



Title: Cerebral Venous Hemodynamics in Pediatric Multiple Sclerosis

Brenda Banwell, MD

The Hospital for Sick Children

Toronto, ON.

Timing: 7/1/10/-6/30/12

Amount: C\$196,579.14 for 2 years

- A series of recent publications have suggested that some people with MS have obstructions in the veins that drain blood in the brain and spinal cord that may contribute to nervous system damage in MS.
- Dr. Banwell, a noted expert in pediatric MS, has assembled a team to study CCSVI in pediatric MS patients – a population where the disease process is at a very early stage, and where advanced age and other health conditions that might affect blood flow do not exist.
- Determining whether the veins are abnormal very early in the MS process in pediatric MS will add additional depth to studies of CCSVI in adult MS.

About the Investigator: Dr. Brenda Banwell is the Director of the Pediatric MS Clinic at The Hospital for Sick Children (SickKids) in Toronto. She earned her medical degree from the University of Western Ontario and completed a residency in pediatrics at the Children's Hospital of Western Ontario, a residency in pediatric neurology at SickKids, and a neuromuscular disease fellowship at the Mayo Clinic, Rochester, Minnesota. Dr. Banwell is the principal investigator of a Canada-wide study of acute demyelination in Canadian children (funded by the MS Scientific Research Foundation). She also serves as the Research Chair of the International Pediatric MS Study Group.

Dr. Banwell has assembled a team that includes – among others – an imaging scientist who is leading a program to evaluate blood flow in children, pediatric neuroradiologists with extensive expertise in cerebrovascular imaging in children, a world-renowned neuroimaging expert in the field of MS, and a pediatric neurologist with experience in venous malfunction in children.

Project Details: Recent preliminary studies have suggested that a phenomenon called Chronic Cerebrospinal Venous Insufficiency (CCSVI), a reported abnormality in blood drainage from the brain and spinal cord, may contribute to nervous system damage in MS. This hypothesis has been put forth by Dr. Paolo Zamboni from the University of Ferrara in Italy. This pilot study warrants subsequent larger and better controlled studies to definitively evaluate the possible impact of CCSVI on the disease process in MS.

Dr. Banwell, a noted expert in pediatric MS, has assembled a team to study CCSVI in pediatric MS patients – a population where the disease process is at a very early stage, and where advanced age and other health conditions that might affect blood flow do not exist. They are determining whether CCSVI occurs in children with MS using non-invasive MRI measures of vein anatomy and novel measures of venous flow and are comparing the results to children without MS. The team also is using “hemodynamic” (blood flow) tests to investigate a hypothesis that might explain how blood flow problems could lead to myelin damage, through the accumulation of excess iron.

Determining whether the veins and vein flow are abnormal very early in the MS process in pediatric MS will add additional depth to studies of CCSVI in adult MS.

Recruitment: A total of 60 participants that includes healthy children and adolescents and pediatric MS participants. Participants with MS will be within 5 years of their first MS attack and recruited from the Pediatric MS Clinic at SickKids. Recruitment number is approximate and is subject to change.

Additional Personnel:

- Dr. Christopher Macgowan, SickKids and University of Toronto
- Dr. Suzanne Laughlin, SickKids and University of Toronto
- Dr. Manohar Shroff, SickKids and University of Toronto
- Dr. John Sled, SickKids and University of Toronto
- Dr. Rae Yeung, SickKids and University of Toronto
- Dr. Susanne Benseler, SickKids and University of Toronto
- Dr. Jeffrey Traubici, SickKids and University of Toronto
- Dr. Mahendranath Moharir, SickKids
- Dr. Douglas Arnold, Montreal Neurological Institute, McGill University
- Dr. Sridar Narayanan, Montreal Neurological Institute, McGill University
- Dr. Amit Bar-Or, Montreal Neurological Institute, McGill University
- Dr. Ruth Ann Marrie, MS Clinic director, University of Manitoba

Quotes – Dr. Brenda Banwell

- “For children and adolescents living with MS, this study provides a unique opportunity for participation in cutting edge research with therapeutic potential - access that is typically denied to young patients.”
- “We will study pediatric MS patients to determine whether the venous system is abnormal in a population where the disease process is at a very early stage and without the confounding effects of advanced age and co-existing health conditions.”



Title: Determining the relationship between chronic cerebrospinal venous insufficiency (CCSVI) and multiple sclerosis (MS)

Fiona Evanne Costello, MD, FRCP
Hotchkiss Brain Institute
Faculty of Medicine, University of Calgary
Calgary, Alberta
Timing: 7/1/10-6/30/12
Amount: C\$199,994.18 for 2 years

- A series of recent publications have suggested that some people with MS have obstructions in the veins that drain blood in the brain and spinal cord that may contribute to nervous system damage in MS.
- Dr. Costello's team is examining a cross-section of 120 people with MS compared to 60 healthy controls, seeking linkages between vein abnormalities and different aspects of MS activity and tissue damage.
- Their results should provide insight into the significance of differences in vein drainage and the implications for the future treatment of MS.

About the Investigator: Fiona Costello is a member of the Hotchkiss Brain Institute at the University of Calgary's Faculty of Medicine, as well as an MS treating neurologist and neuro-ophthalmologist at Foothills Medical Centre. She is also Director of the NeuroProtection and Repair Evaluation Unit of the Hotchkiss Brain Institute's Arresting MS Program. She trained at Memorial University of Newfoundland, where she completed her medical degree and residency training in neurology. In 2000, Dr. Costello did a clinical fellowship in neuro-ophthalmology at the University of Iowa Hospitals and Clinics before taking her first faculty position as Assistant Professor at the University of Ottawa. She moved to the University of Calgary in 2007, where is currently Associate Professor in the Departments of Clinical Neurosciences and Surgery. She has authored numerous relevant publications in the areas of MS and the use of optic neuritis as a system model of MS. She has received many honors including the North American Neuro-Ophthalmology Society Young Investigator Award; and was recently named one of Caldwell Partners Canada's "Top 40 Under 40" for advances in MS research. Dr. Costello, with co-investigator Dr. Michael Hill, Associate Dean of Clinical Research and a member of the Hotchkiss Brain Institute at the University of Calgary who has expertise in clinical epidemiology; has assembled a highly experienced team of collaborators including radiologists specializing in imaging of the blood vessels, interventional radiologists, and magnetic resonance imaging experts.

Details: This controlled study will carefully compare vein drainage between a cross-section of 120 people with MS with that seen in 60 healthy controls. In those MS patients who

exhibit signs of abnormalities of vein drainage, the investigators will explore whether the sites and severity of vein abnormalities correlate with common markers of MS disease activity, seeking linkages between any venous abnormalities observed and many different aspects and measures of MS activity and tissue damage.

The team is using ultrasound as originally used by Dr. Zamboni, and magnetic resonance studies of the veins (MR venography) to further explore the prevalence of venous insufficiency. The technologists and radiologists who interpret all scans will be blinded as to the clinical status of the participants.

This study should help quickly determine whether there are significant differences in venous drainage in people with MS, and their implications for the future treatment of MS.

Recruitment: A total of 180 participants including adults and children with MS and healthy participants. Participants with MS will be recruited from the Calgary MS Clinic at Foothills Medical Centre. Recruitment number is approximate and is subject to change.

Additional Personnel:

- Dr. Mayank Goyal, Hotchkiss Brain Institute, University of Calgary
- Dr. Richard Frayne, Hotchkiss Brain Institute, University of Calgary
- Dr. Jean K. Mah, Hotchkiss Brain Institute, University of Calgary
- Dr. Jephtha Davenport, Hotchkiss Brain Institute, University of Calgary
- Dr. James Scott, , University of Calgary

Quotes – Dr. Fiona Costello:

- “Dr. Zamboni’s findings have raised intriguing questions about the role of CCSVI in MS. At this point, our goal is to determine the prevalence of venous outflow insufficiency in a sizeable MS population, with validated and reliable measures of venous anatomy. Furthermore, we aim to study the concordance between the extent of venous obstruction and other established measures of disease activity.”
- “The data we obtain from our study will enhance our understanding about the role of venous insufficiency and possible consequences of myelin loss, axonal damage, and neuronal degeneration in MS.”



Title: Chronic Cerebrospinal Venous Insufficiency in relation to Multiple Sclerosis

Carlos Torres, MD
The Ottawa Hospital
Ottawa, Ontario
Timing: 7/1/10-6/30/12
Amount: C\$102,866 over 2 years

- A series of recent publications have suggested that some people with MS have obstructions in the veins that drain blood from the brain and spinal cord, and this may contribute to iron deposition and nervous system damage in MS.
- Dr. Carlos Torres is leading a team employing powerful MRI and Doppler ultrasound technology to explore vein anatomy and look for iron deposits in the brains of 50 people who have MS and 50 age-matched healthy volunteers.
- This study works towards mapping out normal variations in vein anatomy of the neck and providing insight into CCSVI in MS.

About the Investigator: Dr. Carlos Torres is a neuroradiologist at The Ottawa Hospital and an Assistant Professor of Radiology at The University of Ottawa. He is a clinical researcher with a particular interest in MS and other myelin-damaging diseases and has significant experience in MRI, Doppler ultrasound and computed tomography. He earned his MD at the University Javeriana in Colombia, South America, and did a residency in radiology there before becoming an Assistant Professor. He then went to McGill University Health Centre for a fellowship in Neuroradiology, where he earned the “Fellow Teacher of the Year” Award. He has been at the The Ottawa Hospital and University of Ottawa since 2008, and is now also the Director of the Neuroradiology Fellowship Training Program. Dr. Torres has assembled a top-notch team to address this project, including MS clinical research experts, physicists with a deep understanding of MR physics and imaging, clinical researchers with expertise in vascular (blood vessel) pathology and neurointerventional radiologists.

Details: This team is employing “3 Tesla” MRI technology that is twice as powerful as a standard MRI magnet to explore differences in the anatomy of veins in the neck, chest and spine and to assess for iron deposits in the brain. They are comparing findings in 50 people who have MS with those in 50 age-matched healthy volunteers. They are also using Doppler ultrasound techniques that were used by originators of the CCSVI hypothesis, and seeking verification that there is a relationship between blocked veins and areas of iron deposition in the brain by measuring levels of iron in the brain in those with and without vein blockages. The questions the team is focused on include: How frequent are the vein blockages and abnormalities in people who do not have MS? How frequently do they occur in people with MS? Can the team detect brain iron pooling in patients with blocked veins?

These studies should lead to a better understanding of normal variations in the anatomy of the veins that drain the brain, and the potential role of venous insufficiency in MS.

Recruitment: A total of 100 participants including participants with MS and healthy individuals. Participants will be recruited through The Ottawa Hospital MS Clinic Research Unit. Recruitment number is approximate and is subject to change.

Additional Personnel (all are affiliated with The Ottawa Hospital, the Ottawa Hospital Research Institute and the University of Ottawa):

- Dr. Ian G. Cameron, Department of Diagnostic Imaging (MRI Unit)
- Dr. Matthew J. Hogan, Division of Neurology
- Dr. Mark E. Schweitzer, Department of Radiological Sciences and Department of Diagnostic Imaging
- Dr. Cheemun Lum, Department of Diagnostic Imaging
- Dr. Miguel E. Bussière, Division of Neurology
- Dr. Santanu Chakraborty, Department of Diagnostic Imaging
- Dr. Mark S. Freedman, Division of Neurology (MS Research Unit)

Quotes – Dr. Carlos Torres:

- “Before undertaking large expensive studies to examine the benefits of treatment of these blockages, several important questions must be answered: Do these blockages occur in patients that do not have MS? Do they occur in all patients with MS? Can we detect brain iron pooling in patients with blocked veins? We hope to answer these questions.”
- “Results of this study will definitively confirm whether venous obstructions are clearly associated with MS or are a normal phenomenon. In addition, it will indicate whether excess iron deposition in the brain correlates with the presence of associated venous obstruction. Only with such results could a treatment trial aimed at relieving obstructions be considered.”



Title: Investigation into Venous Insufficiency in Multiple Sclerosis

Anthony Traboulsee, MD

Medical Director, MS Clinic at UBC Hospital, Vancouver Coastal Health and University of BC Vancouver, BC

Katherine Knox, MD

Saskatoon MS Clinic, University of Saskatchewan
Saskatoon, Saskatchewan

Timing: 7/1/10/-6/30/12

Amount: C\$200,000 over two years

- The team is studying the prevalence of CCSVI in 200 people including those with MS and controls without MS, using catheter venography, ultrasound, and magnetic resonance venography.
- Unique to this study is the inclusion of family members, such as identical twins of MS patients who have not developed MS, in control groups.
- The team hopes to verify the usefulness of non-invasive techniques that would make it easier to screen for CCSVI, which would be needed if results from this and other research confirm that future therapeutic trials are warranted.
- The research aims to determine the reliability and accuracy of different imaging techniques for screening for CCSVI. This information will be needed if results from this and other research confirms that future therapeutic trials are warranted.

About the Investigators: Dr. Anthony Traboulsee is an experienced MS clinician and researcher who plays many roles at the UBC Hospital including Medical Director of the MS Clinic, Director of the MS Clinical Trials Research Group, and Assistant Director of the MS/MRI Research Group. He is also Assistant Professor of Medicine/Neurology at UBC Faculty of Medicine. He began his career earning a BS in biology from McGill University, then went to Dalhousie University for his MD degree. He was a neurology resident at UBC Hospital, part of Vancouver Coastal Health Authority, then got further training there as a postdoctoral fellow in multiple sclerosis. He also received training in MS and neurology and was a visiting research assistant at the Institute of Neurology in the UK. He returned to UBC Hospital in 2001 and became head of the MS clinic there in 2009. He has broad experience in MS clinical trials, and has authored numerous research papers. Dr. Traboulsee will lead the research team at the BC site.

Dr. Katherine Knox is the Director of the Saskatoon MS Clinic and Assistant Professor with the College of Medicine, University of Saskatchewan. She is a primary investigator with the Cameco MS Neuroscience Research Centre at Saskatoon City Hospital. She completed her specialty training in Physical Medicine and Rehabilitation at the University of Saskatchewan

and her MD at McMaster University. At the University of Saskatchewan she is involved in teaching medical students and residents, multidisciplinary rehabilitation and research focusing on physical activity in MS. Dr. Knox will lead the research team at the Saskatchewan site.

Together the SK and BC sites will have assembled an excellent team from Vancouver Coastal Health (VCH) /University of British Columbia (UBC) and Saskatoon City Hospital/University of Saskatchewan that includes highly experienced MS neurologists, radiologists, interventional radiologists, physicists and a neuroethicist.

Details: This team is taking a comprehensive approach to study the prevalence of venous insufficiency in 200 people with MS and controls without MS, using catheter venography, Doppler ultrasound such as what was originally used to identify CCSVI, and magnetic resonance studies of the veins (MR venography). A unique aspect of this program is that they are including family members – including identical twins of MS patients who have not developed MS -- as control groups to gain further insight into CCSVI. The team hopes to verify the usefulness of non-invasive techniques that would make it easier to detect venous insufficiency, should this and other research suggest that future therapeutic trials are warranted.

Recruitment: A total of 200 participants including eligible persons with MS and their family members who are registered with the Canadian Collaborative Project on Genetic Susceptibility to MS (CCPGSMS). Recruitment number is approximate and is subject to change.

Additional Personnel:

- Dr. David K.B. Li, UBC Hospital, VCH/UBC
- Dr. Lindsay Machan, UBC Hospital, VCH/UBC
- Dr. Alexander Rauscher, MRI Research Centre, VCH/UBC
- Dr. Alex MacKay, MRI Research Centre, VCH/
- Prof. Judy Illes, Brain Research Centre, VCH/UBC
- Dr. Christopher Voll, Faculty of Medicine, University of Saskatchewan
- Dr. Sheldon Wiebe, Department of Medical Imaging, University of Saskatchewan
- Dr. Peter Szkup, Royal University Hospital, University of Saskatchewan
- Dr. Michael Kelly, Royal University Hospital, University of Saskatchewan

Quote – Dr. Anthony Traboulsee

- “The strength of our study is that it employs a comprehensive imaging protocol and a unique comparison group of individuals with an increased risk to develop MS. Our study will determine if CCSVI is strongly and uniquely associated with MS.”

Quote – Dr. Katherine Knox

- “The unique inclusion of a family member control group in this study may allow us to gain further insight into the possible role of CCSVI in the mechanisms leading to MS.”