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SUMMARY REPORT

CIHR and MS Society of Canada
Joint Invitational Meeting on
Multiple Sclerosis Research
August 26, 2010, Ottawa, Ontario

Overview

The Canadian Institutes of Health Research (CIHR), in collaboration with the Multiple Sclerosis (MS) Society of Canada, convened a meeting of top researchers in Ottawa on August 26, 2010, to identify priorities for Canada that would accelerate research and innovation on treatments for MS. The meeting focused, in particular, on links between neurovascular issues and MS.

There was a wide range of internationally recognized participants with expertise in neurology, vascular surgery, neurosurgery, neuro- and vascular imaging, neuropathology, neuro- and cardioimmunology, basic science, and epidemiology. Participants also included federal and provincial government representatives and a person living with MS.

The objectives of the scientific meeting were: to review evidence, current international efforts, and knowledge gaps related to the etiology and treatment of MS, with a special emphasis on neurovascular issues including the recently proposed condition called chronic cerebrospinal venous insufficiency (CCSVI); to review past, current and proposed international clinical trials related to the diagnosis and treatment of MS; and finally, to identify clinical research priorities for CIHR and the MS Society of Canada for the diagnosis and treatment of individuals with MS.

Presentations relating to the objectives were made to set the stage for the ensuing discussion. The discussions were open, animated and frank, while at the same time remaining empathetic and mindful of the burden of illness borne by people living with MS and their families. The complementary medical and scientific expertise provided for a thorough and unbiased consideration of the many complex aspects of MS disease etiology, pathology, diagnosis and treatment options, including related risks. Participants were actively engaged in the discussion topics and carefully considered the evidence on neurovascular issues and MS, including CCSVI.

Opening remarks by the Presidents of CIHR and the MS Society of Canada, and by the representative deputy ministers of health set the context for the proceedings. This included an overview of the unprecedented television and media coverage of the "MS Liberation procedure" witnessed with great intensity in Canada. As there are presently no "cures" for MS, a debilitating chronic disease, a large number of people with MS have understandably become very engaged by the prospect of this proposed experimental treatment.

Meeting participants were emphatic about the crucial requirements for strong evidence-based decision making, at both medical and political levels, and the ethical responsibility of ensuring patient safety first and foremost before recommending a new treatment for any disease, including MS. Participants agreed that the impact of MS in Canada, where there is a disproportionately high incidence of this disease, warranted an in-depth discussion of the major scientific and clinical issues, in order to identify priorities for accelerating the diagnosis and treatment of MS. All agreed that this discussion was critical to better understand the complex scientific issues related to MS therapy and thereby provide the best information and evidence upon which to establish an appropriate policy response.

A significant part of the meeting was devoted to discussing the data presented in the manuscript that describes the venous angioplasty treatment proposed by Dr. Zamboni (of Italy) for patients with MS, and the advisability and feasibility of carrying out a pan-Canadian therapeutic clinical trial, given current questions about the safety and efficacy of this proposed treatment.

<u>Some background about MS and an analysis of Dr. Zamboni's work on MS therapy.</u>

What is Multiple Sclerosis?
MS is a chronic neurological disease characterized by brain lesions or "plaques" that are infiltrated by immune cells. This condition was first described over 150 years ago by Charcot. Lesions occur in the brain, optic nerves, and in the spinal cord, and result in the loss of the insulation or myelin coating of nerve fibres, which is why MS is called a "de-myelinating disease". Many, but not all areas of inflammation in MS surround small veins.

With MS there is most typically early adult onset of disease symptoms, with the clinical diagnosis being made around age 30 (on average). Brain imaging techniques suggest that by the time the disease is actually diagnosed many plaques have already formed. However, most of these brain lesions are asymptomatic (up to 95%).

MS starts in one of two ways: in 85% of patients, it begins with attacks of symptoms followed by improvements, while in 15% there is a progressive increase in symptoms without attacks. The first type is called relapsing-remitting MS (RRMS) and the second is primary progressive MS (PPMS). After a period of years, many RRMS patients begin to show a progressive increase in neurological disability, and at this point their condition is called secondary progressive MS. Importantly, the available disease-modifying MS therapies that slow down the condition are useful only for the RRMS stage of MS, and there is no disease-slowing therapy currently available for patients with progressive MS. These medications can reduce the number of attacks

in patients with RRMS, and slow down the increase in lesions seen on the Magnetic Resonance Imaging (MRI) of the brain over time.

The population distribution of MS shows a remarkable geographic localization of the disease: MS is more common as one moves further away from the Equator. Accordingly, the prevalence is quite high in Canada, particularly in the prairie provinces, with an estimated 55,000-75,000 Canadians being affected with MS. Gender also appears to be a factor, as women are 2-3 times more likely than men to have MS.

With this background about the disease, what follows is a brief description of Dr. Zamboni's studies regarding the diagnosis and treatment of CCSVI, the two most important of which being an initial assessment of the frequency of abnormal veins in MS patients published in April 2009 (1), followed by a pilot, non-randomized, single centre clinical study, in which selected veins of MS patients were dilated with a balloon catheter. This study was published in December of 2009 (2).

What did Dr. Zamboni's initial study report?
Using a non-invasive ultrasound method for imaging veins in the head and neck (called "trans-cranial and extra-cranial colour-coded Doppler sonography"), Dr. Zamboni and his colleagues examined 65 MS patients and 235 controls (1). The technician performing the studies was aware whether a subject had MS or not (i.e., was not "blind" to the patient's medical status). For each patient, five separate factors were evaluated that were intended to identify vein abnormalities. The study reported that 100% of MS patients and none of the controls had vein abnormalities.

Based on finding at least two out of five changes in the ultrasound evaluation of either blood flow or the diameter of specific veins that drain the brain or spinal cord, Dr. Zamboni has proposed that impaired venous drainage of the brain (specifically narrowing or blockage of the Internal Jugular Veins) or spinal cord (via narrowing or blockage of the Azygous Vein), and the subsequent breakdown of the blood-brain barrier cause an accumulation of iron within the brain, which triggers MS. He has coined the term "Chronic Cerebrospinal Venous Insufficiency" or CCSVI to describe this phenomenon. There do not appear to be other references to this proposed condition in the medical literature. Curiously, it is well known that patients who develop blood clots in these veins, or who have these veins removed during head and neck cancer surgery, do not develop MS. In addition, patients with MS do not have any clinical or radiologic evidence of impaired venous drainage, such as a swollen face or bulging veins in the retina (which can be easily seen with an eye scope).

To avoid experimenter bias, international standards for objective clinical trials require researchers to be 'blind' to the medical status of the patient during the process of data collection and analysis. This is an essential control to avoid the natural human tendency to "find what one is looking for." The Zamboni study was not performed in a blinded manner.

Furthermore, there are difficulties with using ultrasound as an investigative tool: the methodology tends to compress the veins being observed, thus giving rise to potential errors in measurement of size, and it is difficult to determine flow in the deep cerebral veins since the

angle of insonation is very large. Additionally, interpretation of the ultrasound data is subjective, and if the investigators are not blinded, it may result in numerous false positives (3). Another factor that would affect the interpretation of the data is that many MS patients having the treatment are advised not to discontinue their medications, thus confounding the interpretation of the results from venous angioplasty.

Dr Zamboni's interventional clinical trial (2), in which the Internal Jugular or Azygous veins were dilated with balloons, was an un-blinded pilot study in which both patients and the treating physician knew that a treatment procedure was being performed. There was no control comparison group, i.e., patients with MS who had a catheter placed in a vein, but did not have a balloon dilation. Patients also remained on disease-modifying drugs for their MS symptoms. In this study, no benefit on disability was seen for MS patients with the more progressive forms of MS (2). Finally, a high proportion (47%) of treated veins became narrowed again with the passage of time. It is also worth noting that the results of venous angioplasty reported are no better than those achieved with standard MS drug regimens (2).

What do we know about the normal venous drainage of the brain?
The arterial supply to the brain, head and neck has been well-understood for centuries and is well-described. In contrast, human venous anatomy and drainage is extremely variable even in healthy people. As a consequence, it has been difficult to provide standard reliable descriptions of the "normal" anatomy for the venous system in the human body.

We do know, however, that variability in the diameter of cerebral veins is regularly observed in the normal, healthy population and varies under differing physiologic states, as well as with individual and local anatomy, e.g., nearby muscles and bones will affect the natural topography of the veins. To the best of our knowledge there are no known gender differences in cerebral and spinal venous anatomy.

Is there such a condition as "chronic cerebrospinal venous insufficiency, or CCSVI"?
The venous drainage of the brain is a highly flexible system naturally designed to have many alternate and redundant routes. The reasons for this are that if one vein is damaged, other veins draining the brain and spinal cord can easily handle the blood flow out of these organs. Further complicating factors arise from the involvement of different veins depending whether a person is standing up or lying down. A proportion of the brain's venous drainage runs through the Internal Jugular Veins when a person is standing, however when a person is lying down, that proportion of the venous return tends to flow through alternate venous routes.

Cancer surgeons routinely tie off and remove one or both Internal Jugular Veins during surgery to treat head and neck cancer, with no deleterious effects on patients. Blockage of one or both Internal Jugular Veins, due either to injury or disease (e.g., stroke, venous thrombosis, cancer) has never been associated with MS. Furthermore, there is no evidence to date that any vascular diseases have resulted in MS. Also, as noted, patients with MS do not have any clinical or radiologic findings consistent with increased pressure in the veins draining the brain or spinal cord.

For these reasons, there is little support for the notion that "venous insufficiency" for the brain or spinal cord contributes to the development of MS.

Is "venous insufficiency" linked to MS?
Dr. Zamboni's publication of April 2009 (1) asserted that CCSVI perfectly matches with a diagnosis of MS, and his group reported 100% specificity, 100% sensitivity, 100% positive and 100% negative predictive value for the ultrasound evaluation his group carried out. In other words, Dr. Zamboni's group reported that 100% of MS patients have internal jugular or azygous venous abnormalities, and 0% of normal healthy controls show CCSVI. It is rare, in clinical research for any test, especially for a single test such as ultrasound, to be perfectly diagnostic of any condition.

Dr. Zamboni acknowledged that the balloon venoplasty treatment does not work for MS patients with progressive disease (1). Subsequent to his assertions that CCSVI plays a key role in determining the course of the disease, several clinical studies have been published that provide contradictory evidence.

Reports by two different German groups (4,5) do not support the hypothesis that CCSVI is present in patients with MS, either in terms of the association of narrowed veins or of reduced blood flow from the brain. Using a similar ultrasound technique as reported in the Zamboni studies, Doepp et al. (4) studied 56 MS patients and 20 healthy controls; they reported no statistically significant differences in venous drainage between MS patients and the healthy subjects. Krogias et al. (5) studied 10 MS patients and 7 controls and found only 2 of the 10 MS patients fulfilled the criteria of CCSVI defined by Dr. Zamboni. Another case-control study by a Swedish group utilizing similar ultrasound methodologies as the Zamboni study, as well as more sensitive imaging MRI techniques, found no evidence of differences between 21 MS and 20 healthy control subjects that would support the CCSVI hypothesis (6). In this latter study, the researchers evaluating the images of the veins were unaware whether they were from a patient with MS or a control with no evidence of MS.

The results of an observational study from Dr. Robert Zivadinov in Buffalo, using ultrasound to examine 260 MS patients and 161 healthy controls, reported a wide variation in the incidence of venous abnormalities among normal healthy subjects (ranging from 22.4% to 25.9%), and as well as among MS patients (56.4% to 62.5%) (7). Patients with other neurological diseases were reported to have a 45% rate of abnormalities, all of which clouded the interpretation of this data.

These recent studies have demonstrated a wide variation in the patterns of venous drainage of the brain in both MS patients and people with no evidence of MS (controls), underlining the difficulty involved in concluding that a vein that is 'narrowed or blocked' will cause MS.

Does venous angioplasty work?
Arterial angioplasty and the insertion of stents into certain arteries are established medical procedures. However, it is very important to emphasize that the walls of arteries differ greatly from veins. Arteries are muscular, thick-walled vessels that carry oxygenated blood under high pressure from the heart to the tissues. Veins on the other hand, are thin-walled and collapse

naturally when not filled with blood; if blocked either by a malformation or by external pressure from a muscle or bone, narrowed veins will return to their pre-surgical shape (i.e., re-stenose) after being artificially expanded by insertion of an inflatable balloon.

Venous angioplasty is rarely used because the incidence of re-stenosis is so high. This is because narrowed veins are usually scarred, and the scar tissue is very elastic. So, if a narrowed vein is treated by balloon venoplasty, it is like stretching an elastic; remove the balloon from the vein and its elastic properties make it return to its original shape. Balloon venoplasty is used in patients with dialysis access conduits or with scarred central veins secondary to the damaging effect of central venous catheters; recurrence rates for these procedures are very high. The prevailing medical opinion is that while "balloon angioplasty" for veins may be relatively safe, it is difficult to justify the procedure as the veins eventually will re-stenose. In addition, there is a distinct possibility that the damage to the inner lining of a vein (that happens when a vein is artificially dilated) can increase the risk of thrombosis (clotting) of that vein: such clots are unstable, and can break free, travel through the heart and block major vessels in the lungs. This sequence of events, known as pulmonary embolus, can cause debilitating lung disease or death.

Insertion of stents into veins is not commonly performed because stents in veins may clot, or in rare cases may become dislodged and move towards a patient's heart – such an event was reported in a patient following a venous angioplasty procedure. Venous stent placement usually requires the use of blood thinners, which have their own complications, including bleeding. Potentially fatal outcomes due to the migration of a venous stent into the heart have been reported (8,9). There are also risks of brain hemorrhage associated with blood thinner use which can lead to stroke or death.

Is the venous angioplasty treatment safe and efficacious?
In order to evaluate whether any treatment is efficacious and safe, it is essential to compare the treatment in a blinded fashion to a control MS population that does not receive the treatment. The measures used to assess the treatment should be as objective as possible and should include an evaluation of relapses, changes in neurological disability, and changes in MRI scan measures of MS.

To date, the only published clinical trial data related to the proposed condition CCSVI is that of the pilot trial of Dr Zamboni (2) which was, as noted above, un-blinded and did not include a control comparison group. These serious deficiencies in trial design compromise the ability of the scientific community to accept the conclusions reached by Zamboni et al. regarding the existence of CCSVI. Complicating the interpretation of the data reported by Dr. Zamboni, there is also a pronounced placebo effect noted in all MS clinical trials, which suggests that the results reported to date may be inaccurate and should therefore be treated with great caution. In the opinion of the expert panel assembled by CIHR and the MS Society of Canada, there is currently no scientifically valid evidence in support of the existence of CCSVI in patients with MS, and there is currently no scientifically valid evidence to support the use of venous angioplasty in the treatment of patients with MS.

<u>Summary</u>

- To date, the published evidence that venous abnormalities (i.e., CCSVI) play a role in the cause or propagation of MS is contradictory and, as such, should be treated with circumspection. This is a subject that needs prompt further study. To address this pressing need, the MS Societies of Canada and the US have funded seven studies to further determine if patients with MS have venous abnormalities that differ from age-matched controls.

- Seven North American studies ($2.4 million in funding by the MS Societies of Canada and USA) will carefully evaluate whether CCSVI occurs. The studies will define mechanisms of how venous drainage from the brain might be of relevance to MS, an issue that has not yet been adequately explored.

- In the absence of clear and convincing evidence for CCSVI, the performance of an interventional venous angioplasty trial with its attendant risk to MS patients is not appropriate at this time. It is unlikely that a proposal based on the current procedure of Doppler assessment of venous narrowing and subsequent venoplasty would pass a peer review panel (the international standard of scientific excellence and the standard for much of the funding in Canada), because evidence that CCSVI exists is currently lacking. Similarly, there are serious ethical issues associated with doing such a trial given the lack of convincing evidence for CCSVI.

- If a clinical treatment trial for CCSVI in MS were to be considered, one cannot expect a quick outcome given the natural course of the disease. Indeed, a meaningful clinical trial could take as long as several years, with regular and repeated post-operative measurements of the key symptoms of the disease, which would add greatly to the expense of the trial. A trial of CCSVI for symptoms of MS such as fatigue or weakness would have to be compared to other available symptomatic MS therapies.

A clinical treatment trial for CCSVI in MS will require careful observation of the outcome of treated patients.

Recommendations

1. Effective immediately, establish a scientific expert working group made up of the principal investigators of the seven MS Society-sponsored studies (four from Canada and three from the US), scientific leadership from CIHR and the MS Societies, and a representative from the provinces and territories, to monitor and analyze preliminary and final results from these studies, as well as from related studies from around the world related to venous anatomy and MS. The first meeting of this expert working group should take place in this calendar year.

2. Based on the outcomes of these studies, the scientific expert working group should reach conclusions regarding (1) a common standard for reliably diagnosing the proposed CCSVI condition using imaging or other techniques, and (2) clarity regarding a potential association between impaired cerebral venous drainage and MS.

3. Depending on these conclusions, the scientific expert working group should make recommendations on further studies including, if appropriate, a pan-Canadian interventional clinical trial that would evaluate the safety and efficacy of venous angioplasty in patients with MS.

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