State of the art in the diagnosis and treatment of patients with chronic cerebrospinal venous insufficiency

Our experience

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Chronic cerebrospinal venous insufficiency (CCSVI)

was discovered and published by prof. Paolo Zamboni in 2009 as pathological process in vein system of head and neck mainly in patients with multiple sclerosis.

The process is characterised by multiple stenoses of the extracranial veins – internal jugular (IJV) and azygous (AZV) veins as well as the spinal cord venous system.

Zamboni et al. J Neurol Neurosurg Psychiatry 2009;80:392-399
Zamboni noted that narrowing of the veins in the neck or spine was restricting blood flow and dangerous levels of iron were accumulating in the brain (65 case studies, April 2009)

Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis

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ABSTRACT
Background: The extracranial venous outflow routes in clinically defined multiple sclerosis (CDMS) have not previously been investigated.

Methods: Sixty-five patients affected by CDMS, and 235 controls composed, respectively, of healthy subjects, healthy subjects older than CDMS patients, patients affected by other neurological diseases and older controls not affected by neurological diseases but scheduled for venography (HAV-C) blindly underwent a combined transcranial and extracranial colour-Doppler high-resolution examination (TCCS-ECD) aimed at detecting at least two of five parameters of anomalous venous outflow. According to the TCCS-ECD screening, patients and HAV-C further underwent selective venography of the azygous and jugular venous system with venous pressure

Collaboration with MC Medicor Slovenia started in September 2009
The vascular hypothesis and multiple sclerosis

- The new vascular hypothesis and its relationship to multiple sclerosis (MS) developed many dilemmas in the neurological, neurovascular and other scientific communities.

- The demonstration of the venous transluminal changes in the extracranial venous pathway has provided a completely new insight in the field of demyelinating disease.
Traboulsee AL, Knox KB, Machan L et al. Prevalence of extracranial venous narrowing on catheter venography in people with multiple sclerosis, their siblings, and unrelated healthy controls: a blinded, case-control study. 

*Lancet* 2014;383:138-45

- narrowing greater than 50% in 74% people with MS
- in 66% of their siblings
- in 70% of unrelated controls

The significance of venous narrowing to MS symptomatology remains unknown.
CRT-87 New Advances in the Diagnostic and Treatment of Patients with Chronic Cerebro Spinal Venous Insufficiency - Our Experiences

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Anatomical analysis of venous structures in MS subjects (our investigation)

- Classical anatomical preparation of neck veins (eight subjects)
- Using special cast technology
- Seven cases with IJV stenosis
- One case with hypoplasia of IJV
Important anatomical findings
Patient with diagnosis of MS
Postmortem study in MS patient

Left IJV

Right IJV
Histology of internal jugular vein
Autopsy after suicide
Histology of internal jugular vein

Infiltration of venular wall
Histological analysis of brain biopsy in MS patient
Clinical investigations and results
Open label study
200 patients

• The primary endpoints were to detect and highlight the occurrence of obstruction in the extracranial venous pathway – the jugular and/or azygous veins of MS patients and the distribution of venous lesions.

• The secondary endpoints were to evaluate the relationship of the venous pathology to the clinical course and the disability of the disease.
Our experiences
Demographic and clinical data

N 200 patients
Age 42.82 ± 11.35 years
Sex 85 male + 115 female
Duration 10.66 ± 2.07 years

EDSS: 5.31 ± 2.07
EDSS_{SP}: 5.75 ± 1.73
N 84
EDSS_{PP}: 6.12 ± 1.64
N 63
EDSS_{RR}: 3.41 ± 2.13
N 53
MC Medicor Slovenia created international collaboration with multidisciplinary approach

In special research work we join together:

- neurologists
- vascular specialists
- interventional radiologists
- cardiologists
- pathohistologists
- basic researchers
TEAM:

Prof. M. Zorc, MD, PhD,
Prof. M. Denislic, MD, PhD,
Asist. Prof. Z. Milosevic, MD, MSc,
M. Clemenz, MD, MSc,
Prof. R. Zorc-Pleskovic, MD, PhD,
Prof. R. Favaloro, MD, PhD
Prof. O. Mendiz, MD, PhD,
Prof. O. Vraspir Porenta, MD, PhD,
Prof. D. Ravnik, MD, PhD
How we could precisely identify pathological process in vein system of head and neck in MS patients?

Our experiences

- Doppler sonography (screening method with the use of special ultrasound system developed by prof. P. Zamboni – My Lab Vinco Esaote)
- IVUS (multimodal approach)
- Selective venography
- Additional non specific diagnostic procedures - CT venography and Magnetic Resonance venography
Patients and methods

Normal veins
Patients and methods

Venous pathology of the internal jugular vein; a – membrane, b – wall narrowing
Different stenoses of internal jugular veins
Technique of percutaneous vein angioplasty
Stenosis of azygous vein before and after dilatation
Our protocol

Invasive diagnostic procedure and treatment

- Jugular and azygous veins venography
- Selective balloon angioplasty of the target vessel

Medical treatment

- Periprocedural antithrombotic therapy with Heparin (7.500 IU)
- Postprocedural antithrombotic therapy with Fragmin (5.000 IU 21 days after procedure)
- Aspirin 100 mg/day

Follow up

- Doppler sonography (every 6 months up to 24 months)
Safety profile
200 patients

Major events

- Death – 0%
- Major blending requiring hemotransfusion – 0%
- Procedural complication due to balloon rupture removed without complication – one patient
- Procedural complication requiring surgical management: incision in femoral vein (1cm), due to balloon rupture - one patient
Results

Mean number of venous lesions in three MS patient groups
Clinical results
EDSS score and dilatation
EDSS > 1.0

EDSS before: 5.65, 5.47
EDSS after: 5.42, 5.07
Influence of venous dilatation on Fatigue Severity Scale (FSS) and on Visual Analogue Scale (VAS, quality of life)

* $p < 0.001$
Micturation disturbance

OAB-V8 before: 17.56*

OAB-V8 after: 10.96*
Disability caused by multiple sclerosis is associated with the number of extra cranial venous stenoses: possible improvement by venous angioplasty. Results of a prospective study

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Abstract

Objective: Chronic cerebrospinal venous insufficiency (CCSVI) was recently described in patients with multiple sclerosis (MS). The hypothesis of the vascular aetiology provides a new approach in the investigation and treatment of MS.

Methods: Our open-label study included 94 MS patients who fulfilled ultrasound sonographic criteria required for CCSVI. The internal jugular and/or azygous veins by a catheter venography were diluted.

Results: In 34.8% of the patients unilateral, in 65.2% bilateral venous abnormalities and in 2.1% no luminal obstructions were demonstrated. The patient group with the higher disability score had a significantly higher number of venous lesions ($P < 0.005$). Significant improvement of clinical disability in relapsing-remitting patients was ($P < 0.001$) achieved. In our study no stents were used. Re-stenosis occurred in 21.7% of the patients.

Conclusion: The number of venous narrowings is higher in more disabled patients. A significant improvement in clinical disability in the relapsing-remitting group was observed.

Keywords: venous pathology; angioplasty; interventional radiology; multiple sclerosis
Conclusions

- The analysis of our study suggests that venous anomalies in MS patients exists.
- Inflammatory process described in an early stage of disease could be the reason of venous lesions.
- Early angioplasty prevents the new attack.
- The venous pathology contribute to the clinical disability.
- The treatment of CCSVI represents potential benefit for MS patients.
In the tunica intima a significant derangement and loss of the endothelial cells have been described. Interestingly scanning electronic microscopy showed absence of endothelium in the defective jugular valves. In the adventitia it has been described an inverted ratio between type I and type III collagen, with prevalence of the latter. Finally, in the adventitia layer it has been found the presence of calcifications arranged around the vena venarum. (Pedriali M, Zamboni P, Journal of Multiple Sclerosis, 2015)

Our data suggest that early treatment for CCSVI may be beneficial, but more research is needed to support our recommendation.
Percutaneous treatment of venous stenoses in patients with MS could be bright!
Our vision for the future treatment of MS patients

First line therapy of MS

Immunomodulatory drugs (GA, IFNβ) + Angioplasty