



MSIF CCSVI Research Bulletin, 04 November 2011

Research papers:

Monti L, Menci E, Olivelli M, Cerase A, Bartalini S, Piu P, Marotti N, Leonini S, Galluzzi P, Romano DG, Casasco AE, Venturi C. **"Quantitative Colour Doppler Sonography Evaluation of Cerebral Venous Outflow: A Comparative Study between Patients with Multiple Sclerosis and Controls."** *PLoS One*. 2011;6(9):e25012. Epub 2011 Sep 22.

[PMID:21966398](#) [Free full text](#)

Abstract:

BACKGROUND: Internal Jugular Veins (IJVs) are the principle outflow pathway for intracranial blood in clinostatism condition. In the seated position, IJVs collapse, while Vertebral Veins (VVs) increase the venous outflow and partially compensate the venous drainage. Spinal Epidural Veins are an additional drainage pathway in the seated position. Colour- Doppler-Sonography (CDS) examination is able to demonstrate IJVs and VVs outflow in different postural and respiratory conditions. The purpose of this study was to evaluate CDS quantification of the cerebral venous outflow (CVF) in healthy subjects and patients with multiple sclerosis (MS).

METHODOLOGY/PRINCIPAL FINDINGS: In a group of 27 healthy adults (13 females and 14 males; mean age 37.8 ± 11.2 years), and 52 patients with MS (32 females and 20 males; mean age 42.6 ± 12.1 years), CVF has been measured in clinostatism and in the seated position as the sum of the flow in IJVs and VVs. The difference between CVF in clinostatism and CVF in the seated position (Δ CVF) has been correlated with patients' status (healthy or MS), and a number of clinical variables in MS patients. Statistical analysis was performed by Fisher's exact test, non-parametric Mann-Whitney U test, ANOVA Kruskal-Wallis test, and correlation coefficient. The value of Δ CVF was negative in 59.6% of patients with MS and positive in 96.3% of healthy subjects. Negative Δ CVF values were significantly associated with MS ($p < 0.0001$). There was no significant correlation with clinical variables.

CONCLUSIONS/SIGNIFICANCE: Negative Δ CVF has a hemodynamic significance, since it reflects an increased venous return in the seated position. This seems to be a pathologic condition. In MS patients, a vascular dysregulation resulting from involvement of the autonomous nervous system may be supposed. Δ CVF value should be included in the quantitative CDS evaluation of the cerebral venous drainage, in order to identify cerebral venous return abnormalities.

Damadian RV, Chu D. **"The possible role of cranio-cervical trauma and abnormal CSF hydrodynamics in the genesis of multiple sclerosis."** *Physiol Chem Phys Med NMR*. 2011;41:1-17.

[PMID:21970155](#)

Abstract:

UPRIGHT Multi-Position MR scanning has uncovered a key set of new observations regarding Multiple Sclerosis (MS), which observations are likely to provide a new understanding of the origin of MS. The new findings may also lead to new forms of treatment for MS. The UPRIGHT MRI has demonstrated pronounced anatomic pathology of the cervical spine in five of the MS patients studied and definitive cervical pathology in the other three. The pathology was the result of prior head and neck trauma. All eight MS patients entered the study on a first come first serve basis without priority, and all but one were found to have a history of serious prior cervical trauma which resulted in significant cervical pathology. The cervical pathology was visualized by UPRIGHT MRI. Upright cerebrospinal fluid (CSF) cinematography and quantitative measurements of CSF velocity, CSF flow and CSF pressure gradients in the upright patient revealed that significant obstructions to CSF flow were present in all MS patients. The obstructions are believed to be responsible for CSF "leakages" of CSF from the ventricles into the surrounding brain parenchyma which "leakages" can be the source of the MS lesions in the brain that give rise to MS symptomatology. The CSF flow obstructions are believed to result in increases in intracranial pressure (ICP) that generate "leakages" of the CSF into the surrounding brain parenchyma. In all but one MS patient, anatomic pathologies were found to be more severe in the upright position than in the recumbent position. Similarly, CSF flow abnormalities were found to be more severe in the upright position than in the recumbent position in all but one MS patient. Images of the MS patient anatomic pathologies and CSF flow abnormalities are provided with comparison images from normal examinees in Figures 1-15.

Zivadnov R, Poloni GU, Marr K, Schirda CV, Magnano CR, Carl E, Bergsland N, Hojnacki D, Kennedy C, Beggs CB, Dwyer MG, Weinstock-Guttman B. **"Decreased brain venous vasculature visibility on susceptibility-weighted imaging venography in patients with multiple sclerosis is related to chronic cerebrospinal venous insufficiency."** *BMC Neurol.* 2011 Oct 19;11(1):128. [Epub ahead of print]

[PMID: 22011402](#) [Free full text](#)

ABSTRACT:

BACKGROUND:

The potential pathogenesis between the presence and severity of chronic cerebrospinal venous insufficiency (CCSVI) and its relation to clinical and imaging outcomes in brain parenchyma of multiple sclerosis (MS) patients has not yet been elucidated. The aim of the study was to investigate the relationship between CCSVI, and altered brain parenchyma venous vasculature visibility (VVV) on susceptibility-weighted imaging (SWI) in patients with MS and in sex- and age-matched healthy controls (HC).

METHODS:

59 MS patients, 41 relapsing-remitting and 18 secondary-progressive, and 33 HC were imaged on a 3T GE scanner using pre- and post-contrast SWI venography. The presence and severity of CCSVI was determined using extra-cranial and trans-cranial Doppler criteria. Apparent total venous volume (ATVV), venous intracranial fraction (VIF) and average distance-from-vein (DFV) were calculated for various vein mean diameter categories: <.3 mm, .3-.6 mm, .6-.9 mm and >.9 mm.

RESULTS:

CCSVI criteria were fulfilled in 79.7% of MS patients and 18.2% of HC ($p < .0001$). Patients with MS showed decreased overall ATVV, ATVV of veins with a diameter $< .3\text{mm}$, and increased DFV compared to HC (all $p < .0001$). Subjects diagnosed with CCSVI had significantly increased DFV ($p < .0001$), decreased overall ATVV and ATVV of veins with a diameter $< .3\text{mm}$ ($p < .003$) compared to subjects without CCSVI. The severity of CCSVI was significantly related to decreased VVV in MS ($p < .0001$) on pre- and post-contrast SWI, but not in HC.

CONCLUSIONS:

MS patients with higher number of venous stenoses, indicative of CCSVI severity, showed significantly decreased venous vasculature in the brain parenchyma. The pathogenesis of these findings has to be further investigated, but they suggest that reduced metabolism and morphological changes of venous vasculature may be taking place in patients with MS.

Bastianello S, Romani A, Viselner G, Colli Tibaldi E, Giugni E, Altieri M, Cecconi P, Mendozzi L, Farina M, Mariani D, Galassi A, Quattrini C, Mancini M, Bresciamorra V, Lagace A, McDonald S, Bono G, Bergamaschi R. **“Chronic Cerebrospinal Venous Insufficiency in Multiple Sclerosis: Clinical Correlates from a Multicentre Study.”** *BMC Neurol.* 2011 Oct 26;11(1):132. [Epub ahead of print]

[PMID: 22029656](#) [Free full text](#)

Abstract

BACKGROUND:

Chronic cerebrospinal venous insufficiency (CCSVI) has recently been reported to be associated with multiple sclerosis (MS). However, its actual prevalence, possible association with specific MS phenotypes, and potential pathophysiological role are debated.

METHOD:

We analysed the clinical data of 710 MS patients attending six centres (five Italian and one Canadian). All were submitted to venous Doppler sonography and diagnosed as having or not having CCSVI according to the criteria of Zamboni et al.

RESULTS:

Overall, CCSVI was diagnosed in 86% of the patients, but the frequency varied greatly between the centres. Even greater differences were found when considering singly the five diagnostic criteria proposed by Zamboni et al. Despite these differences, significant associations with clinical data were found, the most striking being age at disease onset (about five years greater in CCSVI-positive patients) and clinical severity (mean EDSS score about one point higher in CCSVI-positive patients). Patients with progressive MS were more likely to have CCSVI than those with relapsing-remitting MS.

CONCLUSION:

The methods for diagnosing CCSVI need to be refined, as the between-centre differences, particularly in single criteria, were excessively high. Despite these discrepancies, the strong associations between

CCSVI and MS phenotype suggest that the presence of CCSVI may favour a later development of MS in patients with a lower susceptibility to autoimmune diseases and may increase its severity.

Doepf F, Würfel JT, Pfueller CF, Valdueza JM, Petersen D, Paul F, Schreiber SJ. **“Venous drainage in multiple sclerosis: A combined MRI and ultrasound study.”** *Neurology*. 2011 Oct 26. [Epub ahead of print]

[PMID:22031530](#)

Abstract

BACKGROUND:

Chronic cerebrospinal venous insufficiency (CCSVI) was proposed as the causal trigger for developing multiple sclerosis (MS). However, current data are contradictory and a gold standard for venous flow assessment is missing.

OBJECTIVE:

To compare structural magnetic resonance venography (MRV) and dynamic extracranial color-coded duplex sonography (ECCS) in a cohort of patients with MS.

METHODS:

We enrolled 40 patients (44 ± 10 years). All underwent contrast-enhanced MRV for assessment of internal jugular vein (IJV) and azygos vein (AV) narrowing, graded into 3 groups: 0%-50%, 51%-80%, and >80%. ECCS analysis of blood flow direction, cross-sectional area (CSA), and blood volume flow (BVF) in both IJV and vertebral veins (VV) occurred in the supine and upright body position.

RESULTS:

MRV identified 1 AV narrowing. IJV analysis yielded 12 patients for group 1 (30%), 19 patients for group 2 (48%), and 9 patients for group 3 (22%). By ECCS criteria, 4 patients (10%) presented with venous drainage abnormalities. Jugular BVF was different only between groups 1 and 3 (616 ± 133 vs 381 ± 213 mL/min, $p = 0.02$). No other parameters in supine position and none of the parameters in the upright body position, apart from the IJV-BVF decrease in groups 1 and 3 (479 ± 172 vs 231 ± 144 mL/min, $p = 0.01$), were different.

CONCLUSIONS:

Our ECCS data contradict the postulated 100% prevalence of CCSVI criteria in MS. MRV seems more sensitive to detect IJV narrowing compared to ECCS. A measurable hemodynamic effect only exists in vessel narrowings >80%. Our combined data argue against a causal relationship of venous narrowing and MS, favoring the rejection of the CCSVI hypothesis.

Khalil M, Langkammer C, Ropele S, Petrovic K, Wallner-Blazek M, Loitfelder M, Jehna M, Bachmaier G, Schmidt R, Enzinger C, Fuchs S, Fazekas F. **"Determinants of brain iron in multiple sclerosis: A quantitative 3T MRI study."** *Neurology*. 2011 Nov 1;77(18):1691-7. Epub 2011 Oct 5.

[PMID:21975210](#)

Abstract

OBJECTIVES:

Abnormal high cerebral iron deposition may be implicated in chronic neurologic disorders, including multiple sclerosis (MS). R2* relaxometry has been recently validated in a postmortem study to indicate brain iron accumulation in a quantitative manner. We used this technique to assess brain iron levels in different stages of MS and healthy controls (HC) and determined their relation with demographic, clinical, neuropsychological, and other imaging variables.

METHODS:

We studied 113 consecutive patients (35 clinically isolated syndrome [CIS], 78 MS) and 35 HC with 3 T MRI and clinical and neuropsychological examination. Iron deposition in subcortical gray matter structures was assessed by automated, regional calculation of R2* rates.

RESULTS:

Basal ganglia (BG) R2* levels were significantly increased in MS compared to CIS ($p < 0.001$) and HC ($p < 0.005$). They were correlated with age ($r = 0.5$, $p < 0.001$), disease duration ($r = 0.5$, $p < 0.001$), Expanded Disability Status Scale ($r = 0.3$, $p < 0.005$), and the z values of mental processing speed ($r = -0.3$, $p < 0.01$). Stepwise linear regression analysis revealed gray matter atrophy as the strongest independent predictor of BG R2* levels ($p < 0.001$), followed by age ($p < 0.001$) and T2 lesion load ($p < 0.005$).

CONCLUSION:

BG iron accumulation in MS occurs with advancing disease and is related to the extent of morphologic brain damage, which argues for iron deposition as an epiphenomenon. The absence of increased iron levels in patients with CIS indicates that iron accumulation does not precede the development of MS.

Case study:

Radak D, Tanaskovic S, Marinkovic S, Antonic Z, Kolar J. **“Internal jugular vein duplication: a further truncular malformation in a patient with multiple sclerosis.”** *Phlebology*. 2011 Oct 28. [Epub ahead of print]

PMID:22037279

Abstract

Different internal jugular vein (IJV) abnormalities can be found in patients with multiple sclerosis (MS): stenoses, complete occlusion, distortions and intraluminal structures, such as membranes, webs and inverted valves. IJV duplication is a very rare phenomenon. We report a case of right IJV duplication as an incidental finding during IJV morphological and haemodynamic assessment in a patient with MS. A 55-year-old female patient was admitted to our Institute for IJV and vertebral veins morphological and haemodynamic assessment. During the last seven years she had been treated for MS. Colour Doppler ultrasonography in our patient did not reveal IJV or vertebral veins stenoses or abnormal valves, but instead right IJV duplication. This finding was confirmed using multislice computed tomography angiography and by selective phlebography. In conclusion, to our knowledge, a case of IJV duplication in a patient with MS has not been described yet. This further venous malformation can be assessed by the means of Doppler ultrasounds.

Meta-analysis

Laupacis A, Lillie E, Dueck A, Straus S, Perrier L, Burton JM, Aviv R, Thorpe K, Feasby T, Spears J. **“Association between chronic cerebrospinal venous insufficiency and multiple sclerosis: a meta-analysis.”** *CMAJ*. 2011 Oct 3. [Epub ahead of print]

[PMID:21969411](#) [Free full text](#)

Abstract

BACKGROUND: It has been proposed by Zamboni and colleagues that multiple sclerosis is caused by chronic cerebrospinal venous insufficiency, a term used to describe ultrasound-detectable abnormalities in the anatomy and flow of intra- and extracerebral veins. We conducted a meta-analysis of studies that reported the frequency of chronic cerebrospinal venous insufficiency among patients with and those without multiple sclerosis.

METHODS: We searched MEDLINE and EMBASE as well as bibliographies of relevant articles for eligible studies. We included studies if they used ultrasound to diagnose chronic cerebrospinal venous insufficiency and compared the frequency of the venous abnormalities among patients with and those without multiple sclerosis.

RESULTS: We identified eight eligible studies: all included healthy controls, and four of them also included a control group of patients with neurologic diseases other than multiple sclerosis. Chronic cerebrospinal venous insufficiency was more frequent among patients with multiple sclerosis than among the healthy controls (odds ratio [OR] 13.5, 95% confidence interval [CI] 2.6-71.4), but there was

extensive unexplained heterogeneity among the studies. The association remained significant in the most conservative sensitivity analysis (OR 3.7, 95% CI 1.2-11.0), in which were moved the initial study by Zamboni and colleagues and added a study that did not find chronic cerebrospinal venous insufficiency in any patient. Although chronic cerebrospinal venous insufficiency was also more frequent among patients with multiple sclerosis than among controls with other neurologic diseases (OR 32.5, 95% CI 0.6-1775.7), the association was not statistically significant, the 95% CI was wide, and the OR was less extreme after removal of the study by Zamboni and colleagues (OR 3.5, 95% 0.8-15.8).

INTERPRETATION: Our findings showed a positive association between chronic cerebrospinal venous insufficiency and multiple sclerosis. However, poor reporting of the success of blinding and marked heterogeneity among the studies included in our review precluded definitive conclusions.

Reviews:

Flynn LC, Moster ML. **“Current thoughts on chronic cerebrospinal venous insufficiency in multiple sclerosis.”**

Curr Opin Ophthalmol. 2011 Sep 13. [Epub ahead of print]

Abstract

PURPOSE OF REVIEW: To review the most current literature relating to chronic cerebrospinal venous insufficiency (CCSVI).

RECENT FINDINGS: Recently, a vascular phenomenon known as CCSVI was proposed to be the cause of multiple sclerosis (MS). Its prevalence reportedly reflected 100% sensitivity and specificity for the disease. The authors went on to perform invasive procedures for the treatment of CCSVI with questionable success. Since then, many have tried to duplicate the data outlined in the original studies, but none have achieved remotely similar outcomes. Furthermore, there is conflicting information regarding the safety of invasive treatment for CCSVI.

SUMMARY: MS is a complex and devastating disease with imperfect treatment strategies. Further research is needed to determine what role, if any, venous insufficiency plays in the course of MS and also the most appropriate treatment course based on those results.

Werner JD, Siskin GP, Mandato K, Englander M, Herr A. **“Review of Venous Anatomy for Venographic Interpretation in Chronic Cerebrospinal Venous Insufficiency.”** *J Vasc Interv Radiol.* 2011 Oct 4. [Epub ahead of print]

[PMID:21975259](#)

Abstract

Chronic cerebrospinal venous insufficiency (CCSVI) represents a recently described condition that may potentially contribute to the symptoms experienced by patients with multiple sclerosis. The evaluation of a prospective patient for CCSVI often involves an invasive evaluation with venography of the internal jugular and azygos veins. The purpose of this article is to review the normal anatomy of the internal

jugular, vertebral, and azygos veins, as an understanding of these veins is necessary for appropriate interpretation of the venograms obtained to evaluate patients for CCSVI.

Thapar A, Lane T, Nicholas R, Friede T, Ellis M, Assenheim J, Franklin IJ, Davies AH. **“Systematic review of sonographic chronic cerebrospinal venous insufficiency findings in multiple sclerosis.”** *Phlebology*. 2011 Oct 23. [Epub ahead of print]

[PMID: 22021635](#)

Abstract:

OBJECTIVE:

The sonographic findings of chronic cerebrospinal venous insufficiency (CCSVI) are used by some as selection criteria for venography. We performed a systematic review to establish the prevalence and strength of association between sonographic CCSVI and multiple sclerosis (MS).

METHOD:

Two reviewers searched PubMed and EMBASE from 1948 to date using the keywords 'chronic cerebrospinal venous insufficiency' according to PRISMA guidelines.

RESULTS:

Four cross-sectional studies met the criteria for inclusion. The prevalence of CCSVI ranged from 7% to 100% in MS patients and from 2% to 36% in healthy controls. Diagnostic odds ratios for MS varied between 2 and 26, 499 (I(2) = 94%). Sensitivities of CCSVI for MS varied between 7% and 100% (I(2) = 98%). Specificities varied between 64% and 100% (I(2) = 95%).

CONCLUSION:

There is substantial variation in the strength of association between CCSVI and MS beyond that explained by demographic differences or sonographer training. Reliable evidence on which to base decisions requires sonographic consensus and assessment of the reproducibility of individual criteria between trained sonographers.

Williams R, Buchheit CL, Berman NE, Levine SM. **“Pathogenic implications of iron accumulation in multiple sclerosis.”** *J Neurochem*. 2011 Oct 17. doi: 10.1111/j.1471-4159.2011.07536.x. [Epub ahead of print]

[PMID: 22004421](#)

Abstract

Iron, an essential element used for a multitude of biochemical reactions, abnormally accumulates in the central nervous system of patients with multiple sclerosis (MS). The mechanisms of abnormal iron deposition in MS are not fully understood, nor do we know whether these deposits have adverse consequences, i.e., contribute to pathogenesis. With some exceptions, excess levels of iron are represented concomitantly in multiple deep gray matter structures often with bilateral representation, while in white matter pathological iron deposits are usually located at sites of inflammation that are associated with veins. These distinct spatial patterns suggest disparate mechanisms of iron accumulation between these regions. Iron has been postulated to promote disease activity in MS by various means: 1) iron can amplify the activated state of microglia resulting in the increased production of proinflammatory mediators; 2) excess intracellular iron deposits could promote mitochondria dysfunction; and 3) improperly managed iron could catalyze the production of damaging reactive oxygen species. The pathological consequences of abnormal iron deposits may be dependent on the affected brain region and/or accumulation process. Here we review putative mechanisms of enhanced iron uptake in MS and address the likely roles of iron in the pathogenesis of this disease.

Gasca-Salas C, Gomez-Ibanez A. **[Chronic cerebrospinal venous insufficiency and multiple sclerosis: a review and update of the subject]**. [Article in Spanish] *Rev Neurol*. 2011 Nov 1;53(9):555-60.

[PMID:22012819](#)

Abstract

The aetiology of multiple sclerosis remains unknown at the present time, although the most likely explanation is that it has an autoimmune inflammatory origin. During the history of this disease a vascular pathophysiology was once proposed, and it has recently re-emerged as a result of the work by Paolo Zamboni with the name of 'chronic cerebrospinal venous insufficiency'. Following this hypothesis, Zamboni puts forward a curative treatment for multiple sclerosis by means of endovascular treatment of the internal jugular vein and the azygos vein. However, several teams have attempted to replicate his findings without success. In this review, we offer a chronological description of the studies carried out by Zamboni and the later attempts to replicate his work. Our main conclusion is that, given the results we currently have available, we should be cautious and, for the time being, it would be advisable not to recommend the systematic use of this treatment for our patients.

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Oral Presentations:

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Anatomical and histological analysis of venous structures associated with chronic cerebro-spinal venous insufficiency

C. Diaconu, S. Staugaitis, J. McBride, C. Schwanger, A. Rae-Grant, R. Fox (Cleveland, US)

Background: Chronic cerebro-spinal venous insufficiency (CCSVI) is a new theory for MS pathogenesis. CCSVI includes alterations in cerebral venous outflow and is often assessed by ultrasound or magnetic resonance venography (MRV). No gross anatomical description of venous outflow in MS has been reported to date.

Methods: We harvested bilateral internal jugular (IJV), subclavian, brachiocephalic, and azygous (AZY) veins from 7 deceased MS patients and 6 non-MS controls. Veins were injected with silicone, dissected en bloc, incised longitudinally to expose the luminal surface, and fixed. All valves and structural abnormalities were characterized and photographed using a stereomicroscope. Vein wall stenosis was defined as a $\geq 50\%$ reduction in cross-sectional area, defined from vein wall circumference and compared to a normal appearing region in the same vein.

Results: A variety of vein abnormalities were identified. The incidence of vein wall stenoses was similar in MS and controls: eight stenoses in 4 of 7 MS patients and five in 3 of 6 controls. Marked valvular and other intraluminal abnormalities with potential hemodynamic consequences were identified in 5 of 7 MS patients (7 abnormalities) and in 1 of 6 controls (1 abnormality). These abnormalities included circumferential membranous structures (1 MS and 1 control), longitudinally oriented membranous structures (3 MS), single valve flap replacing IJV valve (2 MS), and enlarged and malpositioned valve leaflets (1 MS). In addition, minor anatomic variations without expected hemodynamic consequences were observed similarly in both MS and controls. These included valves with >2 leaflets, the presence of valves in the AZY, additional (duplicate) normal-appearing IJV valves, and small membranous septa.

Conclusion: Post mortem examination of the IJV and AZY veins of MS patients and non-MS controls demonstrated a variety of structural abnormalities and anatomic variations. Vein wall stenosis occurred at similar frequency in MS and non-MS controls. However, the frequency of intraluminal abnormalities with possible hemodynamic consequences was higher in MS patients compared to healthy controls, although the current sample size is limited. These results suggest that MRV (which predominantly evaluates vein wall stenoses) may be less effective than ultrasound in identifying venous abnormalities in CCSVI. In addition, examining only wall circumference in CCSVI ultrasound studies may miss some intraluminal abnormalities.

Disclosures:

Claudiu Diaconu has nothing to disclose.

Susan Staugaitis, MD, PhD, has nothing to disclose.

Jennifer McBride, PhD, has nothing to disclose.

Cynthia Schwanger has nothing to disclose.

Alexander Rae-Grant, MD, presented a lecture for Teva Neuroscience and Biogen Idec with personal compensation.

Robert Fox, MD, has received personal consulting or speaking fees from Biogen Idec, Genentech, Novartis, and Teva Neuroscience, and has served on clinical trial advisory committees for Biogen Idec.

The current project is supported by the National MS Society (RC 1004-A-5).

Posters:

P630

No signs of stenosis or insufficient venous outflow of internal jugular veins have been found in patients with relapsing-remitting multiple sclerosis

G. Panczel, K. Kovacs, A. Rozsa, C. Rozsa (Budapest, HU)

Objectives: The idea that chronic cerebrospinal venous insufficiency (CCSVI) may cause multiple sclerosis (MS) has been proposed. Our goal was to determine if internal jugular vein (IJV) stenosis in MS patients could be demonstrated and if hemodynamic parameters differ in patients and controls. Methods: 122 patients with RR-MS (mean age 40,4 ±10,6 y; 34 male, 88 female) and 55 controls (mean age 41,4 ±11,4 y; 17 male, 38 female) were examined by duplex ultrasound. Morphologic and hemodynamic parameters were measured in the proximal (near to skull base) and distal parts (just above the subclavian vein junction) of IJVs.

Results: Mean values of cross-sectional areas (A) in the proximal part of IJV were 0,37 and 0,33 cm² (right and left side) in patients and 0,33 and 0,37 cm² in controls. In the distal part of IJV the mean A values were 0,99 and 0,76 cm² in patients and 0,99 and 0,85 cm² in controls. Volume flow values (VF) in the proximal part were 329 and 304 ml/min (right and left) in patients and 256 and 360 ml/min in controls while in the distal part 728 and 635 ml/min were measured in patients and 452 and 387 ml/min in controls (p < 0.05 in the distal part both sides). In 2 patients and 1 control a 50% lumen reduction was caused by venous valves in the distal IJV, without hemodynamic consequences, VF values were >300 ml/min in all cases. Reflux was not observed proximally, while in the distal IJV the mean reflux times (Tr) were 125 and 95 ms (right and left) in patients, and 307 and 317 ms in the controls (p

Conclusion: Doppler sonography is a suitable method for the investigation of IJV. We have not found any hemodynamically significant stenosis. No correlation was found between Tr and VF suggesting that reflux is not an indicator of venous insufficiency. Reflux was not observed in the proximal part but was observed in the distal part, where lumen area is substantially larger and venous valves are found, suggesting that the turbulence due to lumen dilation and valve movements is the real cause of the reflux. We have not found any significant difference in hemodynamics that might support the idea of CCSVI in MS patients. Based on these results catheter-dilatation does not seem to be a rational and acceptable approach in the treatment of MS.

Disclosures:

Gyula Panczel has nothing to disclose.

Krisztina Kovacs has nothing to disclose.

Aniko Rozsa has nothing to disclose.

Csilla Rozsa has nothing to disclose.

P631**CCSVI prevalence in a northern Italian population of MS patients and controls**

P. Cavalla, M. Vercellino, M. Matta, A. Romagnolo, A. Mattioda, S. Masera, F. Dematteis, L. Di Maggio, D. Rossato, G. Gandini, L. Lopiano, L. Pinessi (Turin, IT)

Introduction: Recent studies assessing chronic cerebrospinal venous insufficiency (CCSVI) prevalence by means of venous ecocolor Doppler (ECD) in MS patients and controls have led to widely variable and conflicting results (1, 2, 3). In this study, we wished to assess CCSVI prevalence in a population of MS patients and controls from Northern Italy, with a blinded ECD study design.

Materials and method: This study was performed on 45 healthy subjects (HS) and 133 MS patients (relapsing-remitting MS 79.7%, secondary progressive MS 18.0%, primary progressive MS 1.5%, CIS 0.8%). Median age was 38 years in HS (range 21-64), 40 years in MS patient (range 23-70). An informed consent was obtained for all MS patients and HS. ECD was performed by experienced and trained sonologists, blinded to patient/control status, using an Esaote Vinco Lab scanner. CCSVI Zamboni's criteria (1) were used; a sonologic pattern of CCSVI was considered present when two out of five criteria were fulfilled. Venous hemodynamic insufficiency severity score (VHISS) was also evaluated.

Results: CCSVI was present in 33.4% of HS and 53.4% of MS patients ($p = 0.02$). No significant differences were noted between CCSVI and non-CCSVI MS patients regarding gender, disease duration, age, age of onset, EDSS, disease course. Mean VHISS was higher in secondary progressive MS (3.12 vs 2.29; $p = 0.015$) than in relapsing-remitting MS; a weak correlation between VHISS and EDSS was also observed.

Discussion and conclusion: In our population, CCSVI assessed by ECD appears to be more frequent in MS patients than in controls; however, CCSVI is found in more than one third of normal controls. These data are similar to those obtained with a similar protocol in a larger North American population (3). The issue of anomalous venous drainage in MS needs to be further clarified, also evaluating patients affected by other neurological diseases. The high frequency of CCSVI also in healthy controls suggests poor specificity of the current CCSVI criteria. 1 Zamboni P et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2009 Apr;80(4):392-9. 2 Baracchini C et al. No evidence of chronic cerebrospinal venous insufficiency at multiple sclerosis onset. *Ann Neurol*. 2011 Jan;69(1):90-9. 3 Zivadinov R et al. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. *Neurology*. 2011 Apr 13. [Epub ahead of print]

Disclosures:

The Authors have nothing to disclose

P632

Cerebral venous drainage in multiple sclerosis studied by near infrared spectroscopy and venous Doppler ultrasonography

S. Viola, P. Viola, P. Litterio, M.P. Buongarzone, L. Fiorelli (Vasto, Atessa, IT)

Background: Chronic cerebrospinal venous insufficiency is a reported abnormality caused by narrowing of the veins which drain the oxygen depleted blood from the brain and spinal cord. It is theorised that the slowed draining of blood can cause cerebral venous congestion leading to a lack of oxygen in the brain of patients with Multiple Sclerosis (MS). A recent study has assessed intracranial venous pressure using ophthalmodynamometry in MS patients and suggests no evidence of an increased intracranial venous pressure.

Objective: the aim is to elucidate the presence of cerebral venous congestion in patients with MS. **Methods:** We investigated 30 patients affected by MS (11 M and 19 F, age 42.3+-9.2 years, Expanded Disability Status Scale 3.01 +- 2.1, and 20 age and sex matched healthy controls. The MS group included: 21 patients with relapsing-remitting clinical course, 2 with secondary progressive and 2 with primary progressive course and 5 with clinically isolated syndrome. We studied the cerebral microcirculation (arterioles, capillaries, venules) of frontal cortex bilaterally by near-infrared spectroscopy (NIRS), safe, repeatable and non-invasively technology. By means of NIRS we measured the increase of cerebral blood volume (CBV) over zero arbitrary baseline in unit Nirs (UNIRS) after compression for 10 seconds of the internal jugular veins of both side in sitting position, and from the sitting to the supine position. By means of Doppler ultrasonography (4 Mhz probe) we measured the blood flow velocity of the internal jugular veins (BFVJV) in supine position.

Results: after compression of the internal jugular veins the increase of CBV was 8,3 +- 11,1 U-NIRS in the MS patients and 42,5 +-11,6 U-NIRS in the healthy controls. The CBV increase is significantly lower in the MS patients - 80.4 %, $p < 0.88$.

Conclusion: Our findings seem to indicate the absence of cerebral venous stasis. The presence of a lower post-capillary venous flow/pressure seems to be present in the frontal cortex of the MS patients. Further studies are needed to clarify the underlying mechanisms of this haemodynamic impairment.

Disclosures:

The authors have nothing to disclose.

P633

Intracranial venous pressure in MS is normal: ophthalmodynamometry data

C. Haug, R. Meyer-Schwickerath, A. Hacker, F. Fink, D. Seidel, H.P. Hartung, M.R. Haupts (Isselburg-Anholt, DE)

Introduction: It has been postulated that stenoses in extracerebral veins may result in intracerebral congestion and thus cause multiple sclerosis (MS). No recent studies with imaging techniques could

verify the hypothesis so far. As intraocular venous occlusion pressure (VOP) is based on intra- and extracerebral venous pressure through an anastomotic net with outflow through jugular and spinal veins, we used this methodology to assess venous pressure data in MS.

Methods: In 30 MS- and ADEM-patients (1 ADEM, 5 remitting-relapsing MS, 24 progressive forms, mean age 47.3 ± 11.4 yrs, mean EDSS 6.0 ± 1.2 ; duration of MS 15.1 ± 8.8 yrs.), we assessed intracranial venous pressure in MS via ophthalmodynamometry. Details of this methodology have been described previously.

Results: VOP (15.1 ± 2.1 cm Hg) in MS patients was not different from 30 healthy controls (15.3 ± 2.4 cm Hg, mean age 54.2 ± 16.8 yrs; $p: 0.67$ n.s.).

In 13 patients with proven intracranial pressure (ICP) pathology (brain tumors, cerebral venous thrombosis, pseudotumor cerebri, intracerebral hemorrhage, age 41.8 ± 24.4 yrs.) VOP was pathologically raised (27.2 ± 5.0 cm Hg; $p < 0.001$).

Conclusions: As VOP depends on the same anatomical substrate that has been postulated for CCSVI mechanisms in MS, ophthalmodynamometry is promising for testing the CCSVI hypothesis. Our data give no evidence however of an increase in intracranial venous pressure. Venous congestion in MS patients is implausible.

Disclosures:

All authors have nothing to disclose.

P634

Italian multicentre study on venous haemodynamics in multiple sclerosis

M.A. Battaglia (Italian Foundation of Multiple Sclerosis) on behalf of the CoSMo Study Steering Committee

In the recent literature it has been proposed the involvement of the cerebrospinal venous haemodynamics in multiple sclerosis. The aim of the study is to compare the prevalence of Chronic Cerebro-Spinal Venous Insufficiency (CCSVI) in patients with Multiple Sclerosis (MS), with the prevalence in patients affected by other neurodegenerative disorders and in healthy subjects. This is a multicenter, observational, prevalence study. A minimum of 1200 adults with MS, 400 healthy subjects and 400 subjects with other neurodegenerative disorders will be enrolled in the study. In particular, will be enrolled in the study MS patients with different clinical course of disease (RR, SP, PP and CIS) and patients affected by other neurodegenerative disorders. The Echo Color Doppler (ECD) examination will always be blind and performed according to a standard protocol. The basic protocol includes the evaluation of several criteria and the measurement of parametric data in few relevant point, and is also a blinded procedure. The neurosonologists involved in the study were properly trained for the application of the protocol. The ultrasound examination at each clinical site will be followed by a second centralized blinded evaluation. In addition, in order to control the potential methodological pitfalls of these studies, mainly in the ultrasound procedure, an advanced protocol, including additional optional measurements, was designed, in a subgroup, to achieve a definite conclusion from a huge

sample of subjects by using a strict and controlled neurosonological protocol. The prevalence of CCSVI in MS will be estimated, with confidence intervals at 95%, and compared with that of other groups. The sensitivity, specificity and accuracy of the technique will be estimated with their 95% confidence intervals. Values of p less than or equal to 0.05 will be considered significant. The statistical power of the study will allow to perform comparisons among different clinical course of MS. The results of interim analysis will be presented. Overall the aim of the Italian Multiple Sclerosis Foundation is to support the people with MS to be empowered to take control of the decisions affecting their lives and to self-manage the disease as much as possible. Moreover, it is important to highlight that the results of this study could be useful to provide insights into the use of ECD examination as a new diagnostic approaches for neurological diseases.

Disclosures:

no conflict of interest to declare

P1103

No need for “liberation” in MS patients

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Background and Objectives: Cerebrospinal venous congestion has originally been claimed as a cause and more recently as a consequence of multiple sclerosis (MS) leading to disability. Angioplasty of internal jugular vein (IJV) and/or azygos vein, named “the liberation procedure”, has been suggested to improve the symptoms of MS and reduce relapses. We investigated these pathophysiological hypotheses in a large cohort of MS patients and in age-/gender-matched normal controls (HC).

Methods: Extracranial and transcranial venous echo-color Doppler sonography (ECDS-TCDS) was performed in 320 subjects (50 possible MS [pMS], 60 relapsing remitting [RR], 35 secondary progressive [SP], 15 primary progressive [PP], 160 HC). The CCSVI-Doppler positive subjects were asked to undergo selective venography (VGF). The sonographer was blinded to the status of the subjects (patient/control), while the radiologist was blinded to the ultrasound findings.

Results: TCDS was normal in all MS patients and controls. Sixteen (10%) MS patients (8 pMS, 4 RR, 3 SP, 1 PP) fulfilled the ultrasound diagnosis of CCSVI. VGF performed in 14 of these patients showed bilateral IJV stenoses in two (1.2%).

Conclusions: This study shows that CCSVI is definitely not the cause of MS nor is it a late secondary phenomenon of MS, as it is not associated with disability. Therefore, there are no bases for “decongestant” procedures in MS patients. We strongly recommend extreme caution in interpreting an ultrasound-based diagnosis of CCSVI as absolute evidence of a pathological process involving the brain and the spinal cord, which in our opinion requires confirmation by VGF.

Disclosures:

C. Baracchini has received compensation for being a board member, expert testimony, payment for development of educational presentations including service on speakers' bureaus, and has had travel/accommodation expenses covered or reimbursed.

P. Perini has received honoraria from Biogen-Dompe¥ Italy, Sanofi-Aventis, and Merk-Serono; and has had travel/accommodations expenses covered or reimbursed by Sanofi-Aventis, Biogen-Dompe¥ Itali, and Merk-Serono.

F. Causin has nothing to disclose.

M. Calabrese has been a member of the board of Merk-Serono, Sanofi-Aventis, and Bayer-Shering; a consultant for Merk-Serono and Sanofi-Aventis; given expert testimony for Biogen-Dompe¥ Italy and Bayer-Shering; received honoraria from Merk-Serono, Sanofi-Aventis, and Bayer-Shering; and had travel/accommodations expenses covered or reimbursed by Biogen-Dompe¥ Italy, Merk-Serono, Sanofi-Aventis, and Bayer-Shering.

F. Rinaldi has nothing to disclose.

P. Gallo has been a member of the board of Novartis, Biogen-Elan, Merk-Serono, SanofiAventis, and Bayer-Shering; has been a consultant for Biogen-Elan, Sanofi-Aventis, and Bayer-Shering; has given expert testimony for Biogen-Dompe¥ Italy, Sanofi-Aventis, and Merk-Serono; has received honoraria from Novartis Farma, Biogen-Elan, Sanofi-Aventis, Merk-Serono, and Bayer-Shering; and has had travel/accommodations expenses covered or reimbursed by University of Padova, Novartis Farma, Sanofi-Aventis, Biogen-Dompe¥ Italy, Merk-Serono, and Bayer-Shering. and received research grants from the Veneto Region of Italy, the University of Padova and the Ministry of Public Health of Italy.

P1104

Ultrasound assessment of chronic cerebrospinal venous insufficiency

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Background: Chronic cerebrospinal venous insufficiency (CCSVI) is a new theory of MS pathogenesis involving alterations in extracranial and intracranial venous outflow. Proposed diagnostic criteria for CCSVI is derived from ultrasound assessments, although different studies have found varying incidence of MS patients and non-MS controls meeting CCSVI criteria.

Objective: To perform an independent, blinded study of CCSVI in MS and non-MS controls.

Methods: After obtaining formal training in ultrasound assessment for CCSVI, we performed CCSVI assessment in MS and non-MS controls. All ultrasounds were conducted using a Biosound MyLab25Gold machine, which included Quality Doppler Profiles (QDP) technology for assessment of flow in the deep cerebral veins. The internal jugular, vertebral, and deep cerebral veins were assessed in both supine and sitting positions. Both QDP and traditional Doppler were used to assess intracranial venous flow in the deep cerebral veins. Ultrasound technicians were blinded to diagnosis, including the use of separate research staff to position patients prior to arrival of the technician. All ultrasounds were over-read by a trained physician, who was also blinded to the MS diagnosis.

Results: The study is ongoing, but initial pooled results from the first 20 subjects found that 6 (30%) met ≥ 2 criteria for CCSVI. 1 subject met 3 criteria. Four subjects met no criteria. No subjects met criteria for reverted postural control of cerebral venous outflow. Nine subjects (45%) had a flap and/or septum/abnormal valve. No flow in the IJV was observed in only one patient. Deep cerebral vein reflux was observed in 7 (35%) of subjects using QDP, but never using transcranial color Doppler (TCCD). Additional ultrasound evaluations are ongoing, and results according to diagnosis (MS vs. non-MS

controls) will be presented.

Conclusion: Initial pooled results found that 30% of subjects met criteria for CCSVI. A high proportion of subjects (45%) had valvular or intraluminal abnormalities on B-mode. Surprisingly, no subjects were found to have reverted postural control. Identification of deep cerebral vein reflux depended upon the ultrasound technique: QDP found reflux in half of subjects, but traditional Doppler found reflux in none. This observation highlights the importance of ultrasound methodology in performing and interpreting deep cerebral vein assessments. Ongoing studies will help clarify the potential relationship between CCSVI and MS.

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Dr. Kim has been involved in consulting for Philips with compensation, and received financial support for research from American College of Cardiology supported by GE.

Dr. Lu, Diaconu, Baus, Gratten and Raber have nothing to disclose.

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P1105

Chronic cerebrospinal venous insufficiency is not associated with clinically isolated syndrome or mild multiple sclerosis

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Since Paolo Zamboni first proposed CCSVI as a cause of MS and venoplasty as a new treatment modality there have been several studies showing marked variation in prevalence of CCSVI in MS and healthy controls. Lack of blinding, variable interpretation of the Zamboni ultrasound criteria, and different case-mix may all contribute to inconsistent results.

We designed a prospective case-control study of patients with clinically isolated syndrome (CIS) and relapsing-remitting MS with expanded disability status score (EDSS) ≤ 2 and age-and-sex-matched healthy controls to test the hypothesis that CCSVI is more prevalent in patients with CIS or mild MS. Assuming CCSVI rates of 50% in patients and 25% in controls, $\alpha = 0.05$, and power = 0.8, the required sample size was 66 in each group. We set a target of 100 patients and 100 controls to provide a safety margin. All subjects were examined using a Siemens Antares duplex ultrasound machine. The internal jugular (upper, mid, lower), vertebral, and intracranial veins were studied in supine and sitting postures. The measures proposed by Zamboni and volume flow values were recorded. The presence of CCSVI was defined as ≥ 2 Zamboni criteria. The examination protocol was designed to ensure the sonographer was blind to clinical status, and the sonographer completed a blinding test at the conclusion of each examination.

An interim blinded analysis of the first 33 patient-control pairs (66 subjects, 12 male, 54 female, mean age 41.5 years, age range 24-60 years) revealed zero cases of CCSVI. However, one subject had reflux in extracranial veins, and 14 had internal jugular vein stenosis. Recruitment will continue in order to determine if there are more sensitive ultrasound criteria for CCSVI.

Our findings indicate that CCSVI, as defined by the Zamboni ultrasound criteria, is not seen in CIS and mild RRMS (EDSS \leq 2), and provide further evidence that CCSVI does not have a causal role in the pathogenesis for the onset of MS.

Disclosures:

This study is funded by MS Research Australia. Each author has nothing to disclose.

P1106

Prevalence of venous abnormalities in a paediatric MS cohort using magnetic resonance venography 3 Tesla

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Background: Several studies have recently provided contrasting results on the possible pathogenic role of chronic impaired venous outflow in multiple sclerosis. Venous abnormalities can be diagnosed noninvasively by conventional magnetic resonance venography (MRV). No studies have been performed so far in paediatric MS.

Objective: To evaluate prevalence of azygos (AZY) and internal jugular veins (IJVs) abnormalities in MS patients with paediatric onset and in a control group consisting in children or adolescents with juvenile epileptic disorder.

Methods: Conventional magnetic resonance imaging (MRI) and MRV were carried out in patients with paediatric MS; sex- and age-matched subjects with seizures served as control group. Each participant was examined with a 3T-MR unit operating with eight-channel body-array coils. A multi-channel head and neck coil was used to perform the following sequences: unenhanced 2D TOF and 3D TRICKS venography. An intravenous gadolinium-based contrast agent was injected by using a pressure injector followed by a 20 ml saline flush. Because the morphological features of the AZY and IJVs can vary along the vessel, we considered the narrowest point in both the inferior and superior segments, respectively. We considered only absent flow or strictures \geq 50% in the AZY and IJVs as abnormal. Data were analyzed by two radiologist blind to the disease history.

Results: Fifteen MS patients (14 F, 1 M) with mean age of 15.8 \pm 2.2 years, and 15 children with idiopathic epilepsy and normal brain MRI findings were tested to assess flow morphology of the AZY and IJVs. Eight MS patients (53.3%) and 2 (13.3%) epileptic children showed IJV stenosis. Reduction of calibre or anomalies (septum) in the AZY were been detected in 4 (26.6%) MS patients, but not in the control group. In the MS cohort, patients with at least one stenosis showed an EDSS score slightly worse and annual relapse rate in the previous 3 years significantly higher when compared to patients without venous anomalies (1.7 \pm 0.7 versus 1.0 \pm 0.5; $p=0.05$). The two MS patients with more

aggressive disease in terms of both relapses and EDSS score showed more than one venous abnormalities.

Conclusion: MRV shows venous abnormalities in half of patients with paediatric MS, suggesting that chronic impaired venous outflow has not a primary causative role in the development of the disease. However, the presence of AZY and/or IJV stenosis may affect the prevalence and the clinical course of paediatric MS.

Disclosures:

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