

Summary – CCSVI Working Group Meeting, May 11, 2011

The CCSVI Working Group met by teleconference.

Linda Lumsden, Chair
Shelley Black
Anthony Feinstein
Marilyn Lenzen
Samuel Ludwin
Lindsay Machan
Linda Molyneux

T.J. (Jock) Murray
James Orr
Julian Spears
Ron Unger
Brock Winterton
Yves Savoie (ex officio)

Staff resource

Deanna Groetzinger

Issues from last meeting

There was discussion as to whether the group should discuss setting guideposts for success of the seven studies funded by the Canadian and US MS societies. It was noted when researchers submit proposals they have to have a hypothesis and an outline of how they would prove or disprove it. Guideposts are set at the beginning and once a study begins, the research team must stay with what they have proposed. In terms of the seven studies, the two MS societies established the parameters to be investigated and at this point in the process, investigators don't share any findings since that might colour the interpretation of other findings.

Discussion of research progress and publications

CCSVI research reported at the International Society for Neurovascular Disease CSVI meeting in Italy

Dr. Julian Spears reported on the meeting he attended in Bologna on March 14-15. There were 150 to 200 participants at the meeting in Italy.

The **first plenary session** of the first day was dedicated to CCSVI Imaging. From this session, it emerged that multiple-modality investigation will be extremely important in the future evaluation of CCSVI. The specific role of ultrasound, intravascular ultrasound (IVUS), CT angiography, catheter venography as well as fusion imaging were reviewed. The heterogenous nature of CCSVI in MS was highlighted with the following concepts emerging: findings in early versus late disease and the presence of extra cranial venous stenosis; whether CCSVI represents a late manifestation of MS or a causal factor; the role of emerging technologies such as IVUS; and the important role of fusion imaging in CCSVI.

There was significant discussion regarding the variable imaging findings of venous anatomy and some pitfalls of diagnosing CCSVI, specifically in the difficulty in imaging the azygous vein. Dr. Robert Zivadinov from the University of Buffalo reported on investigational findings of CCSVI using MRI and elaborated on differences between progressive and non-progressive MS, and concepts such as patients with early disease having problems much better seen on ultrasound compared to those with late disease. Dr. Zivadinov reiterated the need to establish standardized

guidelines for imaging due to the hemodynamic nature of CCSVI.

The **second plenary session** was dedicated to reviewing current mechanisms of neurodegenerative diseases such as Alzheimer's disease as well as MS, and updating possible mechanisms of disease with a predominant emphasis on the role of iron. Specific to MS, Dr. Zivadinov presented a review of whether the iron deposition in MS is primary or secondary. The question is whether CCSVI has a role in the early development of MS or later on its development. There was general agreement that environmental, genetic and biological factors play a significant role in the development of MS. Dr. Zivadinov reported that on MRI, fewer vessels are seen in MS patients and speculated on two possible mechanisms for this observation, being either a reduction in brain metabolism or a reduction of veins seen in MS patients using SWI sequences on a 3.0 T MRI. Many more vessels were noted in controls on MRI than in MS patients with no pathophysiology for this offered. The questions still remain to whether iron is accumulated early in the disease process or later on, does atrophy come first or iron deposition and should the measurement of iron be a marker for MS?

Abstracts session - The Albany, NY, group, led by Dr. Manish Mehta, presented results of a prospective analysis in treating 150 MS patients with presumed CCSVI with a threshold for treatment of greater than 50% stenosis in either internal jugular vein or azygous veins as measured by catheter venography. The subtypes of MS were relapsing remitting 55%, secondary progressive 31%, and primary progressive 11%. This group reported the following complications/re-interventions at four month mean follow up: IJV occlusion 2%, IJV recurrent stenosis 9%, new onset atrial fibrillation <1%, and no deaths or neurological events. They reported statistically improvements in the MSQOL Physical Health composite score, MSQOL-Mental Health composite score, and the Modified Fatigue Impact score. They concluded that there is an association between MS and CCSVI with associated clinical benefits of venoplasty and that their findings need to be substantiated with future blinded randomized clinical trials. Criticisms from the audience included observations that standard outcome measures were not used.

Concurrently to the abstract section, a **workshop on Echo Colour Doppler (ECD)** for diagnosis of CCSVI was held. An overview of the anatomy of cerebral venous return was presented to the audience followed by presentations on the assessment of equipment and criteria for CCSVI by sonographers that are currently leading the imaging in Drs. Zamboni and Zivadinov's teams. The sonographers also led a discussion on tips to best image for the CCSVI criteria and allowed for discussion of best practices in ECD. The most highly debated topic during the discussion was on the second of the CCSVI criteria, as many doctors and sonographers commented on the difficulty in examining and evaluating CCSVI.

The second day featured a **plenary session on the basic science and pathology** of CCSVI and MS. Within this session, Dr. Porama Thanaporn from Stanford University presented results on a mouse model of CCSVI. The mice underwent external jugular vein ligation or sham operation in an attempt to replicate CCSVI in a murine model. The mice did not develop gross neurological defects after surgery, however, they did observe small functional differences between the mice that had their vein tied versus those that were untied. Further work in this area needs to be done to determine the contribution of CCSVI to the presence of MS.

The **final plenary session** was dedicated to endovascular treatment of CCSVI. The Italian group presented by Professor G. Filippini, reviewed their study design of the Italian multi-centred randomized controlled trial BRAVE DREAMS. They would like to enrol 650 patients over

a 12-month period studying a variety of outcome measures. Criticisms of the proposed trial included management of pain control in the sham venoplasty group, and more important, the estimated number of patients required to demonstrate a benefit of CCSVI in the absence of a previously tested and accepted outcome measures. Concern was also raised regarding the number of patients recruited at each site with the recommended learning curve required of the treatment technique.

Dr. A.N. Siddiqui from Buffalo, NY, presented an update from the **PREMISE trial**, which is an IRB (institutional ethics review board) approved study that is funded by industry and Kaleda Health Inc. The study's primary outcome is to test for the existence of severe adverse events following venoplasty in MS patients with CCSVI. Phase I (10 patients) was completed in the summer of 2010. Phase two with an additional 20 patients should be finalized within in the next two months. Extensive blinding has been put in place for this study. There have been no complications to date.

The largest experience reported at the Congress in the treatment of CCSVI with venoplasty was reported by Dr. M. Zarebinski from Poland. The Polish group reported treating 445 patients with MS who underwent Doppler ECD and MRV prior to catheter venography. Outcome measures evaluated included: the Expanded Disability Scale (EDSS), Fatigue Severity Scale (FSS), and the Multiple Sclerosis Impact Scale (MSIS-29). The procedures were performed by four interventional cardiologists; stenosis on venography in either jugular or azygous vein were treated. The Polish group reported eight complications out of 445 patients treated including: two vein thromboses, and a total of six femoral vein access site complications of which three required open surgery (aneurysm, pseudo aneurysm, AV fistula). They also reported four procedures that were aborted prior to venoplasty due to technical failure in accessing the stenosis. The only statistically significant finding for neurological outcome reported was an improvement in the Fatigue Severity Scale. No statistically significant improvement was reported in either in changes to disability as measured by EDSS or by the MS Impact Scale (MSIS-29).

During the press conference Dr. Zamboni, as president of the ISNVD, stated he was very pleased with the research presented and noted excellent progress was being made in areas of imaging, development of animal models and treatments for CCSVI.

In response to questions from group members, Dr. Spears said his overall impression of the meeting that the quality of the research was reasonable. In his view, the presentation of the Albany trial experience was slightly optimistic, and that while the Polish group presented their work in an interesting way there was no objective improvement post-treatment. He noted most of the treatment research were case reports and not controlled studies. Asked if he agreed with the consensus which was announced after the meeting, Spears said in his view, no consensus was reached at the meeting? Asked about information presented about the risk of the procedure, he noted the rate of complications was low which would lead him to believe that in a spectrum of procedures, angioplasty was relatively safe.

Report – CCSVI research reported at Society of Interventional Radiology

Dr. Lindsay Machan reported on CCSVI presentations at the Society of Interventional Radiology March 26-31 in Chicago. He said only one paper presented anything new which was a single study from an Albany group led by Dr. Gary Siskin. In 231 patients with 247 procedures, the safety profile was excellent. Ninety-nine percent of people were discharged post-treatment with

only transient headache and neck pain. One percent had cardiac arrhythmia. He said to his knowledge none of the studies presented dealt with long-term safety (beyond several weeks following the procedure). He said there was nothing new in the other studies with many calls for placebo-controlled trials.

There was discussion about what is required to obtain the long-term risk profile of the CCSVI procedure with the suggestion that studies that follow people over a lengthy period of time are required. There was discussion about what is required to ensure in a placebo-controlled clinical trial that neither the treating physician nor the patient know who received the active versus the sham procedure. It was noted various techniques are being considered including deep sedation or general anaesthetic and that the safety profile of these techniques are good if administered in a proper clinic setting.

Update – CCSVI panel discussion in June for working group and national board

It was reported the CCSVI panel discussion Dr. Salvatore Sclafani, Dr. Barry Rubin and Dr. Daniel Selchen have been confirmed to participate in the CCSVI panel discussion in June. Dr. Sandy McDonald has been invited and not yet confirmed. If Dr. McDonald is not available, it was agreed another CCSVI-treating physician should be invited. It was agreed that discussion topics for the panel discussion will be circulated in advance to the CCSVI Working Group.

New topics for discussion and what information is needed

The group has covered its first four agreed topics. The following were suggested for future meetings.

- One-year progress reports from the seven MS society funded studies;
- Saskatchewan clinical trial research (if funded and announced) including what are the parameters of the study(s) and the approach. Principal investigator(s) and or head of Saskatchewan Research Foundation could be invited to speak to the group;
- Updates on various government announcements from the past six months and how they are fit into the overall advancement of knowledge about CCSVI and MS
- Discussion of if there is any negative side to people being able to receive treatment for CCSVI immediately, given the risk appears to be relatively low.