

CHRONIC CEREBRO SPINAL VENOUS INSUFFICIENCY (CCSVI): A NEW HYPOTHESIS FOR MULTIPLE SCLEROSIS

 **L'INSUFFICIENZA VENOSA CRONICA CEREBRO SPINALE (CCSVI): UNA NUOVA IPOTESI PER LA SCLEROSI MULTIPLA**

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Citation: Mandolesi S, De Sio S, Di Pastena, et al. Chronic cerebro spinal venous insufficiency (CCSVI):
a new hypothesis for Multiple Sclerosis. Prevent Res 2013; 3 (1): 39-44.
Available from: <http://www.preventionandresearch.com/> .

Key words: chronic cerebro-spinal venous insufficiency, Multiple Sclerosis,
venous compression, Zamboni

 **Parole chiave:** Insufficienza venosa cronica cerebro spinale, Sclerosi Multipla,
compressione venosa, Zamboni

Abstract

A controversial nosologic vascular pattern recently identified by Prof. Paolo Zamboni of Ferrara and called Chronic Cerebro Spinal Venous Insufficiency (CCSVI) was associated with multiple sclerosis, bringing a new diagnostics vision and treatment of a disease which currently affects 70.000 Italians.

CCSVI is an hemodynamic condition, identified for the first time in 2009 by Prof Zamboni, in which there is an abnormal venous drainage of cerebro-spinal fluid. The venous system obstacle through the internal jugular vein, vertebral veins and the azygos system determines cerebro-spinal fluid stasis, venous reflux and flow reverse through a vicarious cerebro-spinal circuit, resulting in a prolongation of the cerebral circulation, verified with diffusion magnetic resonance studies. There are several clinical conditions such as abnormal coagulation, inflammation, neoplastic compression, which can lead an acute obstruction of the cerebrospinal venous system resulting in severe clinical manifestations, such as dizziness, stiff neck, headache, lethargy; in these conditions percutaneous angioplasty and loco-regional thrombolysis treatments causes regression of symptoms. Zamboni has treated individuals suffering from Multiple Sclerosis's CCSVI with jugular and azygos angioplasty having positive results.

Abstract

Un controverso modello nosologico vascolare recentemente identificato dal Prof. Paolo Zamboni di Ferrara e definito Insufficienza Venosa Cronica Cerebro Spinale (CCSVI) è stato associato alla Sclerosi Multipla portando una nuova visione diagnostica e terapeutica di una malattia che ad oggi colpisce circa 70.000 Italiani.

La (CCSVI) è una condizione emodinamica, identificata e stigmatizzata nel 2009 dal Prof. Zamboni per la prima volta, per la quale si ha un alterato drenaggio venoso cerebro-spinale; l'ostacolo al deflusso venoso attraverso il sistema della vena giugulare interna, le vene vertebrali e il sistema dell'azygos determina stasi liquorale, reflusso venoso e inversione del flusso cerebro-spinale attraverso un circuito vicariante, determinando un prolungamento del tempo di circolo cerebrale, verificato con studi di diffusione con Risonanza Magnetica (RM). Esistono diverse condizioni cliniche, come anomalie della coagulazione, infiammazioni, compressioni neoplastiche, che possono determinare un'ostruzione acuta del sistema venoso cerebro-spinale con conseguenti gravi manifestazioni cliniche, quali confusione mentale, rigidità nucale, cefalea, letargia; nelle suddette condizioni il trattamento percutaneo mediante angioplastica e trombolisi loco-regionale determina regressione della sintomatologia. Su queste premesse Zamboni ha operato i primi soggetti con Sclerosi Multipla affetti da CCSVI mediante angioplastica delle giugulari e Azygos con positivi risultati.

Description

The multiple sclerosis (MS) is an inflammatory-demyelinating disease of the brain and the spinal cord with multiple neurological manifestations, above all in young adults (1).

The formation mechanism of the disease involves several steps: inflammation, demyelination and neuro-degeneration of the central nervous system (1-3).

Charcot (4) established a possible link between venous vascular disorders and the inflammatory lesions characteristic of multiple sclerosis, and after him, many researchers have noted the involvement of the venous structures in the pathogenesis of plaque.

Recent studies show that most of the patients with multiple sclerosis are affected by chronic cerebro-spinal venous insufficiency CCSVI (5-9).

As observed in several neurodegenerative diseases, the brain and the spinal cord of patients with MS contain high levels of redox-active metals, especially iron (10), documented by MRI (11, 12) and with histochemical methods (13, 14).

The way it reveals

MS is commonly divided into different clinical types (1, 2, 15):

- RRMS: relapsing remitting multiple sclerosis (85%) (16);
- SPMS: secondary progressive multiple sclerosis (15%) (15, 16);
- SMPP: primary progressive multiple sclerosis (5%) (17).

RRMS is the most common type. Patients affected by this form tend to suffer from an attack or series of attacks (relapses) followed by complete or partial remission (16). SPMS begins with relapsing-remitting MS (RRMS). It 's chronic and progressive. There aren't real periods of remission (15, 16).

PPMS is characterized by a gradual decline without clinical distinct periods, real or remission. The course of the disease is a steady decline since the beginning (17).

The way it is diagnosed

The most commonly used tools in the diagnosis are (1, 2, 18-20):

- neuroimaging with magnetic resonance imaging (MRI) of the brain and the spine, which shows areas of demyelination (lesions or plaques) with gadolinium (21, 22);
- Test of cerebrospinal fluid by a lumbar puncture, which can provide evidence of chronic inflammation of the central nervous system for oligoclonal bands of IgG (23);
- The evoked potential by the stimulation of the optic nerve and sensory nerves, caused by demyelination. These brain responses can be examined using visual and sensory evoked potentials (24).

Magnetic resonance venography (MRV) (7, 25) and post-mortem studies (26) show a correspondence between topographic plaques of multiple sclerosis and cerebral venous system.

News in research

Recently, Prof. Zamboni (27) has raised the possibility that the chronic cerebro-spinal venous insufficiency could play a decisive role in the genesis of the disease: he assumes that the obstructed venous outflow causes a redistribution of the flow through the vicarious side insufficient to ensure an adequate flow resulting in stasis of red blood cells and T lymphocytes at the level of endothelial junctions resulting in diapedesis of cells at the level of the brain tissue with consequent accumulation of the same and hemosiderosis and inflammation.

Another important consideration in the genesis of vascular sclerosis is represented by the constant observation in MRI examinations that the basic lesion is constituted by a ectasic vein at the center, surrounded by a plaque, which shows a significant proportion of iron in its context (6, 7).

The microscopic analysis shows that the basal membrane of these deep veins is thickened with the constant presence of hemosiderin intraparietal and in the surrounding territory; this alteration of the wall would be the basis of the damage of the blood-brain barrier with a consequent infiltration of T lymphocytes and macrophages, which represents the trigger autoimmune cascade mechanism that leads to the final result of demyelination and neurologic manifestations associated with the multiple sclerosis (8, 9).

Prof. Zamboni (28, 29) reported the results of the study on 65 MS patients and 235 healthy controls of similar age. All patients underwent transcranial and extracranial EcoColorDoppler (ECD) with the detection of at least two venous alterations of the following five criteria revealing CCSVI:

- Criterion 1: Reflux in the internal jugular vein and / or vertebral vein in the upright and supine;
- Criterion 2: Reflux in the deep cerebral venous system;
- Criterion 3: Evidence of stenosis of the jugular veins in the ECD;
- Criterion 4: Not perceptible ECD flow in the lumen of the jugular and vertebral veins;
- Criterion 5: negative difference of the cross-section of the internal jugular in supine and standing positions.

The results of that study showed a correlation between Multiple Sclerosis and venous dysfunction in approximately 100% of subjects. Multiple and severe stenosis of the main load cerebrospinal venous segments were observed in the patients, while the control group didn't show any anomaly.

The 65 patients underwent selective venography of the jugular and of the azygos that confirmed in all patients the symptoms described in ECD. The study confirmed the correlation between MS and CCSVI, but didn't explain whether CCSV followed MS or was the causes of it. Other studies (26, 29, 30, 31, 32), found a lower percentage (65%) of MS patients with venous vascular anomalies for example Buffalo. In other studies comparing ECD and phlebography, the percentage of MS patients with CCSVI is between 46% and 70% of those between 86% and 91% show signs of venous steno-obstructive pulmonary disease (14, 15, 16).

Due to these observations the hypothesis that the treatment with vein plastic of the stenosis of the jugular and azygos districts could lead to an improvement of the clinical situation was advanced (1, 2, 4, 17-20).

Actually, in different situation and, sometimes with little scientific rigor, but encouraging results many experiences, gave rise to a widespread use of angioplasty of the venous district.

Future prospects

The Department of Cardiovascular, Respiratory, and Geriatric Nephrology of Sapienza Policlinico Umberto I since October-November 2010 has set up a Centre of Excellence for CCSVI and the National Epidemiologic center CCSVI located in the Institute of Cardiology directed by Prof. Francesco Fedele.

After a short starting period a study protocol and treatment of CCSVI began in collaboration with the service of Interventional Radiology department of the S. Andrea University Hospital. The "Sapienza CCSVI Centre " was the first in Italy to perform ECD and to show the results on a Hemodynamics and Morphologic map (31) which allowed, a specific algorithm to identify three types of CCSVI:

- Type1 with endovascular blocks,
- Type2 with blocks of the venous drainage from compression of the vessels,
- Type3 with both endovascular block and extravascular compression.

The first statistical analysis of over 500 cases with multiple sclerosis studied with intra-and extracranial venous ECD in our "Sapienza" CCSVI Centre found the presence of CCSVI according to the criteria identified by Zamboni in 83% of cases.

Conclusions

After the positive preliminary results we believe a comprehensive epidemiological diagnostic and therapeutic study is necessary for a better understanding of this new nosological entity that may open a new therapeutic hope for the people suffering from MS.

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