syndrome.

***If CCSVI and MS do prove to be related,*** we still must determine how they relate to each other. For example, we know that people with MS have a 75% chance of being female whereas those without MS only have a 50% chance of being female. However, being female is not the cause of MS and does not lead to more severe disease; in fact men with MS are more likely to progress rapidly than women. Furthermore, there are examples of therapies that were tested in MS based on good scientific evidence but which did not work, or even made MS worse. For example, we know that levels of a protein called TNF-alpha are elevated in active MS and that drugs that block TNF-alpha are helpful in rheumatoid arthritis. However, drugs to block TNF-alpha actually made MS

worse in clinical trials. We must be very cautious before we assume that the co-occurrence of CCSVI with MS means it is the cause of MS.

If proven, **the association between MS and CCSVI may actually be explained by MS causing CCSVI.** The inflammatory proteins related to MS travel through the major veins draining the brain, and may cause the veins to simply show changes consistent with inflammatory cell contact. In the Buffalo study, a higher frequency of CCSVI was seen in MS patients with more severe disease; this is most consistent with MS causing CCSVI.

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### ***How could MS actually cause CCSVI?***

We know from many studies that signals within the brain attract inflammatory cells from the circulation. This causes these inflammatory cells to stick to the small blood vessels in the brain. These cells do not get stuck in the vessels due to blocked flow; instead, they become attached to the vessels because molecules called “integrins” on the inflammatory cells exactly match molecules on the vessel wall (“integrin receptors”) like a key in a lock. Once bound to the vessel the inflammatory cells can then pass into the brain.

In fact, there is a very specific MS therapy (a drug called natalizumab) that blocks the ability of integrins to attach to the vessel wall. Blocking the attachment of inflammatory cells to the vessel wall almost completely stops inflammatory cells from crossing into the brain and is very effective in stabilizing “relapsing-remitting” cases of MS. When this inflammatory process occurs however, proteins are released into the circulation and are carried away by the veins draining the brain. **Therefore, current knowledge of MS makes it more likely that constant drainage of inflammatory proteins through the major veins of the brain could cause the venous changes reported to occur frequently in MS.**

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### ***What is the relationship between CCSVI, MS, and iron accumulation in the brain?***

It is well known that iron accumulates in the brains of people with MS but there is absolutely no evidence linking this to CCSVI. However, iron also accumulates in the brains of several other neurodegenerative diseases. “Oligodendrocytes,” the cells that wrap around nerves in the brain to form “myelin,” are very rich in iron; and so are immune cells. In MS, both immune cells and oligodendrocytes regularly die within the brain; when they do, they release iron.

While we have not yet confirmed that this is the only source of the accumulating iron in MS, there is no evidence to suggest this iron accumulation results from red blood cells being pushed into the brain by high pressure in draining veins. In

fact, red blood cells are very rarely seen in inflammatory lesions in the brain and iron is uncommon in MS plaques. Therefore, studies of iron in the brain do not help sort out the relationship between MS and CCSVI, and using iron accumulation as evidence supporting CCSVI as the cause of MS is very misleading.

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

**Generally speaking, and based on current evidence, neurologists and neuroscientists who are up-to-date about the biology of MS and vascular diseases of the brain do *not* believe that CCSVI will be proven to be a cause of MS.** Nor do these experts believe there is likely to be any merit in venous angioplasty for CCSVI. They know that brain injury in MS is caused by the immune system and they are also familiar with vascular diseases that affect the brain (most commonly stroke and conditions such as cerebral venous sinus thrombosis where the veins that drain the brain are blocked).

Thus, neurologists care for people with MS and for people with neurological diseases caused or related to abnormal blood vessels, so they have the expertise to understand the association between the brain and its blood supply and venous drainage, and they are aware of the consequences of blocked veins within the brain and/or the neck. **They also know that MS or an MS-like condition has never been shown to be a result of blocked or sluggish veins.**

***If*** poor venous drainage from the brain were to cause MS, then people with blocked or absent jugular or vertebral veins should develop MS or an MS-like condition. There are many people with true venous insufficiency but they never get MS. In fact, neck surgeons commonly tie off one or both jugular veins during surgery to treat head and neck cancer; this has no medical consequence because the venous drainage of the head and brain is designed to have alternative routes of drainage.

Dr Zamboni reported that venous pressure did not differ above and below the regions of narrowing. If you block flow through a pipe and believe the pressure build up before the blockage causes damage you should be able to measure the increased pressure. Without any change in pressure it is hard to understand how flow is impaired. We know that there are more venous channels to drain the brain than we use at any one time.

Furthermore, if we are sitting, blood is more likely to drain through the vertebral veins at the back of the neck; if we are lying down, it may drain to a greater degree through the jugular veins in the front of the neck. Therefore, posture effects flow and a vessel may not fill if not needed when we are in certain

positions. This may affect how ultrasound and other imaging tests describe the brain's veins at different times and may falsely suggest that there is a block. 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.

**Thus, without blockage, it is hard to imagine how venous angioplasty can possibly do anything but risk injury to a vein.**

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***Arterial angioplasty is done all the time. What is the concern about angioplasty for CCSVI?***

To understand this question it is first important to understand how veins differ from arteries and how angioplasty of veins differs from angioplasty of arteries.

Arteries are thick walled vessels that carry oxygenated blood under high pressure from the heart to the tissues. Arteries commonly get narrowed or blocked by buildup of cholesterol within the wall of the vessel (atherosclerosis). The buildup of cholesterol can tear the lining of the artery which can then cause a blood clot to form on the rough edges of the injured vessel wall. In turn, this might cause the vessel to become narrowed and therefore deliver less blood, or to be completely blocked. It might also cause parts of the blood clot to break off and travel in the bloodstream to a smaller vessel where it can get lodged and block blood flow.

The most common consequence of partially or fully blocked arteries is chest pain when the heart needs more blood flow, or heart attack. Arterial angioplasty (where a balloon is inflated to stretch a narrowed artery) or stenting (where a tube is left in place to hold an artery open) are useful in many cases, although, drugs like aspirin that prevent blood clots from forming are all that many people require. A partially blocked carotid artery may also require angioplasty or surgical removal of the atherosclerosis to prevent strokes that can occur with sudden complete blockage or from small bits of clot traveling to other vessels in the brain.

Because arteries are thick walled and are designed to deal with high pressure, they can tolerate angioplasty. Because arteries carry blood away from the heart and get smaller as they get farther from the heart, a stent will only get properly secured into an artery by its high pressure blood flow.

Veins, on the other hand, are thin walled, collapse when not filled with blood, and do not tolerate injury well. Veins clot off permanently if repeatedly or severely injured. Angioplasty purposely causes the veins to be stretched by a balloon. The veins commonly react by clotting and then often become completely blocked. Similarly, stents will often clot, especially in the low pressure flow seen in veins.

Dr Zamboni reported that 47% of jugular veins are occluded within 18 months (most within 9 months) of venous angioplasty for CCSVI. Furthermore, the consequence of repeat angioplasty is completely unknown. The failure rate of the procedure is very high. Thus, venous angioplasty will therefore predictably cause harm within the first year to about 50% of the people who have the procedure performed.

Although not a satisfactory treatment due to high failure and high complication rates, venous angioplasty is occasionally used in kidney dialysis patients to get through blocked veins that must be accessed for dialysis. In one study of venous angioplasty in dialysis patients 76% of the treated veins remained open at 30 days but only 29% were open at 12 months.

Therefore, high rates of failure seem to be the rule after venous angioplasty. The risks of the procedure are multiplied by the number of times it is performed as repeat angioplasty is associated with repeated trauma to the veins. **For this reason, there are *no* situations where venous angioplasty is an accepted and satisfactory treatment.** This is very different than arterial angioplasty which is known to be useful. **Therefore, the claims that venous angioplasty is a “routinely done procedure” are *not* true.**

Venous angioplasty is a procedure that needs to be properly evaluated in well designed clinical trials that determine both the risks and the benefits. **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.** Patients considering leaving the country for this purported treatment should also consider this.

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***What does it mean when people return from having venous angioplasty elsewhere and report that they feel better?***

Without a randomized, blinded, placebo-controlled trial it is impossible to interpret these individual or anecdotal reports. Randomization means that a random method, like flipping a coin, is used to determine if each person gets the experimental treatment or the placebo. Blinding means that the person participating in the trial, and usually the physician following their progress, do not know which treatment the study participant received. Placebo-control means that the participant receives a ‘fake’ treatment such as a sugar pill or a pretend procedure. ***All of these measures aim to remove bias in interpretation of the results.***

In addition, the outcomes used to measure benefit must be reliable and precise. There are many measures that can be used such as “timed 25 foot walks” but

they must be done properly and the study participant must be trained. Unfortunately, in Dr Zamboni's trials, the participants did not have practice tests which meant that most of them improved the second time they did the test simply because they better understood what to do. Experts conducting MS clinical trials know that these tests must be completed 2-3 times before the baseline measure, to be sure that they are accurately done and measured.

**The placebo effect is likely to be very powerful for venous angioplasty.** If you believe a treatment will improve your walking, your confidence will improve and you will walk better (until you fall). In addition, placebo treatments actually cause changes in brain chemicals. It is possible that this can improve function as well as wellbeing temporarily. Furthermore, the more invasive a treatment is, or the more it costs, the greater the placebo effect. **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.** These reports are consistent with previous anecdotal reports that followed many putative therapies of MS later proven to be of no benefit.

MS also varies greatly. Over 2 years only 30% of people with primary progressive MS will worsen measurably. In addition, in recent clinical trials of "relapsing-remitting" MS placebo treated patients had a 60% chance of remaining stable over a full year. In Dr Zamboni's study, no benefit was seen in people with progressive MS and the annualized relapse rate (relapse rate adjusted for the period of observation) did not change before and after the procedure.

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***People should be careful where they get information and where they go for treatment***

People with MS should be wary about getting information solely from media stories and reports or from patient's "blogs." They should seek out expert advice from knowledgeable MS caregivers and experts, and should carefully determine the credentials of any centre offering "liberation" treatment.

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