CHL5225H

Presentation Project

What a Big Fuss About the Controversial MS "Liberation Treatment"

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What is "Liberation Treatment"?

MS "liberation Treatment" or "liberation therapy" is an 'unofficially proven safe and effective' procedure (angioplasty) that can restore the blood flow in the neck and chest veins in the multiple sclerosis patients

News Headlines

"Disputed MS theory tops health agenda"

(CBC news)

"The 'miracle cure' A controversial new treatment for MS comes to Canada"

(Macleans.ca)

"Newfoundland to fund "observational study" of controversial MS therapy"

(Macleans.ca)

"MS vein surgery innovator urges caution"

(CBC news)

"MS society sets aside funding for clinical trials of controversial procedure"

(The Globe and Mail)

"MS sufferers to rally on Parliament Hill"

(Toronto Sun)

Background

What is Multiple Sclerosis (MS)?

- Believed to be an autoimmune disorder caused by immune cells attacking neurons in the spinal cord and brain
- Symptoms: numbness and fatigue, loss of vision, balance, speech, muscle control
- 60% unable to walk after onset
- Occur mostly in whites females, diagnosed between age 15-40
- Medications: disease modifying therapies and steroids
- Prevalence rate=240/100,000 in Canada (55,000 to 75,000, 1000 new cases/year); 5th highest rate among countries (2004-2005)
- So far no known cure for MS, researchers haven't found a course yet
- Possibly caused by environmental and genetic factors

3 Main Types of CDMS

(1) Relapsing remitting (RR)

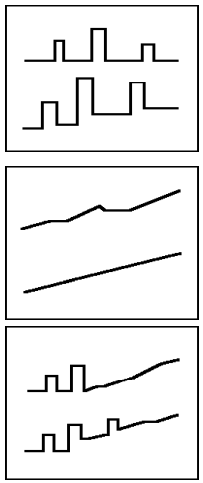
Attacks of symptoms followed by improvements (85% of patients)

(2) Primary progressive (PP)

Progressive increase in symptoms with no superimposed remissions and relapses (15%)

(3) Secondary progressive (SP)

After many years of relapsing remitting (RR), patients begin to show progressive increase in symptoms



The Star Behind the Controversial Issue

Dr. Paolo Zamboni , an Italian vascular surgeon at the University of Ferrara, Italy

His revolutionary research suggests that MS is a vascular disease, not an autoimmune condition

His study said that blocked neck veins can be the cause of MS. The symptoms can be treated using angioplasty (catheter with an inflatable balloon) to open up the damaged veins

Published 2 papers in 2009 (initial assessment of frequency of abnormal veins in MS patients, followed by a pilot study (non-randomized , single centre)

Dr. Zamboni's Discovery of CCSVI

- Helpless as his wife was diagnosed with MS in 1995. So he went on a mission to track down the cause of her disease
- Learnt from other scientists that MS patients have high levels of iron deposits in the brain, so suspected that iron deposits might play a role in causing MS
- Veins in their brains were either narrowed or blocked
- His theory was based on the idea that impaired drainage from the vein that runs through the chest can cause a backup of blood and thus can cause iron to deposit in the brain (term called CCSVI)
- So he thinks the impaired flow of blood from brain can trigger MS symptoms
- Gathered a team of surgeons to begin research
- His hypothesis draws a lot of criticism by many neurologists and researchers
- Some critics suggest patients' positive response could be due to "placebo effect"

Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis (J Neuro Neurosurg Psychiatry 2009 80:392-399)

Hypothesis:

- CCSVI (term used to describe an abnormal condition whereby the venous system cannot remove the blood efficiently due to impaired veins in the neck, chest and spinal) may lead to nervous system damage in clinically diagnosed multiple sclerosis (CDMS)

Method:

- Examined 65 patients with 3 different types of MS and 235 controls who were either healthy or had other neurological disorders
- Underwent advanced ultrasound techniques to detect abnormalities in venous outflow

Statistical Analysis:

- One way ANOVA analysis of variance, Fisher's exact test, Mann-Whitney test, chi-square test of independence

Results:

- Significant evidence that CDMS patients had slowed and obstructed drainage in the veins draining the brain and spinal code
- Evidence of reverse flow of blood back into the brain
- Medication status (with or without disease modifying therapy) did not seem to influence signs of CCSVI

Conclusions:

- CDMS is strongly associated with CCSVI, however CCSVI has not linked with other neurological conditions or in healthy controls; hence suggesting impaired vein may lead to nerve tissue damage
- The location of the obstructions in the veins can be a cause of MS

A prospective open-label study of endovascular treatment of chronic cerebospinal venous insufficiency

(J vasc Surg 2009 Dec:50(6) 138-58)

Following the results of his initial study that CCSVI is strongly associated with MS

Objective:

- Evaluate the safety of CCSVI endovascular treatment and its influence on the clinical outcome of the associated MS

Method:

- 65 patients - 35 with relapsing remitting (RR), 20 with secondary progressive (SP) and 10 with primary progressive (PP) underwent percutaneous transluminal angioplasty (PTA)
- Assessed pre and postop vascular outcome measures, neurological and QOL questionnaire
- Mean follow-up was 18 months

Statistical Analysis:

- Mann-Whitney test, analysis of variance, Fisher's exact test, KM survival curve

Results:

- Outpatient endovascular treatment of CCSVI was feasible with minor and negligible complication rate
- Significant improvements in clinical outcome measures were seen primarily in relapsing-remitting (RR) MS

Conclusions:

- PTA is safe in patients with CCSVI
- The results of this pilot study warranted that a subsequent randomized control study is necessary to better determine potential safety and benefits of the procedure

New Hopes for MS Patients

- After Dr. Paolo Zamboni presented his preliminary study of CCSVI (chronic cerebrospinal venous insufficiency) in Nov 2009, it made headlines worldwide and is still debated
- His research opened up new roads of research and may lead to potential therapies for MS symptoms
- The MS community especially responded with such great hope and excitement- jammed chat rooms, facebook, etc, some rushed to have surgery done overseas
- The MS society called for an immediate action to pursue this promising research. This call for specific research proposals was said to be unique and unprecedented in the MS Society's 60-year history. They are anxious to clarify the relationship between CCSVI and MS and to identify what treatment potential it may offer to MS patients

CCSVI Research Funding Timeline

The National MS Society (USA) collaborates with the MS Society of Canada

Dec 16, 2009	Expedited invitation calling for worldwide investigators to apply for grants
Feb 9, 2010	Many international CCSVI research proposals were received
May 2010	International review panel of MS and vascular experts conducted a rigorous expedited review of all applications
Jun 2010	Funding announced In Jun 11, 2010 National MS Society (USA) and the MS Society of Canada announced funding of over $2.4 million to support 7 new research projects on the relationship of CCSVI in MS
July 1, 2010	Anticipated start date for funding of any successful research applications for a period of 2 years (4 in Canada, 3 in US)

The 7 New Studies

Dr. Brenda Banwell, The Hospital for Sick Children, Toronto, Ontario: studying vein abnormalities in children and teenagers who have MS, and healthy controls of the same age

Dr. Fiona Costello, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta: examining a cross-section of people with MS compared to other neurological diseases and healthy volunteers.

Dr. Aaron Field, University of Wisconsin School of Medicine and Public Health, Madison: using magnetic resonance (MRI) scans to generate detailed images of the head and neck veins in people with early and later MS, healthy volunteers, and controls with other neurological conditions.

Dr. Robert Fox Cleveland Clinic, Cleveland: studying people with MS or who are at risk for MS (CIS) and comparison groups including healthy volunteers and people with brain atrophy (shrinkage) from Alzheimer's disease.

Dr. Carlos Torres, The Ottawa Hospital, University of Ottawa, Ontario: employing powerful MRI technology to explore vein anatomy and assessing for iron deposits in the brains of people with MS and in age-matched healthy volunteers

Dr. Anthony Traboulsee, UBC Hospital MS Clinic, UBC Faculty of Medicine and Dr. Katherine Knox, Saskatoon MS Clinic, University of Saskatchewan: studying the prevalence of CCSVI in people with MS and controls without MS, using catheter venography, ultrasound, and magnetic resonance venography

Dr. Jerry Wolinsky, University of Texas Health Science Center at Houston: replicating the ultrasound methods used by Dr. Zamboni to investigate the association of CCSVI with major clinical types of MS and in non-MS control groups.

The 7 New Studies

Their studies will address these main concerns:

- ✓Does CCSVI occur in all people with MS and in all types of MS?
- ✓Does CCSVI occur in people who do not have MS?
- ✓Does CCSVI occur in children?
- ✓Is CCSVI caused by MS or vice-versa?
- ✓What are the implications of the blocked veins?
- ✓Are blocked veins due to poor blood flow?
- ✓Can blocked veins cause iron deposits?

Hopefully they will find out the relationship between CCSVI and MS

Goals of 7 New Studies

(1) To confirm the phenomenon described by Dr. Zamboni et al. who reported to find abnormalities in the veins draining the brain and spinal cord and to ascertain that CCSVI is a cause of MS

(2) To resolve conflicting data that were done in previous research, such as how often CCSVI is found in MS patients and those without MS because other studies showed different results

(3) To determine if therapeutic trials can be used to correct blockages in the veins

Researchers are asked to provide 6-month interim updates during the grant progress

Results will be posted once available

Government Involvement in the "Liberation" Therapy Clinical Trials

After an unanimous support from scientific experts and backed up by the MS Society of Canada, CIHR provided recommendations to our Health Ministers

(1) Overwhelming lack of scientific evidence to support safety and efficacy of the procedure

(2) No link between blocked veins and MS

Federal Government, Federal Health Minister, accepted their recommendations

No Pan-Canadian clinical trials of the liberation therapy until results received from 7 North American studies

Newfoundland and Labrador Government

Sep 13: Newfoundland and Labrador announced they will fund an **"observational study"** to investigate the efficacy of the "liberation" therapy

It is not a clinical trial!

Study Proposed:

- MS patients from Newfoundland will have to pay on their own to get treatment overseas like US, Kuwait, India, Poland, etc
- Before leaving, MRI exam will be performed
- After treatment abroad, they will be followed up by local neurologists and data will be collected on their condition

Saskatchewan Government

In earlier summer, Saskatchewan government announced it will fund the trial to determine if liberation therapy works.

Despite concerns of lacking scientific evidence raised by CIHR, the Saskatchewan is ready to fund the clinical trial if it receives a proposal from the researchers

Saskatchewan has a highest rate of MS in Canada

MS society sets aside funding

$1-million is set aside by the MS Society of Canada for a pan-Canadian therapeutic clinical trial

"We want to hit the ground running when a therapeutic trial is warranted and approved," Yves Savoie, president and CEO of the MS Society, said in a statement released Thursday. "Ensuring funds are available to support a Canadian trial will accelerate our ability to get definitive answers to the questions people touched by MS urgently seek."

Limitations / Discussions

- Zamboni's first study: technicians were not blinded, so aware patients were MS or not MS, so could be biased
- Zamboni's interventional pilot study had no control comparison group and was not blinded
- Many placebo effect seen in patients in all MS clinical trials
- 47% of treated veins became narrowed again with time
- Using ultrasound as investigative tool can give rise to potential errors in measurement, so interpretation of data is subjective
- Recent studies have shown contradict results in patterns of venous damage in MS and non-MS patients
- Venous angioplasty is rarely used because incidence of restenosisis is high due to elastic nature of the veins
- Insertion of stents into veins is risky, may cause events like clotting, bleeding, death, etc
- Serious ethical issues given lack of evidence for CCSVI

Conclusion

To confirm 'liberation treatment" is working safely and effectively, conduct randomized controlled clinical trials to address these potential problems after confirming CCSVI is closely associated with MS

Next step after confirming the relationship between CCSVI and MS

Determine the effects of treatment

- ✓Do the effects of the treatment work in all types of MS?
- ✓How long do the treatment effects last?
- ✓Can the results be replicated in a 'blinded' study?
- ✓What are the reliability, risks and benefits of the treatment?
- ✓Is this treatment comparable in effectiveness and safety to existing therapies?

Advice to MS sufferers

Please be patient and cautious
Do not listen to “blogger patients”!

Dr. Zamboni said on Apr 14, 2010:

“People with multiple sclerosis should not rush to seek out a new surgical procedure to unblock veins outside of proper clinical studies.”

More research is still needed

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