



## **CCSVI News Bulletin, 07 April 2011**

### **College of Physicians and Surgeons of Alberta guidelines on post-CCSVI treatment monitoring**

The College of Physicians and Surgeons of Alberta has published guidelines on the management of MS patients who have undergone treatment for CCSVI.

[http://www.cpsa.ab.ca/Libraries/Res/Managing\\_patients\\_with\\_MS\\_after\\_out-of-country\\_endovascular\\_treatment\\_for\\_CCSVI.pdf](http://www.cpsa.ab.ca/Libraries/Res/Managing_patients_with_MS_after_out-of-country_endovascular_treatment_for_CCSVI.pdf)

### **MS Society of Canada launch new website on CCSVI and MS**

The MS Society of Canada has launched a new website reporting on the latest CCSVI news and providing information for people with MS about the procedure.

<http://ccsvi.ca/>

### **Italian Minister of Health issues two documents on CCSVI and CCSVI therapy**

The Italian Minister of Health wrote a letter dated March 4, 2011 addressed to Regional Health Authorities stating that the Advisory Health Committee had evaluated the CCSVI matters and has published its advice in two different documents (see ItalianAHC\_CCSVI\_1.doc and ItalianAHC\_CCSVI\_2.doc attached), inviting Regions to modify accordingly their clinical and research activities and to inform the stakeholders in the health service.

### **International Society for Neurovascular Disease (INSVD) holds first annual meeting**

The INSVD, established in July 2010 with Dr. Paolo Zamboni as president, held its first annual meeting in Bologna, Italy, on March 14-15, 2011.

<http://www.isnvd.org/2010/11/annual-meeting-italy/>

### **Canadian Government announces new national MS monitoring system**

The federal government of Canada has announced that it will provide funding through the Public Health Agency of Canada to support development of a national monitoring system that will capture information to help identify disease patterns and track treatments and long-term outcomes for people living with MS.

The system will be developed by the Canadian Institute for Health Information (CIHI) in close collaboration with the Canadian Network of MS Clinics and the MS Society of Canada. The monitoring system will be able to track Canadians with MS who have chosen to have the Zamboni procedure abroad and monitor MS symptom changes over time and any complications.

[http://mssociety.ca/en/releases/nr\\_20110323.htm](http://mssociety.ca/en/releases/nr_20110323.htm)

<http://www.phac-aspc.gc.ca/cd-mc/ms-sp/index-eng.php>

### **Society for Interventional Radiology (SIR) discusses CCSVI treatment**

At the Society for Interventional Radiology's annual meeting in Kenneth Mandato M.D. stated that angioplasty of the internal jugular or azygous veins is safe, citing an unpublished study undertaken at the Albany Medical Center.

In a press release SIR stated that:

"SIR agrees that the preliminary research is very promising and supports studies aimed at understanding the role of CCSVI in MS, at identifying methods to screen for the condition and at designing protocols for exploratory therapeutic trials"

[http://www.sirweb.org/news/newsPDF/3\\_MS\\_final.pdf](http://www.sirweb.org/news/newsPDF/3_MS_final.pdf)

### **Government of Manitoba announces funding for clinical trials of CCSVI treatment**

The government of the province of Manitoba has announced that it is providing \$5 million to fund clinical trials of CCSVI therapy for MS, in a process that is intended to complement that announced by the government of the province of Saskatchewan in December 2010.

<http://news.gov.mb.ca/news/index.html?archive=&item=11189>

Having regard to the request from the Minister concerning the “Chronic cerebro-spinal venous insufficiency (CCSVI) and Multiple sclerosis (MS)”;

Having regard to the M.D. of July 15<sup>th</sup>, 1997 concerning the “Implementation of the EU guidelines related to the clinical good practice to be applied to medication clinical trials” and its subsequent modifications and amendments;

Having regard to the M.D. of November 23<sup>rd</sup>, 1999 concerning the “Setting up of the Italian Ethics Committee and its role related to medication clinical trials, as per Legislative decree no. 229, June 19<sup>th</sup> 1999” and its subsequent modifications and amendments;

Having regard to the L.D. no. 46, February 24<sup>th</sup>, 1997 concerning the “Implementation of the directive 93/42/EEC on medical devices”;

Having regard to the opinions of the Italian Bioethics Committee (Comitato Nazionale di Bioetica - CNB) concerning biomedical research and clinical practice;

- ❖ Whereas the chronic cerebro-spinal venous insufficiency (CCSVI) has been acknowledged by the “*World Consensus Conference on Venous Malformations*” (Montecarlo, September 2009), it is recognized as a syndrome characterised by compromised outflow of blood from the CNS due to stenosing malformation at the level of the large neck and chest vessels (jugular and/or azygous veins). This may cause increased venous pressure and blood stasis, thus allowing iron and catabolites deposition in the brain, it may cause direct or indirect harmful effects to neurons and oligodendrocytes;
- ❖ Whereas many scientific studies have been published stating that such a syndrome does not trigger any vascular, clinical or neurologic symptoms;

Considering that

- ❖ MS might be correlated to CCSVI, so multiple sclerosis might be treated by angioplasty; such an approach has been widely and carefully debated by the Council of the Board of Health (Consiglio Superiore della Sanità ), whose opinion was published on June 8<sup>th</sup>, 2010 (Annex 1) and states that “*no vascular therapeutic procedure has proved to be effective up to now, so the acceptance of those is to be postponed to scientific data proving that CCSVI and MS are correlated*”;

Having regard to the research and studies carried out by an *ad hoc* Workgroup that was set up by the Health Secretary;

Considering that the Minister of Health sent a notification to the regional Health Councillors on October 27<sup>th</sup>, 2010, which was based on the work carried out by the above mentioned Workgroup;

Having clarified that the following sentence *“the National Health System will administer those treatments needed to diagnose, monitor and – if necessary – repair any pathologic anomaly of the arterial and venous system by means of hospitalization and under the responsibility of physicians* is valid regardless and patients may or may not be suffering from MS;

Considering that such problem is under the spotlight of the media, since MS is a very widespread neurological disease, is widely debated and has a strong impact on the NHS - as a matter of fact 1.3 million people is affected by MS in the world, 400,000 MS patients live in Europe and 57,000 MS patients live in Italy;

Considering that what is needed is identifying the opinions of the Italian and international scientific communities concerning:

- The nosological, clinical and diagnostic definition of CCSVI as a syndrome existing by itself and the possible therapies to be used to repair the stenosis of the extra-cranial venous system, if the clinical picture of the patient justifies such a procedure;
- The possible relation between CCSVI and MS and the repair – if possible – of the stenosis of the extra-cranial venous system as a treatment for MS;
  
- ❖ Having considered the meta-analysis of the available medical literature, which has been carried out by US researchers working at the University of Detroit, what is stated is that the invasive nature and harmful effects of endovascular procedures performed on MS patients – both percutaneous transluminal angioplasty (PTA) and stent procedures – suggest not using such procedures. Before considering such procedures as actual therapies, more studies need to be carried out and involve a larger number of patients;
- ❖ Having considered the opinion of Stanford University which suspended the use of the above mentioned endovascular procedures on patients suffering from CCSVI;

Considering that the international scientific community is very careful as far as these procedures are concerned and deems it necessary to carry out more studies before reaching oversimplified and misleading conclusions;

Considering that results from medical data are very different, either completely negative or slightly positive (CCSVI has been diagnosed in healthy patients or patients suffering from other neurological diseases), or positive but characterised by discrepancies: positive correlation (characterised by effects that may be indirectly correlated to the disease) or negative correlation to the development of the disease (characterised by congenital or predisposing factors);

Having considered the development and events related to this problem;

Having met the following Scientific Societies on January 19<sup>th</sup>, 2011:

- ❖ Italian Society of Angiology and Vascular Pathology (Società Italiana di Angiologia e Patologia Vascolare - SIAPAV)
- ❖ Italian Society for Vascular and Endovascular Surgery (Società Italiana di Chirurgia Vascolare ed Endovascolare - SICVE)

- ❖ Italian Society of Medical Radiology (Società Italiana di Radiologia Medica - SIRM)
- ❖ SIRM Interventional and Vascular Radiology Section (Sezione di Radiologia Vascolare ed Interventistica della SIRM)
- ❖ Italian Society of Neurology (Società Italiana di Neurologia - SIN)
- ❖ Italian Society of Vascular Diagnostics (Società Italiana di Diagnostica Vascolare - SIDV)
- ❖ Italian Society of Neurosurgery (Società Italiana di Neurochirurgia - SINCH)
- ❖ Italian Society of Neurosonology and Cerebral Hemodynamics (Società Italiana di Neurosonologia Emodinamica Cerebrale - SINSEC)

Having considered the opinions that have been stated during the debate and after having carefully examined the various highlighted and correlated factors and, in particular:

- ❖ The CCSVI syndrome, described by Dr Zamboni, might be diagnosed by using sonology based on published criteria, which envisage that 2 detectable criteria out of 5 must be positive;
- ❖ The above mentioned criteria have not been validated as “*gold standard*” criteria yet, since venography (which might be validated as *gold standard*) is a variable test: it depends on the pressure used to inject the contrast medium, the position of the patient and more inter-individual variables;
- ❖ The above mentioned criteria have not been validated with regard to the prognostication for changes to brain hemodynamics, which have already been mentioned by medical literature;
- ❖ One of the 5 criteria that are used to diagnose CCSVI envisages the use of transcranial ultrasound scan through a bone window (supracondylar) that has never been used in medical literature, so no data related to age groups are available;
- ❖ The results concerning CCSVI presence and role are still contradictory, therefore more studies and research are needed; they must be carried out by using accurate research tools, and by the appropriated selection of patients;

Having seen that

- ❖ On the basis of what is now known, no proved correlation between CCSVI and MS does exist, but further research is needed to
  - Define the responsiveness - specificity, repeatability and dependency from the operator and how much the sonologic methods may contribute to the diagnosis of the “cerebral venous insufficiency”;
  - Prove (show) that CCSVI as a nosographic entity;
  - Prove (show) that CCSVI as a pathology or normal anatomic alteration;
- ❖ Since what is listed above has not been defined yet, surgical procedures must not be taken into consideration, some of which are not without risks (e.g. stent implantation);
- ❖ Each procedure must be performed within research and study activities, they must be approved by the Ethics Committees and an adequate clinical follow-up of patients must be put in place;

Having also considered that

- ❖ Angioplasty treatment of CCSVI on patients suffering from MS is now a widely used procedure in Italy and abroad and that more than 120 angioplasty treatments are registered on the on line National Registry listing all surgical procedures and published by the SIRM Vascular and

Interventional Radiology Section (which states that only 10% of all surgical procedures are listed in the registry);

Having analysed all documents, including those documents concerning scientific data published by Dr Zamboni;

Having listened to Prof. Zangrillo

It is decided unanimously

- ❖ That no correlation between CCSVI and MS has been proved yet, so performance of vascular repair on patients suffering from MS is not advisable;
- ❖ That what is needed is clear indications concerning procedures to diagnose, monitor and repair anomalies of the arterial and venous vascular system, if physiopathological conditions caused by such anomalies do exist;
- ❖ That dilation treatment may be used on selected patients only and if clear clinical indications do exist irrespective of MS being an existing condition, what is needed is implementing diagnostic procedures that may assess patients from anatomical, functional and hemodynamic points of view and prove changes in brain perfusion.

It is also mandatory that

Treatment of CCSVI on patients suffering from MS may only be performed within controlled and randomized clinical trials, which need to be approved by Ethic Committees and need to be accompanied by a protocol dealing with the conflict of interests, the criteria for the selection or exclusion of patients, any invasive diagnostic test, the techniques used to perform the various tests and procedures, primary and secondary endpoints, the monitoring of any side harmful effects, the modality and time of the follow-up methods and intervals and finally the features of statistical analysis.

Finally it is considered appropriate

- ❖ Any speculative or economic implications must be set aside, since this is a very delicate and complex problem as far as ethics is concerned;
- ❖ Patients must be protected against unjustified enthusiasm, economic interests and risks due to treatments reminding that biomedical research and human subject research, as well as medical practice, must be based on the mandatory principle stating that the psychophysical integrity of individuals must be protected.

Having regard to the request from the Minister concerning the “Chronic cerebro-spinal venous insufficiency (CCSVI) and Multiple sclerosis (MS)”;

Having regard to the M.D. of July 15<sup>th</sup>, 1997 concerning the “Implementation of the EU guidelines related to the clinical good practice to be applied to medication clinical trials” and its subsequent modifications and amendments;

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Having regard to the opinions of the Italian Bioethics Committee (Comitato Nazionale di Bioetica - CNB) concerning biomedical research and clinical practice;

- ❖ Whereas the chronic cerebro-spinal venous insufficiency (CCSVI) has been described as a syndrome characterised by compromised outflow of intracranial blood due to stenosing malformation at the level of the large neck and chest vessels (jugular and/or azygous veins). This may cause increased venous pressure and blood stasis, thus allowing iron and catabolites deposition in the brain, it may cause direct or indirect harmful effects to neurons and oligodendrocytes;
- ❖ Whereas many scientific studies have been published stating that such a syndrome does not correlate to any vascular, clinical or neurologic symptoms;

Considering that

- ❖ MS might be correlated to CCSVI, so multiple sclerosis might be treated by angioplasty; such an approach has been widely and carefully debated by the Council of the Board of Health (Consiglio Superiore della Sanità ), whose opinion was published on June 8<sup>th</sup>, 2010 (Annex 1) and states that *“no vascular therapeutic procedure has proved to be effective up to now, so the acceptance of those is to be postponed to scientific data proving that CCSVI and MS are correlated”*;

Having regard to the research and studies carried out by an *ad hoc* Workgroup that was set up by the Health Secretary;

Considering that the Minister of Health sent a notification to the regional Health Councillors on October 27<sup>th</sup>, 2010, which was based on the work carried out by the above mentioned Workgroup;

Having clarified that the following sentence *“the National Health System will administer those treatments needed to diagnose, monitor and – if necessary – repair any pathologic anomaly of the*

*arterial and venous system by means of hospitalization and under the responsibility of physicians” is valid regardless patients may or may not be suffering from MS;*

Considering that such problem is under the spotlight of the media, since MS is a very widespread neurological disease, is widely debated and has a strong impact on the NHS - as a matter of fact 1.3 million people is affected by MS in the world, 400,000 MS patients live in Europe and 57,000 MS patients live in Italy;

Considering that what is needed is waiting for the opinions of the Italian and international scientific communities concerning:

- The nosological, clinical and diagnostic definition of CCSVI as a syndrome existing by itself and the possible therapies to be used to repair the extra-cranial venous stenosis, if the clinical picture of the patient justifies such a procedure;
- The possible relation between CCSVI and MS and the repair – if possible – of the venous stenosis in patients suffering from MS;
  
- ❖ Having considered the meta-analysis of the available medical literature, which has been carried out by US researchers working at the University of Detroit, what is stated is that the invasive nature and harmful effects of endovascular procedures performed on MS patients – both percutaneous transluminal angioplasty (PTA) and stent procedures – suggest not using such procedures. More studies need to be carried and involve a larger number of patients;
  
- ❖ Having considered the opinion of Stanford University which suspended the use of the above mentioned endovascular procedures on patients suffering from CCSVI;

Considering that the international scientific community is very careful as far as these procedures are concerned and deems it necessary to carry out more studies before reaching conclusive results;

Considering that results from medical data are very different, either completely negative or slightly positive (CCSVI has been diagnosed in healthy patients or patients suffering from other neurological diseases), or positive but characterised by discrepancies: positive correlation (characterised by effects that may be indirectly correlated to the disease) or negative correlation to the development of the disease (characterised by congenital or predisposing factors);

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- ❖ Italian Society of Medical Radiology (Società Italiana di Radiologia Medica - SIRM)

- ❖ SIRM Interventional and Vascular Radiology Section (Sezione di Radiologia Vascolare ed Interventistica della SIRM)
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Having considered the opinions that have been stated during the debate and after having carefully examined the various highlighted and correlated factors and, in particular:

- ❖ The CCSVI syndrome, described by Dr Zamboni, might be diagnosed by using ultrasonographic tests based on published criteria, which envisage that 2 detectable criteria out of 5 must be positive;
- ❖ The above mentioned criteria have not been validated as “*gold standard*” criteria yet, since phlebography (which might be validated as *gold standard*) is a variable test: it depends on the pressure used to inject the contrast medium, the position of the patient, inter-individual variables and the medical devices used;
- ❖ The above mentioned criteria have not been validated with regard to the prognostication for changes to brain hemodynamics, which have already been mentioned by medical literature;
- ❖ One of the 5 criteria that are used to diagnose CCSVI envisages the use of transcranial ultrasound scan through a bone window (supracondylar) that has never been used in medical literature, so no methodological data are available;
- ❖ CCSVI presence and CCSVI-related etiopathogenetic correlations are still debated, therefore more studies and research are needed; they must be carried out by using accurate research tools, exact research methods and by the appropriated selection of patients;

Having seen that

- ❖ On the basis of what is now known, no proved correlation between CCSVI and MS does exist, but further research is needed to
  - Prove (show) that CCSVI as a nosographic entity;
  - Prove (show) that CCSVI as a pathology or anatomic alteration;
  - Define the responsiveness - specificity, repeatability and dependency from the operator and how much the ultrasonographic methods to the diagnosis of the “cerebral venous insufficiency”;
- ❖ Since what is listed above has not been defined yet, there is not any ground to give indications concerning surgeries of revascularization, some of which are not without risks;

Having also considered that

- ❖ in spite of what has been described above, endovascular treatments of CCSVI on patients suffering from MS have been described outside controlled clinical trials either in Italy or abroad;

Having analysed all documents, including those documents concerning scientific data published by Dr Zamboni;

Having listened to Dr Zangrillo

It is decided unanimously

- ❖ That CCSVI, as of today, cannot be yet acknowledged as a nosological entity;
- ❖ That, its epidemiological correlation to MS has not been proved yet, so performance of vascular repair on patients suffering from MS is not advisable;
- ❖ That what is needed is clear indications, regardless MS may or may not be associated with CCSVI, concerning procedures to diagnose, monitor and repair anomalies of the venous vascular system, if physiopathological conditions caused by such anomalies do exist;

It is also mandatory that

Repair of venous anomalies on patients suffering from MS may only be performed within controlled and randomized clinical trials, which need to be approved by Ethic Committees and need to be accompanied by a protocol dealing with the conflict of interests, the criteria for the selection or exclusion of patients, any diagnostic test, the methods used to perform the various tests and procedures, primary and secondary endpoints, the monitoring of any side harmful effects, the modality and time of the follow-up methods and intervals and finally the features of statistical analysis.

Finally it is considered appropriate

- ❖ Any speculative or economic implications must be set aside;
- ❖ Patients must be protected against unjustified enthusiasm, economic interests and risks due to treatments reminding that biomedical research and clinical practice must be based on the mandatory principle stating that the psychophysical integrity of individuals must be protected.